PRESIDENT'S MALARIA INITIATIVE TECHNICAL GUIDANCE

This document provides technical guidance to PMI staff involved in drafting PMI annual Malaria Operational Plans. It also serves as a technical reference tool for PMI country teams as they work with their national malaria control program counterparts and other partners to implement PMI-funded malaria activities. The guidance is updated on an annual basis to reflect the most recent global policies and the state-of-the-art of malaria control.

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PRESIDENT'S MALARIA INITIATIVE

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Revised For FY 2017 Planning (March 2016)

Technical Guidance Table of Contents

Acronyms and Abbreviations

ACCM	all-cause child mortality
ACT	artemisinin-based combination therapies
ANC	antenatal care
AQ	amodiaquine
CcOP	Communications Community of Practice
CDC	Centers for Disease Control and Prevention
CHW	community health worker
COR	contracting officer's representative
CPIR	commodity procurement information request
DOT	directly observe therapy
DHS	Demographic and Health Survey
DHIS2	District Health Information System 2
DP	dihydroartemisinin-piperaquine
EIR	entomological inoculation rate
EPI	expanded program on immunization
EUV	end-use verification
EVD	Ebola-virus disease
FANC	focused antenatal care
FELTP	Field Epidemiology and Laboratory Training Program
FIND	Foundation for Innovative New Diagnostics
FY	fiscal year
G2G	government-to-government
GMP	good manufacturing practices
HFS	Health Facility Survey
HLC	human landing catches
HMIS	health management information system
IAA	inter-agency agreement
ICT	information and communications technology
iCCM	integrated community case management
IDSR	integrated disease surveillance and response system
IMCI	integrated management of childhood illness
IPT	intermittent preventive treatment of women
IPTi	intermittent preventive treatment of malaria in infants
IPTp	intermittent preventive treatment of malaria during pregnancy
IRS	indoor residual spraying
ISTp	intermittent screening and treatment during pregnancy
ITN	insecticide-treated mosquito net
IVM	integrated vector management
K13	kelch protein on chromosome 13
KAP	knowledge, attitude, and practices
LLIN	long-lasting insecticide-treated mosquito net
M&E	monitoring and evaluation
MDG	Millennium Development Goal
MERG	Monitoring and Evaluation Reference Group

MICS	Multiple Indicator Cluster Survey
MIS	Malaria Indicator Survey
MFO	mixed function oxidase systems
MIP	malaria in pregnancy
MOH	Ministry of Health
MOP	malaria operational plans
MSAT	mass screen and treat
NGeNIR	next generation IRS
NGO	non-governmental organization
NMCP	National Malaria Control Program
OR	operational research
PARMA	PMI Antimalarial Resistance Monitoring in Africa
PBO	piperonyl butoxide
PC	Peace Corps
PCR	polymerase chain reaction
PEA	programmatic environmental assessment
PEPFAR	President's Emergency Plan for AIDS Relief
PMI	President's Malaria Initiative
POC	point of contact
QA	quality assurance
QC	quality control
RA	Resident Advisor
RBM	Roll Back Malaria
RDT	rapid diagnostic test
RHIS	routine health information system
SARA	service availability and readiness assessment
SBCC	social and behavior change communication
SEA	supplemental environment assessment
SM&E	surveillance, monitoring, and evaluation
SMC	seasonal malaria chemoprevention
SMS	short message service
SP	sulfadoxine pyrimethamine
SPA	service provision assessment
SRA	stringent regulatory authority
TA	technical assistance
TES	therapeutic efficacy study
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
US EPA	United States Environmental Protection Agency
US FDA	United States Food and Drug Administration
USG	United States Government
WHO	World Health Organization
3GIRS	third generation of IRS

Vector Monitoring and Control

New/Key Messages in the FY 2017 Technical Guidance

- The MOP template has been slightly revised to include an overarching section on vector monitoring and control, where country teams should describe the country's ITN strategy in the context of IRS and vice versa, if applicable.

Two of PMI's four main interventions – insecticide-treated mosquito nets (ITNs) and indoor residual spraying (IRS) – are aimed at controlling mosquito populations. These two interventions are insecticide-based and rely on twelve insecticides from only four insecticide classes (with only one class – pyrethroids – available for ITNs). Therefore, as countries scale up their ITN and IRS programs, it becomes increasingly important that countries develop resistance management strategies/national entomological monitoring plans and National Malaria Control Programs (NMCPs) develop vector control strategies that articulate how and where ITNs and IRS will be used to provide the greatest programmatic impact and mitigate the threat of insecticide resistance.

Combining IRS and ITNs

While there have been a limited number of comparison studies conducted on the possible added benefit of IRS in combination with ITNs, the studies have produced mixed results because of the insecticide chosen for IRS, the resistance status of local vectors, and variations in levels of ITN use. The World Health Organization (WHO) issued revised guidelines for combining IRS with ITNs in 2014, which can be found here: http://www.who.int/malaria/publications/atoz/who-guidance-combining-irs-llins/en/. The statement affirms that countries should rationalize the use of malaria vector control interventions, and justify any areas where ITNs and IRS overlap.

The two most frequent scenarios in which PMI-supported countries justify ITN and IRS overlap are:

- **Areas of profound pyrethroid resistance plus high transmission**: ITNs have been shown to provide protection even in areas with moderate pyrethroid resistance.[1] In the presence of profound pyrethroid resistance, ITNs still provide a physical barrier, yet PMI-supported countries should consider the addition of IRS with a non-pyrethroid insecticide in these areas if there is also high malaria transmission, as the community effect provided

[1] Lindblade et al. 2015. A cohort study of the effectiveness of insecticide-treated bed nets to prevent malaria in an area of moderate pyrethroid resistance, Malawi. http://www.malariajournal.com/content/14/1/31

by high ITN coverage may be compromised. Under this scenario, IRS also serves as a resistance management tool to preserve the effectiveness of pyrethroids on ITNs.

- **Areas of high transmission despite high net coverage**: IRS may be used along with ITNs to drive down transmission in high burden areas. When combining IRS with ITNs, only non-pyrethroid insecticides should be used for IRS and the rationale for selecting targeted IRS districts should be clearly defined. PMI will no longer support spraying of pyrethroid IRS on top of pyrethroid-treated ITNs.

Within countries, all areas at risk should be protected by at least one method of vector control, before adding additional methods to other areas. Countries should ensure that one vector control intervention does not compensate for gaps in another program area (i.e., whether ITNs or IRS is prioritized as the primary vector control intervention, it should be implemented well (e.g., universal coverage, high acceptance/use, etc.) before adding a second intervention).

Frequently Asked Questions for Vector Monitoring and Control

Q1. Are there any other vector control-based technologies on the horizon that PMI funds can support?

A. No. At the present time, there is an inadequate evidence base to support malaria vector control other than by ITNs or IRS in most areas of PMI-supported countries. However, as new tools become available and receive WHO recommendation for malaria control, PMI will develop policy and technical guidance for use within PMI supported program efforts. An overview of new tools in development through the Innovative Vector Control Consortium can be found here: http://www.ivcc.com/creating-solutions/our-work/new-vector-control-tools.

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. The development of these "next generation" ITNs has been progressing and we anticipate new products to become available as early as 2017. PMI will be ready with policy guidance for each product upon its technical recommendation and market availability.

Durable wall linings, a new concept using high-density polypropylene fabric containing a proprietary combination of two non-pyrethroid insecticides, is currently being evaluated by several organizations, including PMI. The concept has moved from pyrethroids to new classes of insecticide so it can be an effective tool in contexts where insecticide resistance remains a concern. Results from the pilot evaluations are expected in early 2017.

Larval control, which involves the treatment or elimination of collections of water where the immature stages of the mosquito vector develop, has been evaluated in a number of trials. In theory, larval control is generally thought to be most appropriate where larval habitats are few, fixed, and findable. This has generally translated to urban settings, areas with seasonal transmission, and lower-transmission areas where mosquito breeding sites are feasibly managed or eliminated. However, evidence for the efficacy of larval control in Africa and elsewhere is limited, even in settings considered amenable to this intervention. PMI does not prioritize its resources to support larval control, instead prioritizing support for other malaria control and elimination approaches within the budget envelop available. However, there may be instances in the future in the context of pre-elimination where PMI would consider supporting larviciding (see Pre-Elimination chapter, "Entomologic Monitoring and Vector Control" section). WHO's interim position statement on larval source management can be found at: http://www.who.int/malaria/publications/atoz/interim_position_statement_larviciding_sub_saharan_africa.pdf.

Other technologies under development, but not yet deployed, include treated clothing and shelter materials, attractive toxic sugar baits, housing improvements, as well as topical and spatial repellents. These potential tools are being developed by a number of commercial groups as well as the U.S. Departments of Agriculture and Defense: http://www.ars.usda.gov/research/projects_programs.htm?modecode=60-36-05-15.

Q2: What vector control strategies are not recommended for support with PMI funding?

A. Some mosquito control strategies are not recommended by PMI for programmatic implementation in Africa. These include: (1) environmental manipulation and biocontrol agents (it is the rare context where this can be effectively implemented); (2) attacking the adult stages through aerial or space spraying of insecticides by ultra-low volume or fog applicators (except in the most rare emergency settings, this is never recommended for malaria control); (3) personal protection through topical and spatial repellents and coils (still under investigation for public health use, although PMI could potentially support social and behavior change (SBCC) efforts to promote use in high-risk occupational settings in the Mekong); and (4) grass cutting (this has been shown to have NO impact on malaria and should not appear in any control strategy).

Entomologic Monitoring and Insecticide Resistance Management

New/Key Messages in the FY 2017 Technical Guidance

- Differences may exist in resistance profiles within the pyrethroid class, due to the specificity of some resistance mechanisms. To use pyrethroids rationally and preserve their efficacy as long as possible, PMI recommends: (1) testing multiple pyrethroids in standard resistance monitoring; (2) conducting resistance intensity assays; and (3) if WHO tube assays and resistance intensity assays show a large difference between two pyrethroids (e.g., 1X resistance vs. 5X resistance), performing cone bioassays on fresh ITNs, using wild mosquitoes, to show operational differences in susceptibility.
- To ensure that the correct species of mosquitoes are assayed for insecticide susceptibility, we recommend that countries conduct molecular typing of a subset of specimens collected via routine monitoring. This recommendation stems from the fact that many malaria vectors are members of morphologically indistinguishable species complexes, which have discrete patterns of behavior and insecticide susceptibility. Meaningful monitoring and interpretation of resistance is thus dependent upon correct species identification. Molecular typing is a useful and necessary adjunct to morphological identification.
- Entomological monitoring in pre-elimination settings: In areas with declining malaria transmission, marked geographic heterogeneity and sparse vectors present challenges for entomological monitoring, making long-term trends more difficult to discern. Moreover, declining vector densities make collections more time-consuming and costly, while sample sizes needed to assess insecticide susceptibility may be more difficult to obtain. To ameliorate these problems, sampling sites for entomological monitoring should focus on areas where transmission is likely to be occurring, as determined by epidemiological data from the routine HMIS, in addition to the typical longitudinal monitoring at other sites.

Introduction

The recent progress in malaria control, including many of the countries receiving support from PMI, has been largely accomplished through a massive increase in vector control from the use of ITNs and IRS.[2] Since both of these prevention measures depend on the ability of insecticides to kill, repel, or reduce the lifespan of female mosquitoes, understanding and monitoring the composition of the vector population, mosquito behavior, and insecticide resistance status are critical to their continued effectiveness.

[2] Nature. 2015 Oct 8;526(7572):207-11

WHO currently recommends twelve insecticides in four different classes for use in IRS programs. In contrast, because of its human safety and insecticidal properties, pyrethroids are the only insecticide class recommended for treatment of bed nets at this time. Pyrethroids are the cheapest and safest insecticides used for IRS and are also among the most popular insecticides for both agriculture and domestic use. While they are potent, safe, and relatively inexpensive, genes that confer resistance to pyrethroids are spreading through the important malaria vectors in Africa, posing a significant threat to malaria control progress.

The first step in responding to the threat of insecticide resistance is increased monitoring to detect changes in insecticide susceptibility. However, responding to insecticide resistance will neither be easy nor cheap; any alternative to the pyrethroids for malaria control will be more expensive, with decisions often based on information that is not definitive. Nevertheless, with changing malaria epidemiology and changing ecology and biology of mosquito vectors – as well as new chemicals and formulations becoming available – it is essential that countries develop the entomological capacity to monitor, adapt, and respond to emerging insecticide resistance.

The guidelines below provide:

- A technical background, including information on insecticides and their modes of action, as well as resistance and sources of selection pressure. While technically detailed, it is important for PMI teams and partners to have a basic understanding of the biological and ecological basis of resistance, the terminology used, and links to online resources available for insecticides and vector control.
- A "tactical" section, describing pertinent entomological indicators, mosquito collection techniques, measures to ensure than the vectors are accurately identified, resistance testing, monitoring site selection, reporting, and program capacity building, with specific PMI guidance in each of these areas. While attempting to be as definitive as possible, the country context will vary requiring interpretation and judgment.
- A "strategic" section, focusing on resistance monitoring and management, including the impact of resistance and long-term resistance management strategies.

Technical Background

Insecticides and modes of action

While about twenty classes of chemicals are registered for use against agricultural or domestic pests,[3] only four classes are registered for use against adult mosquitoes, with another three that can be used in larval control. Further background information on insecticides used in public health, including their safety and efficacy, can be found at the WHO Pesticide Evaluation

[3] http://ipmworld.umn.edu/chapters/ware.htm

Scheme (WHOPES) website (see http://www.who.int/whopes/en/). The WHOPES insecticide based product evaluation and recommendation process is currently undergoing changes to enable quicker product evaluation, develop a mechanism to re-evaluate quality of products once approved, and clearly established normative guidance for product categories through a Gates-funded project called Innovation to Impact (http://innovationtoimpact.org). PMI headquarters staff from both agencies are actively participating in this process, and more details will be forthcoming.

Understanding insecticide modes of action is essential for devising and implementing an insecticide resistance management strategy, which often includes switching or rotating insecticides. An excellent resource for learning more about the modes of action is the Insecticide Resistance Action Committee (http://www.irac-online.org/).

Resistance

Mechanisms

Resistance to insecticides is defined as a heritable change in the sensitivity of a pest population that is reflected in the repeated failure of a product to achieve the expected level of control when used according to the label recommendation for that pest species.[4] Entomologists classify insecticide resistance into two types:

1. *Physiological* resistance is conferred by two primary mechanisms (**Figure 1**). First, a detoxification mechanism, sometimes called metabolic resistance, involves a change or amplification in the enzymes that metabolize (i.e., 'break down') the insecticide, lowering the amount of material that can eventually reach and impact the target site. There are three categories of enzymes involved in metabolic resistance in mosquitoes: (a) esterases that break down organophosphates and some pyrethroids; (b) mono-oxygenases (sometimes referred to as the P450s) that work against all four classes of insecticides; and (c) glutathion S-transferases that work against DDT, pyrethroids, and organophosphates. Resistance is typically the result of complex genetic changes, making easy and rapid molecular characterization of physiological resistance difficult. We therefore emphasize monitoring of mosquito phenotypes for monitoring of physiological resistance.

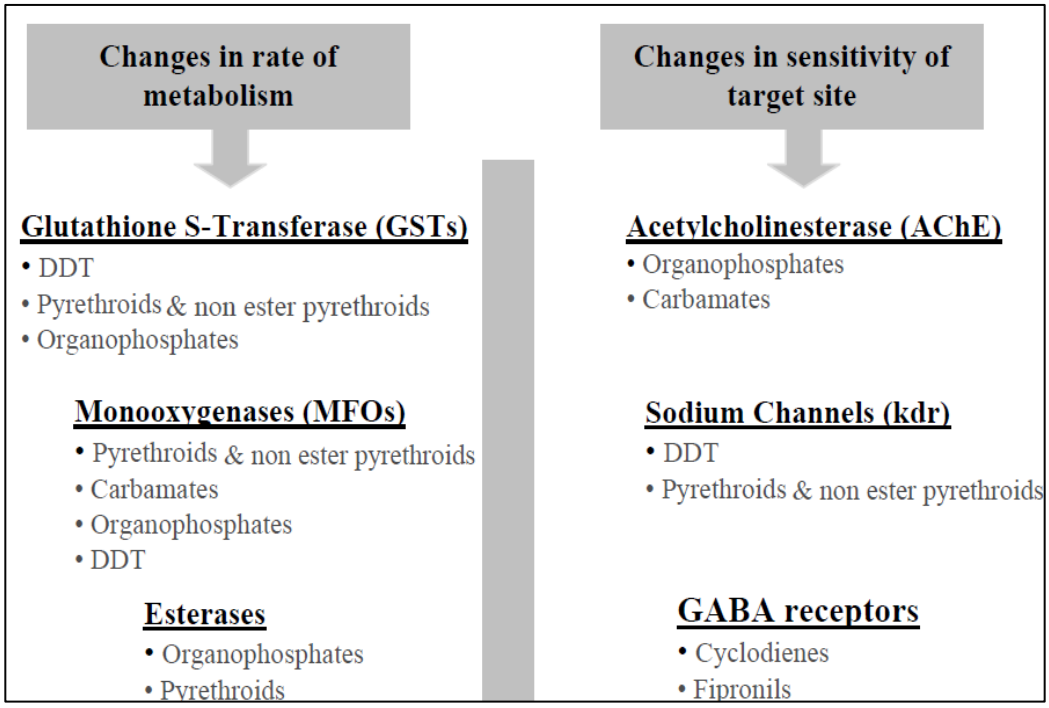
   Metabolic resistance can have a strong impact on malaria vector control efforts, particularly IRS. For example, it was "mono-oxygenase" resistance that enabled the *An.*

[4] Insecticide Resistance Action Committee, 2015, Mode of Action Classification Scheme.

funestus population in Kwa-zulu Natal, South Africa to become highly resistant to pyrethroids, forcing the NMCP to temporarily return to using DDT.[5]

The second major type of physiological resistance, "target site insensitivity," is related to the unaltered insecticide molecule being prevented from binding to its target (e.g., preventing sodium channel binding by DDT and the pyrethroids, and acetyl cholinesterase binding by the organophosphates and carbamates). Probably the best-known example of this resistance mechanism is the change in the sodium channel binding capability detected through a genetic marker, known as the "knock-down resistance," or *kdr* allele. As it is relatively easy to determine the molecular basis for this resistance mechanism, *kdr* is widely reported. However, in its heterozygote form *kdr* has a low association with failure of malaria vector control measures, and even the homozygous Leu-Phe *kdr* mutation produces only minimal resistance to pyrethroids.

Figure 1. Mechanisms of Physiological Resistance



2. *Behavioral* resistance occurs when the vector's normal behavior permanently changes in response to an alteration in its environment, (e.g., a mosquito evolves to an outdoor or more zoophilic feeding pattern (feeding on animals rather than humans)) to avoid indoor insecticide application. While behavioral resistance may not lead to complete control failure, it may reduce the efficacy of the control measure. Care should be taken, however,

[5] http://malariajournal.com/content/6/1/30

when ascribing mosquito behavior change to insecticide exposure, as it might be found that the underlying cause was a change in the vector species composition of an area.

In addition to behavioral and physiological resistance, there can be another biological form of resistance known as *cuticular* resistance, whereby in insects with thicker or waxier cuticles (the insect exoskeleton) there is less penetration of the insecticide. This was recently postulated as an auxiliary mechanism for the pyrethroid resistance of *An. funestus* in South Africa.[6]

Cross-resistance

Resistance to a given insecticide often confers resistance to the other insecticides in the same class, and may also confer cross-resistance to one or more other classes of insecticide. Cross-resistance between insecticides that share a similar mode of action is quite common. For example, it is believed that the common *kdr* target site resistance to pyrethroids in West Africa initially arose due to heavy DDT use in commercial agriculture. Cross-resistance between pyrethroids and DDT, however, is not an automatic outcome. For example, pyrethroid-resistant *An. funestus* in southern Africa are fully susceptible to DDT, but in this case, the *kdr* allele is not present and the resistance mechanism is metabolic.[7]

Because all compounds within a single class share a common mode of action, there is a high risk that resistance to one compound will confer cross-resistance to all compounds in the same class. There is, however, evidence that differences in susceptibility exist between class members, particularly for one of the major mechanisms of pyrethroid metabolic resistance, oxidases. Oxidases show great structural specificity in their detoxification capabilities. This specificity is a result of the complex structure of pyrethroids and the use in insecticide formulations of isomers, and combinations of isomers, that differ in their three-dimensional shapes. There has been documented evidence of differential metabolism of pyrethroid class members (non-cyano-pyrethroids, cyano-pyrethroids, and trifluoro-pyrethroids) by oxidases in *An. minimus*.[8] In addition, field data generated by PMI has been consistent with substrate specificity, whereby mosquitoes are susceptible to lambda-cyhalothrin but show resistance to deltamethrin. Particularly strong data on this was collected from three locations in Zambia. Using CDC bottle bioassays with insecticides at 2x and 5x the diagnostic dosages, *An. funestus* showed resistance to deltamethrin but was fully susceptible to lambda-cyhalothrin.

Cross-resistance among carbamates and organophosphates is highly variable. Resistance to malathion often does not cross to the other organophosphates (notably in Sudanese *An. arabiensis*) and pirimiphos-methyl is also very different from other organophosphates.

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[6] Wood et al (2010) Cuticle thickening associated with pyrethroid resistance in the major malaria vector *Anopheles funestus*. Parasites & Vectors 3:67.
[7] Brook *Bulletin of Entomological* Research 2001
[8] Duangkaew *Arch Insect Biochem Physiol* 2011

Source of selection pressure

Resistance selection from non-public health pesticides, such as agricultural insecticides running off into mosquito breeding sites (e.g., in Latin America,[9] Cameroon,[10] and West Africa[11]) or oil pollutants contaminating the water table,[12] may contribute to selection pressure resulting in resistance. Conversely, in some situations there is evidence that IRS drove the selection of insecticide resistance (e.g., in Sri Lanka and Sudan). [13] In addition, data suggest that the scale-up of ITNs has led to an increased frequency of resistance genes, even if they were not the initial cause.[14]

Detection and impact of insecticide resistance

Resistance is assessed primarily by one of two roughly equivalent *in vivo* assays, the WHO tube assay and the CDC bottle assay. Both are limited by availability of live, accurately characterized mosquito specimens and the skills needed to conduct the tests and interpret the results. In addition to *in vivo* assays, there are laboratory techniques to determine the underlying mechanism of resistance, sometimes referred to as "molecular assays" or "genetic markers". Although these can detect the two primary forms of resistance mechanisms described above, two important caveats must be noted: (1) molecular typing, especially detection of the *kdr* gene, does not always correlate with *in vivo* resistance; and (2) while the *in vivo* results may be an indicator for growing resistance problems, the result by itself does not predict an operational failure of IRS or ITNs.

Additional entomological and epidemiological indicators are needed to show that resistance is having an impact on transmission. Entomological indicators, such as resting on freshly sprayed surfaces, are described in more detail below. Epidemiological indicators, such as rising numbers of confirmed malaria cases, may be more difficult to attribute to resistance, due to non-entomological confounding factors. Preliminary data from a large, multi-country WHO project on the epidemiological impact of resistance was recently presented. One site in Sudan showed a significant reduction in malaria incidence related to a switch from deltamethrin to bendiocarb for IRS (in the context of high ITN usage). However, no correlations were observed between infection incidence and insecticide resistance, as measured by frequency of mortality at the standard diagnostic dose. It should be noted that there were large confidence intervals around mortality point estimates, and resistance frequency showed marked temporal and spatial heterogeneity. A potentially better predictor of the operational impact of resistance is resistance intensity, as opposed to resistance frequency, and PMI will be supporting an operational research

[9] Lines Parasitology Today 1988
[10] Chouaibou Tropical Medicine and International Health 2008, Antonio-Nkondjio Malaria Journal 2011
[11] Diabate Am J Trop Med Hyg 2002, Tia Bull Soc Pathol Exot 2006, Yadouleton Malaria Journal 2009
[12] Djouaka Malaria Journal 2007
[13] Lines Parasitology Today 1988
[14] Czeher Malaria Journal 2008, Mathias et al. Malaria Journal 2011, and Stump Am J Trop Med Hyg 2004

study to establish this association. Until results are available, PMI is still recommending that countries measure resistance intensity alongside resistance frequency.

There appears to be a difference in the potential impact on control failure between *kdr* target-site resistance and metabolic resistance mechanisms. From work in a number of countries, we now know that even the homozygous Leu-Phe *kdr* mutation gives only minimal (1X or 2X) resistance to permethrin and no resistance at all to the cyanopyrethroids. Conversely, there have been well-documented cases where metabolic resistance alone was strong enough to bring about control failure, as was the case with pyrethroid IRS in KwaZulu-Natal directed against *An. funestus*.[15] Additionally, in Benin, a combination of *kdr* and metabolic resistance has been seen to impact the efficacy of ITNs in houses when looking at entomological endpoints.[16] It should be noted, however, that in West Africa reports indicate that a new sodium channel mutation haplotype (N1575Y) can give 5X or higher permethrin resistance when it appears together with Leu-Phe *kdr*. Although resistance may diminish ITN efficacy, ITNs still provide a substantial protective effect over no net at all. Please refer to the **ITN** chapter for further guidance on the importance of maintaining universal coverage.

Entomological Monitoring

As countries scale up ITN and IRS programs, there is increased insecticide selection pressure on vector mosquito populations. One can expect to see changes in species composition, as well as changes in susceptibility to insecticides and possibly changes in vector behavior. The large investments in ITNs and IRS made by the Global Fund, PMI, and other donors, and our dependency on a limited number and classes of insecticides, make it imperative that national programs monitor and evaluate entomological parameters. The exact number and location of entomological monitoring sites should be discussed and approved by the PMI Headquarters Entomology Team. For more information, see the "Monitoring Sites" section below. Supplies for entomological monitoring can be procured through the current IRS task order or a bilateral implementing partner. Certain supplies may be provided by CDC (via CDC country entomologists and funded through PMI core funds to the CDC Interagency Agreement (IAA)). No entomological monitoring supplies should be budgeted for using the CDC mechanism in FY 2017 malaria operational plans (MOPs).

Entomological indicators

Basic entomological indicators

These indicators are considered basic to any well-performing vector control program and should be measured in all PMI-supported IRS and ITN programs.

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[15] Maharaj *SAMJ* 2005
[16] Guessan *Emerging Infectious Diseases* 2007 and Asidi *Emerging Infectious Diseases* 2012

1. Species composition and seasonality of malaria vectors in intervention areas

Purpose: To determine which vectors exist, their abundance, relative proportions, and distribution in intervention areas over time. Malaria vector species may differ in key characteristics, such as behavior and insecticide resistance, that have operational impact. The major vectors of malaria in Africa are species complexes, whereby different species are morphologically identical (e.g., *Anopheles gambiae, An. arabiensis*, and *An. Coluzzii*). For IRS, baseline data should be collected before a spray campaign begins, or data should be collected simultaneously from a comparative non-IRS site (e.g., a control village), in order to enable programs to determine the entomological impact of the intervention. It is important to monitor species composition and seasonality even if IRS is not conducted in order to determine sibling species proportions for insecticide resistance testing, to see if changes in species composition occur after introduction of LLINs (for example a shift to outdoor and early feeding species in response to net introduction), and as part of determining if there are changes in mosquito behavior.

Method: Mosquito identification is basic to all collections and analyses. The same basic mosquito collection techniques are used to calculate abundance, proportions, and seasonality. These include, where appropriate, human landing collections (HLCs), indoor resting collections, CDC light trap, exit trap and pyrethrum spray collections, and are described in more detail below. Where feasible, larval collections may also be conducted, especially in cases where there may be significant outdoor feeding. It should be noted that in homes with complete ITN coverage, indoor resting densities, as measured by pyrethrum spray collections, may be extremely low and therefore an alternate collection method, such as a CDC light trap hung next to a person sleeping under a bed net, is recommended. The PMI-supported Integrated Vector Management Project produced training videos for hand collection and pyrethrum spray collections available for viewing and download at https://vimeo.com/ivmproject/videos.

Where specimens are morphologically identified to the *An. gambiae* or *An. funestus* complexes, a subsample will need to be sent to a laboratory for molecular identification of species by polymerase chain reaction (PCR). The number of specimens in this subsample will be determined by the relative abundance of the sibling species, the capacity of the reference laboratory, and the purpose of the molecular identification tests. For example, a smaller subset of samples from larval collections for resistance assays may be identified as a spot check on the accuracy of morphological identification, vs. a larger proportion of adult mosquitoes found in houses may be assayed to determine vector species distribution. It should be noted that as control efforts have progressed, formerly ‘minor’ vectors of malaria may become predominant. Molecular identification

is a useful adjunct to morphological identification and should be carried out on a sample of specimens where changes in species composition have occurred.

Please consult with the PMI Headquarters Entomology Team to determine appropriate sample sizes, to develop a plan for molecular testing, and for suggested reference laboratories to which samples may be sent.

If low numbers of mosquitoes are being collected during the peak rainy/transmission season, the collection method being employed might need to be changed, the location of collections altered, or, as a last resort, the number of collection sites increased. Resting collections should take place early in the morning (prior to 8 am) before mosquitoes exit houses. If the issue of low collection numbers arises, the PMI Headquarters Entomology team will be able to advise on the best actions to take.

For additional information on mosquito collection techniques, WHO's excellent *Manual on Practical Entomology for Malaria Control* is available for reference (see http://whqlibdoc.who.int/offset/WHO_OFFSET_13_(part1).pdf and http://whqlibdoc.who.int/offset/WHO_OFFSET_13_(part2).pdf).

Time frame: To accurately capture seasonality, collections should be performed once per month throughout the transmission season. If countries have longitudinal data for a region on mosquito seasonality, then collections do not need to be conducted during the dry season. However, if enough vectors are present, baseline data should be collected prior to the transmission season. Beyond morphological identification of species, the PCR species identification should be conducted at the beginning and at the end of the transmission season.

2. Vector feeding time and location

Purpose: To determine vector feeding locations, (i.e., outdoors versus indoors) and feeding times to understand where and when transmission is occurring.

Method: Human landing catches are the preferred method. These will enable the determination of indoor and outdoor human biting rates (i.e., the number of mosquito bites people receive in a particular location per unit time). In some countries, ethical approval will need to be obtained before HLCs can be conducted. Where HLCs are not feasible, light traps may be used to provide some indication of indoor feeding but not on the time of feeding or the relative importance of outdoor transmission. Supplemental sporozoite ELISA testing may be done to determine the potential extent of outdoor

transmission; teams should ensure that morphological identifications are correct via molecular confirmation of sample of specimens, as outlined above.

Time frame: Collections should be conducted monthly during the transmission season.

3. **Insecticide susceptibility and resistance intensity**

Purpose: To determine vectors' susceptibility to insecticides currently in use or to be used in the future, and to determine the intensity of identified resistance.

Method: For susceptibility testing, either the CDC bottle assay or the WHO tube bioassay depending on availability of materials, capacity, and NMCP preference. The CDC bottle assay is used to determine resistance intensity.

The CDC bottle assay and WHO tube bioassay are roughly equivalent[17] and either may be used for insecticide resistance testing. However, unlike the WHO test, the CDC assay allows for the creation of dose-response curves to determine the intensity of resistance in a given area and to detect incipient resistance. Additionally, the CDC bottle assay can be used with synergists to determine the resistance mechanism. Concerns about standardization and quality assurance when technicians are coating their own bottles can be alleviated if pre-dosed bottles are used. Therefore, the CDC is distributing free-of-charge premeasured samples of all WHOPES-approved insecticides to anyone any country that needs them. The premeasured doses were agreed to by a consortium of laboratories and have been shown to work equally well for American, African, and Asian anophelines.

Ideally, resistance testing should be done on 1 to 5 day old, non-blood fed, female mosquitoes reared from larvae, or on F1 (first) generation mosquitoes raised from the eggs of field-caught females. Larval collections should cover multiple sites and eggs for an F1 generation should be from a large number of field-caught females to ensure adequate representation of resistance frequencies in the field populations. Sampling mosquitoes along transects may offer an advantage over isolated monitoring sites in order to get a representative sample of mosquitoes for resistance testing. Mosquitoes should be morphologically identified as vectors, to the best of the technician's ability, prior to the resistance assay. Mosquito species should be positively identified after the assay, and a sub-set of samples should be preserved for PCR diagnostics, when necessary.

[17] http://malariajournal.com/content/8/1/208

Where F1 mosquitoes cannot be obtained and field-caught females themselves have to be used for testing, it is likely that resistance will be underestimated, as metabolic resistance often declines dramatically with age of the mosquito.[18] In contrast, if mosquitoes are collected resting indoors on sprayed surfaces, the F1 generation of these mosquitoes may provide an overestimate of the frequency of resistance. If males are tested due to lack of female samples, the data for each sex should be recorded separately since males are likely to show somewhat more susceptibility in bioassays than females.

Tests should be undertaken on at least one representative insecticide per class and on insecticides that represent all available modes of action.[19] Protocols for the WHO and CDC bottle assay are available online (see http://apps.who.int/iris/bitstream/10665/80139/1/9789241505154_eng.pdf and http://www.cdc.gov/malaria/resources/pdf/fsp/ir_manual/ir_cdc_bioassay_en.pdf). Where possible, a known laboratory-reared, susceptible strain of mosquitoes (e.g., KISUMU strain) should be used as controls. All susceptibility results should be entered into the PMI resistance database, which can be accessed via our global IRS implementing partner or by contacting the PMI Headquarters Entomology Team.

In 2013, WHO published its guidelines for interpretation of susceptibility tests in *Test Procedures for Insecticide Resistance Monitoring in Malaria Vector Mosquitoes*. The new recommendations in this document are that 98-100% mean mortality in WHO bioassays indicates susceptibility and less than 98% mortality is suggestive of the existence of resistance. If the observed mortality is between 90% and 97%, the presence of resistance in the vector population must be confirmed. If mortality is less than 90%, confirmation may not be necessary, as long as a minimum of 100 mosquitoes of each species was tested. These criteria are based on the grounds that greater than 2% survival

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[18] Note, however, that if sufficient specimens are available, determining the susceptibility of wild-caught, adult mosquitoes may provide additional supplementary information

[19] The tests should include multiple replicates totaling ~100 females per insecticide. For susceptibility frequencies of 98 -100% or <90% this sample size is adequate. For values of 90-97% larger samples sizes would be beneficial. Where mosquito numbers are limited, whatever mosquitoes are available should be tested even if a sample of 100 cannot be achieved, as this will give an indication of the susceptibility status of the population, but results will need to be confirmed. For WHO bioassays, mortality should be recorded after a 24-hr holding period. For some slower acting insecticides, mortality may need to be recorded at 48 hrs. Mortality is recorded over time with the bottle assays. A control paper/bottle should be used each day that tests are undertaken. If 24-hr mortality in controls exceeds 20% using WHO tube assays, all results from that day's tests must be discarded. If mortality in the control is between 5-20%, results must be corrected for control mortality using Abbott's formula. Control mortality is assessed at 2 hours using the CDC bottle assay. When control mortality is > 10%, test results should be discarded; use Abbott's formula to correct for control mortalities of 3 to 10%. For WHO tests and CDC bottle assays each treated paper or bottle should ideally be used no more than 6 or 3 times, respectively, before being replaced. The temperature in the room should be recorded for each test. Bioassays should ideally be carried out at $27 \pm 2^{o}C$ and never at temperatures exceeding $30^{o}C$.

is unlikely to be due to chance alone, as long as tests have been conducted under optimum conditions of temperature and humidity with adequate mosquito numbers and replicates using fresh insecticide impregnated papers.

In terms of levels of resistance, it cannot be categorically stated that a program should discontinue an insecticide when the mortality falls below 98% in an *in vivo* assay, especially if the tests were not conducted under ideal conditions, but mosquito mortality of less than 98% does indicate that there should be follow-up investigations, including the identification of potential resistance mechanisms, as described in more detail below.

Resistance intensity

All PMI-supported countries should collect data on resistance intensity. Until recently, program decisions on vector control strategies were made on the basis of insecticide resistance as measured by frequency of mortality at diagnostic doses of insecticides, and pyrethroid resistance based on this definition is now widespread across Africa. All PMI-supported countries now have sites with either confirmed or suspected resistance to pyrethroid insecticides. However, control failure – the practical expression of resistance significance – may depend far more upon resistance intensity. There is evidence from PMI-supported entomological work in Zambia that mosquito survival, when exposed to higher concentrations of insecticide (e.g., survival at five or ten times the diagnostic dose), is associated with blood fed mosquitoes in houses where ITNs were recently distributed. These results indicate that it is not just the frequency of resistance in a mosquito population that is important (e.g., seeing 22% of mosquitoes surviving in standard 1X dose bioassays), but in fact the level of intensity of resistance (e.g., seeing 7% percent of mosquitoes surviving at 5X the diagnostic dose) might be most important from an operational perspective. Resistance intensity can be measured using the CDC bottle assay. Particularly when using the intensity assay as a rapid diagnostic test to determine if resistance has potential operational impact, it is beneficial to use field caught mosquitoes, whether collected indoors using backpack aspiration or outdoors by HLC.[20]

- ***Differential pyrethroid resistance***

  Previous data has shown that drastic differences in resistance profiles can occur within the pyrethroid class, due to the specificity of some resistance mechanisms. In order to use pyrethroids rationally and preserve their efficacy as long as

[20] Bagit J, Grisales N, Corkill R, Morgan J, N'Fale S, Brogdon WG, and Ranson H. When a discriminating dose assay is not enough: measuring the intensity of insecticide resistance in malaria vectors. *Malaria Journal* 2015 12(10. Accessible at http://www.malariajournal.com/content/14/1/210

possible, PMI recommends collecting further data where such differences are found, using the following methods:

1. Testing multiple pyrethroids in standard resistance monitoring. If collecting adequate mosquito numbers are an issue, it may be acceptable to test different pyrethroids each year (for example, if deltamethrin shows consistently low mortality over several years, it may be a better use of mosquito samples to test an alternate pyrethroid). Currently, deltamethrin, permethrin, and alphacypermethrin should be prioritized.
2. Resistance intensity assays should be performed with pyrethroids for which resistance was detected.
3. If WHO tube assays and resistance intensity assays show a large difference between two pyrethroids (e.g., 1X resistance vs. 5X resistance), cone bioassays on fresh LLINs, using wild mosquitoes, should be performed to show operational differences in susceptibility.

- **Time frame:** Baseline insecticide susceptibility should be established before an intervention is initiated and then conducted annually as long as bioassays indicate 98-100% susceptibility. Testing frequency should be increased and expanded in geographic range, and resistance intensity assays should be conducted, if susceptibility falls below 98%. The frequency of testing should also be increased if there is an unexpected increase in the number of malaria cases in the area in order to confirm the presence and levels of resistance.

4. <u>Mechanism of resistance</u>

Purpose: Once resistance is suspected to an insecticide (mortality rates in WHO tube or CDC bottle assay fall below 98%), the underlying mechanism of resistance should be identified in order to help determine the operational impact of resistance and potential insecticide alternatives.

Method: Metabolic resistance can be detected by using CDC bottle assays with synergists. Piperonyl butoxide (PBO) will inhibit mixed function oxidases, s,s,s-tributyl phosphorotrithioate will inhibit non-specific esterases, and ethacrynic acid, diethyl maleate, or chlorfenethol will inhibit glutathione transferase activity. By exposing mosquitoes for one hour in synergist-treated bottles prior to exposure in insecticide-treated bottles, resistant mosquitoes will return to apparent susceptibility if the inhibited enzyme is responsible for resistance. Additionally, biochemical assays may be carried out to measure enhanced levels of detoxification enzymes responsible for resistance. Target

site resistance can be detected by PCR tests for *kdr* and acetyl cholinesterase resistance genes.

Time Frame: If resistance is suspected, the mechanism of resistance should be investigated annually.

5. **Quality assurance and residual efficacy monitoring of IRS programs** (see the **ITN** chapter ("LLIN Durability Monitoring Guidelines" section) for quality assurance and residual efficacy of nets)

   Purpose: To determine the quality of IRS (e.g., assays conducted shortly after spraying can be used to assess sprayer performance) and the efficacy of the intervention (e.g., to determine how long insecticides last in killing or knocking down vectors).

   Method: Cone bioassays are currently the only way to measure insecticide decay on sprayed surfaces.

   To perform cone bioassays, known susceptible laboratory-reared mosquitoes (e.g., KISUMU strain) should be used. If these are not available, wild-caught, unfed, female mosquitoes can be used as long as there is no demonstrated resistance in the population. The process for IRS testing is as follows: (1) attach bioassay cones to walls at three different heights (0.5 meter, 1.0 meter and 2.0 meters above the floor) using tape; (2) introduce batches of 10 female mosquitoes into the cones and expose to the wall surface for 30 minutes; and (3) after exposure, transfer the mosquitoes to paper cups, provide them with a sugar solution, and record mortality 24 hours after exposure. Tests should be conducted in enough houses to be representative of different wall surfaces and different groups of spray operators. Control assays should also be conducted – either select houses of similar construction that have not been sprayed or cover sprayed wall with two layers of paper before attaching the cones. Introduce 10 mosquitoes per cone as above.

   It should be noted that pirimiphos-methyl has an airborne effect when initially sprayed. Therefore, any mosquitoes brought into houses freshly sprayed with pirimiphos-methyl will die, even if they are not placed directly on a sprayed surface. Therefore, results from monitoring at one-month post-IRS should be used as baseline for residual efficacy monitoring, and alternative methods for determining spray quality may need to be employed (e.g., examining the visual pattern of insecticide residue on walls after spraying).

   Time frame: If possible, baseline assays should be conducted within a week of spraying. Subsequently, monthly decay rates should be measured.

Data should be shared with the NMCP and implementing partners as soon as results have been collected in order to initiate immediate corrective action, if necessary. Monthly decay rate results will then be used to determine the residual life of the insecticide under local conditions. Obtaining monthly decay rate data is often difficult because of a shortage of susceptible mosquitoes for testing. Nevertheless, for shorter-acting formulations, every attempt should be made to conduct monthly testing. For longer-acting formulations, at least the baseline testing and monthly testing beginning in the fourth or fifth month after spraying should be attempted.

Advanced Entomological Indicators

These indicators are additional to the basic entomological package listed above. They can provide important information to determine program impact but require more entomological capacity to perform the tests. Therefore, emphasis should be placed on ensuring that basic indicators are addressed first.

1. **Identification of mosquito infectivity**

   Purpose: To determine mosquito infectivity by calculating the sporozoite rate (i.e., the proportion of mosquitoes in a population harboring infective sporozoites in their salivary glands). This may serve three purposes. First, detecting differences in sporozoite rates in insecticide-resistant vs. susceptible individual vectors may be an indication of control failure. Second, sporozoite detection is necessary to determine the entomological inoculation rate (EIR), which describes the number of infectious bites an individual is exposed to in a given time period (typically a year or transmission season). In theory, the EIR is a good way to define transmission intensity. Unfortunately, EIR estimates may differ widely depending on the sampling tools used and sampling errors can be great in areas where mosquitoes are rare and/or rarely infected (as in areas with low parasite prevalence and low transmission). Therefore, in general, EIR determination is **not** considered part of the basic entomological monitoring package. Third, there may be situations, such as in the Mekong Sub-region and in countries in Africa where vector composition is changing, where there may be a need to determine the vector status of potential secondary vectors.

   Method: Sporozoite-positive mosquitoes can be identified by ELISA (see http://www.mr4.org/Portals/3/Pdfs/Anopheles/3.3%20Plasmodium%20Sporozoite%20ELISA%20v%201.pdf) or PCR.

   Time Frame: Inclusion of sporozoite determination and reporting time frame will need to be discussed on a case-by-case basis with the PMI Headquarters Entomology Team.

2. **Age grading – to determine the age composition of a vector population; older populations are more likely to transmit malaria because they need to survive the time needed for the parasite to develop inside the mosquito**

Purpose: Since IRS and ITNs work by shortening the lifespan of mosquitoes, the average age of the vector population will decrease if the interventions are effective. In special circumstances, and depending on the capacity of the entomological teams, age grading may be undertaken to monitor mosquito survivorship in the presence of IRS or ITN interventions. Age grading, like the EIR, is fraught with sampling issues. Nevertheless, it can be a powerful indicator of the impact of vector control interventions.

Method: The simplest method involves the dissection of mosquito abdomens and the determination of the parity rate in the mosquito population. By dissecting and microscopically observing mosquito ovaries, skilled technicians can determine if a female mosquito has laid eggs at least one time in her life (i.e., if she is parous). The proportion of parous individuals correlates to the average age of a population. Because the "% parous" indicator is a relative indicator of age, it is best used as a comparison (e.g., before and after an intervention).

Time Frame: Inclusion of age grading determination and reporting time frame will need to be discussed on a case-by-case basis with the PMI Headquarters Entomology Team.

3. **Blood meal analysis**

Purpose: To determine the source of the blood meal in fed mosquitoes. Blood meal analysis enables one to determine what portion of mosquito blood meals are taken on humans versus animals. Repeated collections after the introduction of a vector control intervention may be used to identify shifts in feeding behavior.

Method: Blood-fed mosquitoes can be collected by indoor or outdoor resting collections, pyrethrum spray collections, or CDC light traps. After DNA is extracted from mosquito abdomens, there are a number of molecular assays that can be used to determine the host source of a blood meal.

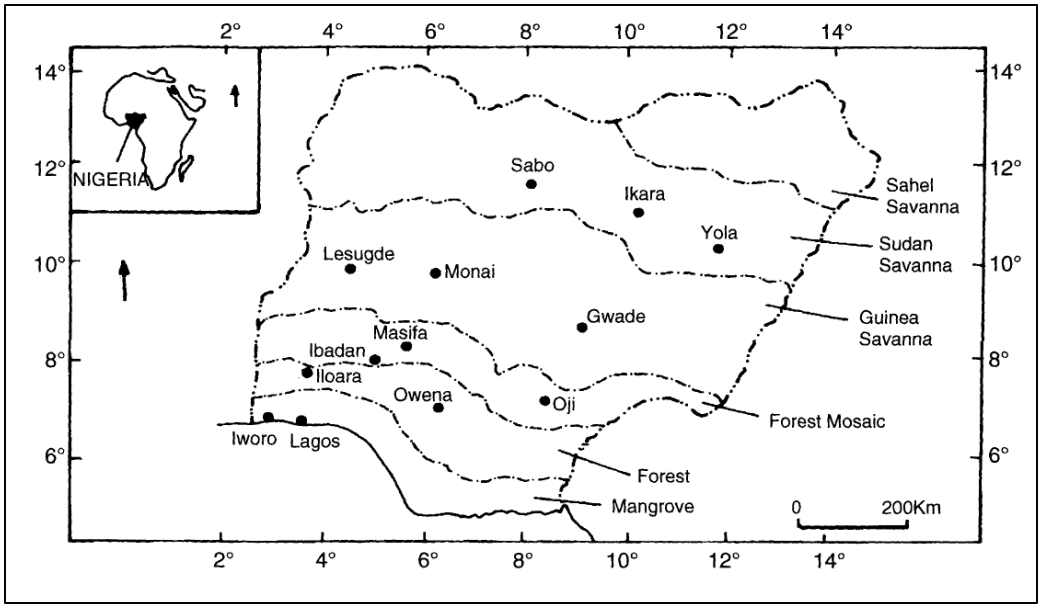
Time Frame: Inclusion of blood meal analysis and reporting time frame will need to be discussed on a case-by-case basis with the PMI Headquarters Entomology Team.

Monitoring Sites

Countries should do an initial stratification of their territory into eco-epidemiological zones and then establish at least one monitoring vector site per zone (see Figure 3 as an example). Sites should be located throughout a country's malarious zones, particularly in areas of greatest malaria incidence and pesticide use (including both agricultural and public health use). For countries where PMI is supporting IRS programs, additional monitoring sites may need to be set up to adequately cover the areas being sprayed. In order to collect data on seasonality, trends, and vector control impact, it is important that continuity be maintained within sites. In areas with stable malaria transmission, entomological monitoring sites should only be changed if there is a good programmatic rationale (e.g., re-targeting of IRS).

In a country such as Nigeria, with a very large population, but with relatively limited eco-epidemiological strata, it would be more appropriate to select 3-5 sites within each zone (**Figure 2**). As an approximate guide, a minimum one monitoring site per 500,000 nets distributed or 200,000 houses sprayed is recommended (the equivalent of one site per million people protected). **The exact number and location of sites should be discussed and approved by the PMI Headquarters Entomology Team.** Keep in mind that PMI works in collaboration with the national program and other partners and should, therefore, not be expected to be the only source of funding for these sites.

Figure 2. Map of Nigeria Showing the Entomological Monitoring Sites in the Different Ecological Zones[21]



Entomological monitoring in pre-elimination settings

In areas with declining malaria transmission, marked geographic heterogeneity can become more apparent within regions and among villages. Further, vector numbers may decline markedly, making collections more time-consuming and costly. Heterogeneity and sparse vectors present challenges for entomological monitoring, making long-term trends more difficult to discern. Sample sizes needed to assess insecticide susceptibility may be more difficult to attain. To ameliorate these problems, sampling sites for entomological monitoring should focus on areas where transmission is likely to be occurring, as determined by epidemiological data from the routine health management information system (HMIS). In pre-elimination settings, there should be a subset of sites used for longitudinal monitoring, for insecticide resistance (e.g., in addition to a subset that can be chosen yearly in response to changing epidemiology). Entomological monitoring should concentrate on foci of transmission (as identified by the NMCP). *Ad hoc* investigations in response to malaria outbreaks and case follow-up will be needed, which will include rapid surveys of vector control intervention coverage, assessment of vector and human behavior to determine the locus of transmission, and assessment of the vulnerability of vectors to larval control. These focal and ad hoc investigations are in addition to routine surveys in foci of transmission (e.g., reactive case detection).

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21 Awolola TS, Oyewole IO, Amajoh CN, Idowu ET, Ajayi MB, Oduola A, Manafa OU, Ibrahim K, Loekemoer LL and Coetzee M. Distribution of the molecular forms of Anopheles gambiae and pyrethroid knock down resistance gene in Nigeria. Acta Tropica 2005, 95.

Reporting

Periodic reports of findings in a standardized format should be provided to both the NMCP and PMI headquarters from each monitoring site. The PMI Headquarters Entomology Team will work with the partners to develop this standard format and recommend the frequency of the reports, and will begin to publish entomology reports online for public access. However, at minimum the following should be reported: (1) results of IRS residual activity, measured by cone assay with a susceptible mosquito strain, within the first few weeks of spraying for quality assurance purposes (i.e., if issues with quality are identified re-spraying may be needed), and (2) semiannual reports highlighting the seasonal collections to date and results for all primary entomological indicators.

All susceptibility data from whatever source should be promptly shared with the NMCP and with district and regional malaria control staff. **Current susceptibility data should be submitted to PMI at least 6 months prior to the next spray operation to allow for evaluation and timely insecticide procurement.** Entomological and epidemiological reports from local health facilities should be compared and shared by health officials. Some countries have a national Technical Advisory Committee that includes PMI, which can review entomological monitoring data and make recommendations. PMI country teams should ensure that the PMI Headquarters Entomology Team receives all relevant entomological information and are involved with these discussions.

Additionally, all susceptibility data and cone assay results should be submitted to the PMI Headquarters Entomology Team via PMI's database forms (currently being managed by our global IRS implementing partner). Access to this raw data will enable better analysis of insecticide resistance distribution and trends.

National Entomological Monitoring Programs[22]

Basic requirements

A national entomological monitoring program should include:

- Trained field technicians with supervisors having a Master's degree or an equivalent level of training and experience.
- Reliable and available insecticide-free transport for mosquito collection teams when needed.

[22] Please note that PMI cannot be responsible to fund a national entomology monitoring program in its entirety but requires commitment from the national program and other partners.

- Access to a laboratory with dissection microscopes, mosquito identification keys, mosquito traps and supplies (these should include entomological collection equipment, bioassay tubes and/or bottles).
- Access to WHO bioassay papers and/or technical grade insecticides, 250 mL glass bottles with caps, and acetone for CDC bottle assays.
- Where possible, an insectary with a colony of an appropriate (local species) insecticide-susceptible mosquito strain, for cone bioassays and to serve as controls in resistance monitoring.
- A written entomology monitoring and evaluation plan with a budget. This should be developed in collaboration with the PMI entomologist supporting the national program. The PMI Headquarters Entomology Team can help with developing a realistic plan and budget, including laboratory, insectary, and collection supplies. The entomology monitoring and evaluation plan should be written into the overall M&E plan for the NMCP.
- Where these capacities do not exist in country, technical assistance, training and mentoring are needed. Local staff should develop needed skills while working with the technical experts. Promising personnel should be selected by the local government to receive long-term training to further bolster local capacity. Trained staff and technical resources available in neighboring countries, or countries sharing the same language, should also be utilized if possible.

Structure of the entomological and insecticide resistance monitoring program

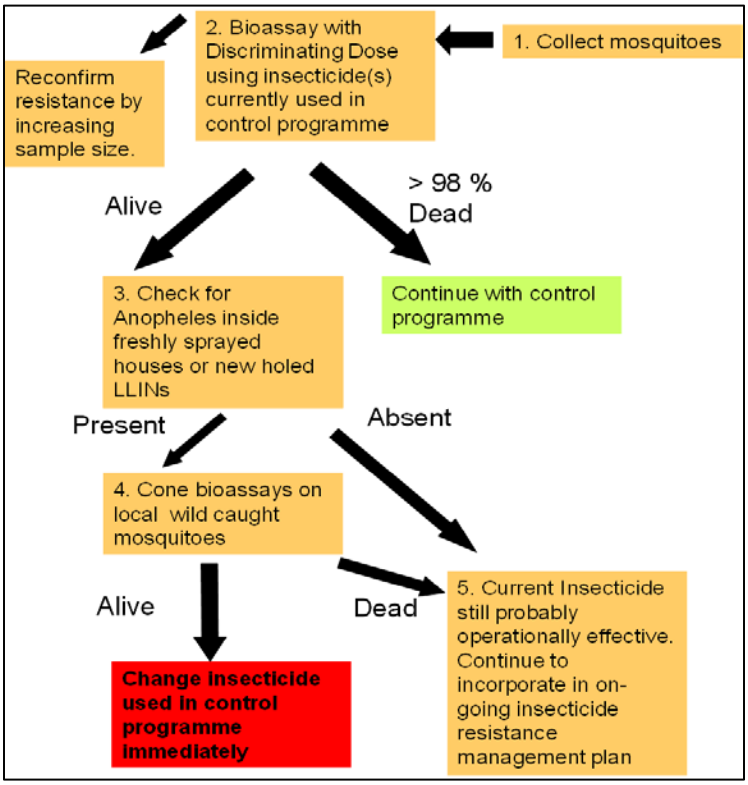
Correct performance of the collections and assays described above requires considerable skill and some basic laboratory and field equipment and supplies. The persons conducting entomological collections, performing the insecticide resistance assays, interpreting the data, and making recommendations will vary from country to country. In some cases, it is the NMCP itself that is supported to perform these tasks. More often, however, data collection is contracted out to national universities, research institutions, or other implementing partners and done under the auspices of the NMCP. Wherever PMI works with NMCPs or district vector control programs, local capacity should be strengthened. An NMCP/Ministry of Health (MOH) Technical Advisory Committee, including PMI representation, should be supported to interpret data and make recommendations and decisions.

Guidance on Insecticide Resistance Management

Monitoring steps

A core part of the basic entomological monitoring program is monitoring insecticide resistance. The objective of resistance monitoring is to assess the distribution, frequency, nature, underlying mechanisms and likely operational impact of any resistance observed. To do this, a number of basic monitoring steps should be performed, which are illustrated in **Figure 3** and described below.[23] Note that the PMI Resident Advisors (RAs) and country entomologist should be involved with this process.

Figure 3. Basic Entomological Monitoring Steps



Step 1 – Monitoring site mosquito collections

Monitoring sites should be established for mosquito collections, and baseline insecticide susceptibilities determined at these sites before interventions are implemented. As stated in the previous section, a rough guide is to have one site per eco-epidemiological zone or per one million people protected, but the exact number and location will have to be determined by the national program and partners in consultation with PMI entomologists and country advisors.

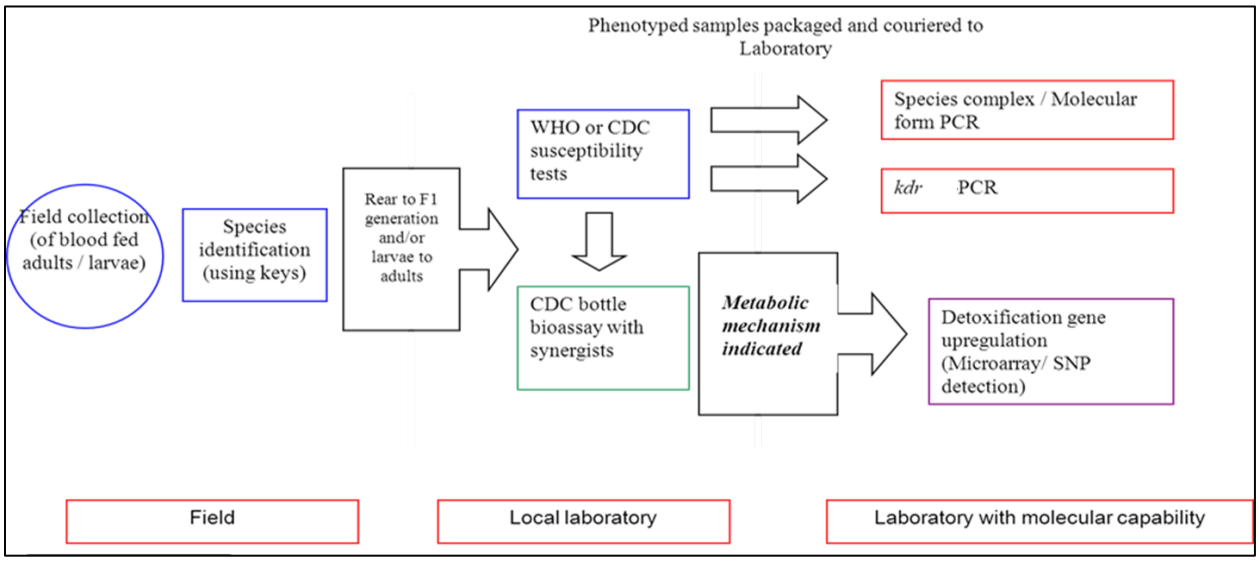
Step 2 – Conduct bioassays

Either the CDC bottle assay or the WHO tube test can be used. While the exact structure will vary from one country to another, **Figure 4** illustrates an idealized flow diagram for sample processing. Adult specimens collected in the field could be morphologically identified using keys and reared to F1 generation, or specimens collected as larvae could be reared to adults and

[23] This flow chart was developed by Maureen Coetzee and Janet Hemingway at the RBM Insecticide Resistance meeting held in Liverpool, October 2010.

tested with either the WHO or CDC assays. If resistance is detected in the *in vivo* assays (i.e., below 98% mortality), the mechanism of resistance should be determined through use of the CDC bottle assay using synergists or through molecular techniques, as this will assist with the decision on the best alternative insecticide. **Resistance intensity assays using the CDC bottle assay should also be conducted as a tool to assess the possible operational impact of resistance**. The PMI entomologist supporting the country will be able to provide guidance on how these further tests should be performed.

Figure 4. Simplified Diagram Indicating Possible Steps in a Resistance Monitoring Program



Source: Insecticide Resistance Action Committee, 2011, Prevention and Management of Insecticide Resistance in Vectors of Public Health Importance

Step 3 – Establish whether mosquitoes are resting in freshly sprayed houses or inside new holed ITNs

If the vectors survive in discriminating dose bioassays (i.e., less than 98% mortality) there is a need to investigate the operational significance of this resistance to vector control. The presence of live mosquitoes in sprayed houses can be assessed using a variety of collection methods, including pyrethrum spray collections or manual collections using aspirators from indoor resting sites or from inside new ITNs that have holes cut in them. If possible, some mosquitoes should be preserved for molecular resistance analysis at a tertiary facility.

Mosquitoes found inside houses after spraying or in holed ITNs could indicate either (a) operational problems with the spraying or with the insecticidal content of ITNs or (b) that mosquitoes are able to survive the insecticide intervention. To distinguish between these two alternatives, a freshly sprayed wall or new ITN should be used to test for insecticide activity.

Cone bioassays with known susceptible mosquitoes can be used for quality testing of either intervention. Additionally, the concentration of insecticide on ITNs can be tested using colorimetric quantification kits,[24] or high-pressure liquid chromatography.

The absence of mosquitoes inside sprayed houses does not necessarily mean that control is working. In these situations, more discussion and a more comprehensive understanding of the susceptibility profile of the local vectors to a range of insecticides will be needed.

Step 4 - Cone bioassays on local field-caught mosquitoes

This step is recommended to ensure that IRS and ITNs are capable of killing local vector populations. This should be done even if no vectors are found resting inside houses or holed ITNs in Step 3 above. Local females collected from the field (e.g., resting catches from untreated houses or outdoor collections) should be used. For IRS, testing should be undertaken on a freshly treated wall of typical local construction using a 30-minute exposure.

- Use bioassay cones and place on walls at different heights. Attach to walls using tape. Introduce batches of 10 female mosquitoes into the cones and expose to the wall surface for 30 minutes. After exposure transfer the mosquitoes to paper cups, provide with sugar solution, and record mortality 24 hours after exposure.
- Control assays – either select houses of similar construction that have not been sprayed or cover sprayed wall with two layers of paper before attaching the cones. Introduce 10 mosquitoes per cone as above. Correct for control morality.

For ITNs, testing should be done on new nets for 3 minutes, using 10 mosquitoes per cone. Mortality should be recorded after 24 hrs.

NOTE: this is not the same as the quality control assays for IRS described above. Those assays should be performed with cone bioassays using a laboratory susceptible strain of mosquitoes. Here, local field caught females are used.

Step 5 - Interpretation of data

Decisions on operational control failure and changing insecticides should not be taken based on bioassay data alone. As defined, mortality below 98% in tube or bottle assays are an indication that further investigation, as described in the steps above, is required. Further field investigation of resistance provides a better indication of control failure or success. While NO one test can incontrovertibly demonstrate that insecticide resistance has resulted in a reduction of the efficacy

[24] http://www.malariajournal.com/content/12/1/57/abstract

of the control measure and in an increase in transmission, if mortality in susceptibility assays falls below 90%, the general recommendation has been to switch away from that insecticide class. It is acknowledged that programs are often forced to make decisions with a paucity of information (e.g., mortality data of 90-97%, with less than the ideal number of mosquitoes tested and geographic variability). In these instances, PMI and the NMCP need to weigh the options and reach a consensus on the way forward.

Indicators of resistance should never be ignored to the point where disease transmission rises substantially, as this is too late to maintain any long-term use of the particular insecticide. Ideally, resistance management should already have been initiated before resistance is detected. Once resistance is detected to an insecticide, the use of that insecticide class within a resistance management strategy is likely to change.

If a national technical advisory committee is in place, they could help assess the information on behalf of the NMCP. The PMI entomology advisors should be involved in these national discussions. The PMI Headquarters Entomology Team can help interpret the data and make recommendations on insecticide selection for IRS.

Insecticide Selection

The choice of which insecticide to use in a particular setting should be made with expert consultation during the planning period for spraying and **at least six months before the spray operation** to allow adequate time for procurement. PMI has specified the following five criteria for determining choice of insecticide: vector resistance, duration of efficacy, risk to human health and environment, livestock, and agricultural trade, acceptability to NMCP, and cost. The range of insecticides that can be used for IRS is limited. Each has its own advantages and disadvantages as outlined in **Table 1**.

Table 1. Advantages and Disadvantages of IRS-Recommended Chemical Classes			
Chemical class	**Advantages**	**Disadvantages**	**Cost/sachet or sachet equivalent**
Pyrethroids	• Low toxicity • Low cost • >7 months duration for longer-lasting formulations	Resistance	$2-3
Carbamates	• Medium toxicity Profile • Less resistance	• High cost • < 4 month duration	$11*
Organo-phosphates	• Less resistance • CS formulation >6 months duration	• Higher relative toxicity • Higher costs	$23.50 for CS formulation
Organochlorines (DDT)	• Low cost • >7 months duration	• Management costs • Resistance • Supply	$4 to $6.70
*The number of structures sprayed per bottle/sachet is approximately equivalent for all insecticides, however, the short residual life of current WHOPES-recommended carbamate formulations means that in areas of year-round transmission, two rounds of spraying are required, effectively doubling the price of carbamates.			

Long-Term Resistance Management Strategy

It is recommended that NMCPs develop long-term strategies for slowing down and mitigating the inevitable evolution of resistance in local vector populations. These strategies should include orientation of the NMCP toward Integrated Vector Management (IVM), as well as steps to ensure quality IRS. Additionally, programs might consider preemptively switching insecticides as part of an insecticide rotation in order to mitigate the development of resistance.

Orientation of the malaria control program toward IVM

Many programs are reorienting towards an Integrated Vector Management approach. The WHO's *Global Strategic Framework for IVM* contains key elements that include:

- Adequate, up-to-date insecticide legislation
- Advocacy, social mobilization, and regulatory control for public health and empowerment of communities

- Collaboration within the health sector and with other sectors through the optimal use of resources, planning, monitoring and decision-making
- Integration of non-chemical and chemical vector control methods, and integration with other disease control measures
- Evidence-based decision making guided by operational research and entomological and epidemiological surveillance and evaluation
- Development of adequate human resources, training, and career structures at national and local level to promote capacity building and manage IVM programs
- Rational utilization of resources, including targeting of IRS

Ensuring quality IRS

Within this "strategic" reorientation of programs towards IVM, there are a number of "tactical" actions that NMCPs and PMI-supported operations should undertake as part of their long-term resistance management plan. The first of these is to ensure the quality of IRS. Haphazard, under-dosed spraying is a waste of resources and, like sub-lethal dosing of medications, will tend to select for the more tolerant mosquitoes in the population. Guidelines for IRS management and supervision checklists are available on the PMI website.

Rationale for introducing an insecticide rotation

There are now sufficient data from control programs in both public health and agriculture to state that using carefully chosen rotations of insecticides (switching classes each round), mosaics (the spraying of one compound on some surfaces and another compound on other surfaces), or mixtures of insecticides (analogous to combination therapy for drugs, using two insecticides on the same surface) work well in slowing down the rate at which operationally significant levels of insecticide resistance will be selected.

While mixtures may be marginally more beneficial in reducing the rate of resistance selection, they have a large cost, that along with potential issues around length of efficacy of the different insecticides within the combination, make them economically and technically difficult to deploy. Until further evidence becomes available, PMI does not support the use of insecticide mixtures. Likewise, mosaic spraying with the use of two different classes of IRS chemicals in the same village is difficult to manage and generally not supported by PMI. In the past, some countries had deployed pyrethroids on "formal structures" with plaster-finished wall surfaces and DDT in "informal" houses with mud-surface walls. This should not be confused with "mosaic spraying" and was done to increase operational persistence of insecticides on the sprayed surfaces and for homeowner acceptability, and not as a resistance management tool, as there is significant cross-resistance between these two classes.

Unlike mixtures and mosaics, PMI will support the phased implementation of insecticide rotations. The WHO's *Global Plan for Insecticide Resistance Management*[25] recommends that in areas where IRS is the primary form of vector control, the insecticide used should be preemptively rotated between classes. Cross-resistance patterns between insecticides can be complex, but as a general rule, insecticides that share a common target site should not be rotated back-to-back. An ideal rotation would deploy insecticides with different modes of action rotated annually. Preemptive rotations are likely the best way to prolong susceptibility and maximize the long-term cost effectiveness of insecticides. However, there are operational challenges to fully implementing the recommendations of the *Global Plan for Insecticide Resistance Management*. In particular, there are limited options for non-pyrethroid, long-lasting insecticides. While longer-lasting formulations of WHOPES-recommended insecticides and new classes of insecticides are under development, actual products are still several years away. In addition, questions remain regarding how successful rotations will be in mitigating the development of resistance, or promoting the return of susceptibility in resistant populations. Therefore, if countries choose to conduct preemptive rotations, the effects of insecticide rotation on insecticide resistance profiles and implementation costs should be closely monitored and evaluated. In addition, country teams should engage PMI Headquarters IRS Team if/when their country counterparts begin to consider pre-emptive rotation of insecticide in order to appropriately consider needed monitoring and support.

[25] http://www.who.int/malaria/publications/atoz/gpirm/en/

Insecticide Treated Nets

New/Key Messages in the FY 2017 Technical Guidance

- **PMI Guidance on ITN Durability Monitoring:** PMI's new guidance document has been launched. Updates and resources are available online through a dedicated website (www.durabilitymonitoring.org). The PMI Headquarters ITN Team has developed these tools and guidance for country teams to fully plan, budget, and implement routine ITN monitoring and are included in this year's guidance document. For more information, contact the PMI Headquarters ITN Technical team.
- At this time, PMI will not procure the pyrethroid plus PBO ITNs in place of ordering standard pyrethroid-only long-lasting ITN for continuous or mass campaign distribution. PMI continues to work with WHO and Global Fund to review existing evidence on insecticide resistance to develop normative guidance on better targeting of these specific nets. PMI will provide further guidance to countries on PBO nets based on the WHO Expert Review Group's recommendation (which is expected to be released in early 2016).

Introduction

Insecticide treated mosquito nets are a highly effective means of preventing infection and reducing malaria transmission. In populations with bednets, ITNs have been shown to reduce all-cause child mortality by about 20%, decrease clinical cases of malaria by about 50%, and severe malaria by 45%.[26] These results were reported in five large trials, one using insecticide-treated screening[27] material and four using ITNs.[28,29,30,31] ITN coverage in these studies was maintained

[26] Lengler C. Insecticide-treated bed nets and curtains for prevention malaria. Cochrane Database of Systematic Reviews, 2004 (2). http://www.thecochranelibrary.com/userfiles/ccoch/file/CD000363.pdf.
[27] Habluetzel A, Diallo DA, Esposito F, Lamizana L, Pagnoni F, Lengeler C, et al. Do insecticide-impregnated curtains reduce allcause child mortality in Burkina Faso?. *Tropical Medicine and International Health* 1997;**2**(9):855–62.
[28] D'Alessandro U, Olaleye B, McGuire W, Langerock P, Bennett S, Aikins MK, et al. Mortality and morbidity from malaria in Gambian children after introduction of an impregnated bednet programme. *Lancet* 1995;**345**(8948):479–83.
[29] Binka FN, Kubaje A, Adjuik M,Williams LA, Lengeler C, Maude GH, et al. Impact of permethrin impregnated bednets on child mortality in Kassena-Nankana district, Ghana: a randomized controlled trial. *Tropical Medicine & International Health* 1996;**1**(2):147–54.
[30]Nevill CG, Some ES, Mung'ala VO, Mutemi W, New L, Marsh K, et al.Insecticide-treated bednets reduce mortality and severe morbidity from malaria among children on the Kenyan coast. *Tropical Medicine & International Health* 1996;**1**(2):139–46.

at levels of 80% or more of sleeping spaces and use among children was typically above 60%. Another study, focused on malaria in pregnancy, reported that ITNs were associated with a 38% reduction in the incidence of malaria parasitemia, a 47% reduction in the incidence of severe malaria anemia, and a reduction in the prevalence of low birth weight by 28% in gravidae 1–4. [32]

In 2005, Roll Back Malaria (RBM) set a target of 80% for protection of all people at risk of malaria using ITNs, IRS, and other environmental and biological measures. PMI's strategic plan calls for 85% coverage of key malaria interventions. In addition to reducing human-vector contact at the individual level (via repellency of insecticide and physical barrier of net), ITNs also kill mosquitoes or, among those surviving immediate death, reduce longevity and prevent transmission. This overall reduction in transmission provides a "community effect" by which even those residents not sleeping under a net have increased protection from malaria infection. The "threshold" coverage whereby ITNs provide a mass, community effect depends on the ecological context. For programmatic reasons, PMI aims for the target of 85%, which is in line with the 80-85% target range set by RBM and the Millennium Development Goals (MDGs). However, in certain ecological situations (e.g., where vectors prefer to feed on humans indoors, and there are few alternate hosts available), modeling indicates that the "threshold" for the community effect may be as low as 35-65% of nightly ITN use by adults and children in the community.[33]

The first ITNs were treated after net fabrication by dipping in pyrethroid insecticide and required periodic retreatment to maintain the protective efficacy of the insecticide. Long-lasting ITNs, which do not require insecticide retreatments, are now the only type of net supported by PMI.[34] PMI does not support retreatment for conventional or untreated nets in Africa. In addition, PMI is procuring long-lasting insecticide-treated hammocks for distribution in the Mekong region to reach and protect migrant mobile populations.

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[31] Phillips-Howard PA, Nahlen BL, Kolczak MS, Hightower AW, ter Kuile FO, Alaii JA, et al. Efficacy of permethrin-treated bed nets in the prevention of mortality in young children in an area of high perennial malaria transmission in western Kenya. *American Journal* of Tropical Medicine and Hygiene 2003;68 Suppl(4):23–9.

[32] ter Kuile FO, Terlouw DJ, Phillips-Howard PA, et al., Reduction of malaria during pregnancy by permethrin-treated bed nets in an area of intense perennial malaria transmission in western Kenya.Am J Trop Med Hyg. 2003 Apr;68(4 Suppl):50-60.

[33] Killeen GF, Smith TA, Ferguson HM, et al. Preventing childhood malaria in Africa by protecting adults from mosquitoes with insecticide-treated net. PloS Medicine (2007) accessed at: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0040229

[34] For a complete list of the LLIN products that have current interim or full WHOPES recommendations, see: http://www.who.int/whopes/Long_lasting_insecticidal_nets_06_Feb_2014.pdf.

ITN Coverage Goal: Universal Coverage of ITNs

When PMI was launched in 2005, most malaria programs and donors targeted ITNs to the most vulnerable groups: pregnant women and children under five years of age. Based on the 2007 WHO position paper on ITNs, PMI's current goal is to help countries reach and maintain universal coverage of long-lasting ITNs for all individuals living in malaria endemic areas, with a specific target that at least 90% of households with a pregnant woman and/or children under five years of age own at least one ITN**.** Universal coverage is operationally defined as one ITN for every two individuals, based on evidence from across sub-Saharan Africa that, on average, two individuals occupy each sleeping space.[35]

In countries where insufficient ITNs and donor support to reach and maintain universal coverage exists, PMI should, at minimum, ensure that routine distribution to children under five years of age and pregnant women remains functional on an ongoing basis.[36] The goal is to ensure that ITN distribution to these biologically vulnerable populations continues uninterrupted while the constraints to achieving universal coverage are addressed. Because of universal coverage goals, most countries no longer conduct mass distribution campaigns targeting these vulnerable groups alone. While the methods vary by country, ITNs for these target groups are generally distributed through antenatal care clinics to pregnant women and through immunization clinics to children under the age of one. This method of continuous distribution is ongoing, and occurs as the targeted cohort interacts with the health system. Though this facility-based distribution is key to ensuring the most vulnerable have access to ITNs, these two channels alone are insufficient to reach or maintain the national universal coverage goals that all PMI-supported African countries have adopted.

Quantification for universal coverage, which relies on some form of delivery based on households, has evolved in recent years. To take into account rounding up of net numbers in households with an odd number of inhabitants (e.g., a household with five inhabitants receives three not two ITNs), WHO now recommends calculating the total amount of ITNs needed for a mass campaign distribution by dividing the total target population by 1.8. This macro-quantification calculation will estimate the minimum number of ITNs needed to provide an ITN-to-person ratio of 1:2.

[35] http://www.who.int/malaria/publications/atoz/itnspospaperfinal.pdf
[36] http://www.who.int/malaria/publications/atoz/who_recommendations_universal_coverage_llins.pdf

ITN Ownership: Key Distribution Channels

Mass distribution campaigns to achieve universal coverage

To rapidly and equitably achieve universal coverage, PMI and many other donors support free-standing, mass distribution campaigns designed to reach every household in malarious areas. These campaigns have proven to be highly successful and have been associated temporally with a drop in child mortality in a number of PMI-supported countries. Mass distribution campaigns are only cost effective when a majority of ITNs need to be replaced; thus, it is currently recommended that campaigns are conducted every three years, based on projections of ITN longevity.

As countries plan for their next mass campaign, they have sought guidance from WHO on how to account for current (existing) net ownership at the household level when preparing the quantification for the next mass distribution campaign. Experience shows that "top up campaigns" are logistically challenging, costly, time-consuming and invariably inaccurate in practice, especially when net access is low. Therefore, WHO/Global Malaria Program recommends that countries do not plan for periodic "top-up campaigns" until a country establishes a robust continuous distribution system where 40% or more of the target population have long-lasting ITNs that are less than two years old.[37] PMI does not allow PMI resources to support top-up campaigns at the present time.

Further information on mass campaigns, including a comprehensive toolkit are available through the Alliance for Malaria Prevention (AMP) website at: http://allianceformalariaprevention.com/amp-tools/amp-toolkit/.

Continuous distribution channels to maintain universal coverage

Following even highly effective mass campaigns, a supply of nets to the community is needed almost immediately to address: (a) those missed by the campaign; (b) new entries to the population by birth or immigration; and (c) the physical deterioration of existing nets. The maximum population reached for each of the continuous distribution approaches described below falls well short of maintaining ITN coverage at levels that will provide a community protection. Therefore, a mix of the following routine distribution approaches will be necessary to maintain a sufficiently high coverage over time. Not all channels are appropriate in all country contexts, and careful planning is needed to identify the optimal combination of continuous channels that will be most effective. Country teams interested in accelerating or exploring the potential for any continuous distribution approaches adapted to specific contexts can contact the PMI Headquarters ITN Team for guidance.

[37] http://www.who.int/malaria/publications/atoz/who_recommendations_universal_coverage_llins.pdf

To help NMCPs and PMI teams determine the best mix of distribution channels, PMI funded the development of NetCALC, an Excel-based modeling tool that is designed to model several scenarios of continuous distribution approaches based on the countries existing ITN coverage data and situation. It also helps provide quantification of ITNs for each channel or approach. It is flexible and has several variables that work towards the best situation for a country to sustain high ITN coverage. Additional information, an on-line training module, and the model itself can all be accessed and downloaded at: http://www.k4health.org/toolkits/continuous-distribution-malaria/netcalc-tool-planning-cd.

The ITN continuous distribution eToolkit is a helpful resource for planners who need to review a variety of delivery options and needs for their setting. It can be accessed at the following website: https://www.k4health.org/toolkits/continuous-distribution-malaria. Along with documents to guide planning and implementation, the website also includes case studies of various delivery models in different settings, and access to many implementation materials used in these case studies.

Analysis is being conducted in 2015 and 2016, through the VectorWorks project, to analyze the relative cost of each channel so that in the near future countries can make fully informed decisions on the best combination of distribution channels.

Routine distribution of ITNs through public-sector[38] antenatal care (ANC) and expanded program on immunization (EPI) vaccination clinics

Routine distribution of ITNs through public-sector[39] ANC and EPI vaccination clinics has the advantage of targeting the most vulnerable groups in the population: pregnant women and children less than five years of age. There is some evidence that these channels also serve as an incentive and thereby increase clinic attendance. In most countries the nets are given free-of-charge, but may also be sold at highly subsidized prices.

Distribution through ANC and EPI at public health clinics will reach a maximum of only about 5% of households, if the annual national cohort of pregnant women attend ANCs and all children

[38] The range of facilities considered to be part of the public sector will differ by country, but includes government-managed facilities that provide public health services specifically for the general population, as well as public health organizations (typically non-government and faith-based) that provide public health services for the general population on behalf of the government. In some countries, partnerships with private sector facilities may also be considered part of the public health sector, if they provide specific services in accordance with public sector policies (e.g. malaria prevention and curative services for free) and on behalf of the government.

[39] The range of facilities considered to be part of the public sector will differ by country, but includes government-managed facilities that provide public health services specifically for the general population, as well as public health organizations (typically non-government and faith-based) that provide public health services for the general population on behalf of the government. In some countries, partnerships with private sector facilities may also be considered part of the public health sector, if they provide specific services in accordance with public sector policies (e.g. malaria prevention and curative services for free) and on behalf of the government.

attend EPI clinics and receive their scheduled vaccinations. Thus, routine distribution of ITNs through these two channels is not sufficient alone to maintain ownership levels achieved through mass distribution campaigns.

School-based distribution channels

Countries are increasingly considering schools as a channel for delivery of long-lasting ITNs, as this channel has the capacity to put large numbers of ITNs into communities throughout the country on an annual basis. Recently Ghana, Nigeria, Tanzania and Senegal have carried out school-based ITN deliveries at scale. Some smaller school-based distributions have also been conducted, for example in Mali and Kenya. School-based distribution should be considered a viable channel in certain circumstances (including high gross school attendance rate) to help countries maintain universal coverage. PMI-funded pilots in Ghana and Nigeria have shown that school-based distribution significantly increases household ownership of at least one ITN without oversupply. Specifically in Nigeria, adding schools to ongoing ANC distributions not only sustained but increased ITN ownership in the study area. School-based distributions have a high level of flexibility, by adding or subtracting classes, based on need.

New! Community-based distribution channels

Community-based distribution makes ITNs available on a continuous basis to community members who meet certain established criteria. Eligible people may approach community agents who distribute coupons that can be redeemed for an ITN at a nearby redemption point (e.g., health facility or other designated storage facility). This channel is most commonly used as a "pull" channel (i.e., a request by a household for a new ITN or additional nets initiates the process). As such, it can help expand the pull component of an overall ITN strategy, which often is largely made up of "push" models (such as ANC clinics) where distribution is driven by attendance of a specific service. This distribution channel may have a useful role to play as part of an overall strategy to maintain ITN coverage levels. Resources specific to this channel can be found at the ITN continuous distribution eToolkit (https://www.k4health.org/toolkits/continuous-distribution-malaria). Community-based distribution is appropriate only if it can increase coverage without too much overlap with other continuous distribution models. Where school-based distribution is already implemented, community-based distribution may not be needed and may be too much of an additional administrative and management burden.

Social marketing of ITNs

Social marketing of ITNs builds on a long history that has been used for the promotion and sale of oral rehydration salts, contraceptives, condoms, and other health commodities. This approach has the advantage that it responds to demand for the product; when the ITNs are generally subsidized, they reach a much larger population than full price nets in the commercial sector. Traditional social marketing programs:

- Usually involve development and promotion of a special brand, sold at a subsidized price
- Often require development and maintenance of a parallel system for distribution of the subsidized commodity to commercial outlets and other points of sale (e.g., health facilities)
- Share costs among the public sector, donors, and consumers, but are still dependent on public sector and/or donor financing
- Are more frequently focused on urban rather than rural settings and are limited to those who can afford a highly subsidized ITN, meaning equity is a concern
- May fill a partial need in a multi-pronged distribution strategy

Commercial sales of ITNs

Commercial sales of ITNs can contribute to the overall level of ITN coverage. This approach makes nets available to those who seek a greater choice in size, shape and color, and who can afford to pay the higher price. This method has a limited coverage (i.e., largely in urban areas), as full market prices are usually unaffordable to those at greatest risk in rural areas where vendor sites (kiosks, shops, pharmacies) and ability to pay tend to be more limited.

Other potential continuous approaches

Other potential continuous approaches may be needed to maintain high coverage and to keep ITNs in targeted communities. Possibilities being tested include:

- Child Health Days, and possibly other periodic health facility or community activities to inject nets into the community.
- A private-sector E-coupon program. PMI supported a pilot in Ghana in 2014 that the NMCP, with funding from DfID, is now taking to scale. The ITN subsidies (paid for by donors and participating private sector companies) are provided to designated target groups (e.g., employees) through SMS messages. E-coupons may support long-term sustainability of distribution by relying on efficient private-sector supply chains, managing multiple sources of funding, and providing reliable and real-time operational information.

Regardless of the channel(s) chosen, each has unique risks that can threaten its effectiveness. All channels require appropriate monitoring and supervision to ensure that the ITNs are responsibly distributed to the intended recipients or households and that abuse of the channels is prevented from happening or identified quickly if it does occur. Resources for organizing and designing continuous distribution efforts can be found under the Continuous Distribution Work Stream link at: http://www.rollbackmalaria.org/architecture/working-groups/vcwg.

Once continuous distribution channels are established, sub-national free distribution campaigns may still be needed periodically in areas where continuous distribution approaches fall short, when funding is limited, or other channels are not feasible.

ITN Use: Ensuring Correct and Consistent Use

New ITN indicators measure access to an ITN

In 2013, the RBM Monitoring and Evaluation Reference Group adopted four new indicators for ITN ownership and use to better reflect the universal coverage strategy. The following new indicators (the supplemental indicator is optional) will be included in all upcoming household surveys (MIS and DHS):[40]

- Proportion of households with at least one ITN for every two people
- Proportion of population with access to an ITN within their household
- Proportion of individuals who slept under an ITN the previous night
- Proportion of existing ITNs used the previous night (supplemental indicator)

These new indicators enable countries to measure the proportion of nets available in each household that are used the night before the survey, thus distinguishing non-use related to access to an ITN from that linked to behavior. The importance of these distinctions is highlighted by the Nigeria example discussed below.

Access to ITNs

The persistent and widespread gap between ownership and use has been a major concern in the malaria community for several years. However, studies as early as 2009[41] demonstrated that the greatest determinant of use of an ITN was ownership. More recent studies supported by PMI have refined that finding and more clearly demonstrated that the persistent and often large gap between ownership and use is frequently due to too few ITNs in the households rather than individual choice to not use an ITN.[42,43] A PMI-supported study, based on reanalysis of the 2010 Nigeria MIS data, revealed that the relatively large, national-level gap between ownership of at least one ITN (42%) and net use the previous night (24%)[44] masked very divergent regional characteristics. The study found distinct differences between the three Northern and the three

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[40] Seventeenth Meeting of the RBM Partnership Monitoring and Evaluation Reference Group (MERG) 15-17th June 2011; http://www.rbm.who.int/partnership/wg/wg_monitoring/docs/17merg_meeting_report.pdf
[41] Assessment of insecticide-treated bednet use among children and pregnant women across 15 countries using standardized national surveys. Eisele TP, et al., 2009. Am Journal Trop Med Hyg, 80:209-214
[42] Universal coverage with insecticide-treated nets-applying the revised indicators for ownership and use to the Nigeria 2010 malaria indicator survey data. 2013. Kilian A, et al., Malaria Jour, 12:314.
[43] Recalculating the net use gap: a multi-country comparison of ITN use versus ITN access. 2014. Koenker,H and Kilian, A, PLoS ONE, 21;9(5):e97496.
[44] Nigeria Malaria Indicator Survey 2010.

Southern geopolitical zones.[45] A key difference was that among people with access to a net within their household, net use was 89% in the North versus only 64% in the South. This clearly shows that for the Northern zone, low availability of nets may largely explain the significant use gap, and that use will improve with an increase in ITN availability. In the Southern zone, on the other hand, a significant gap between net access and use may indicate that a sizable proportion of the population do not use ITNs even when they are available. In this case, promoting behavior change along with increasing ITN availability may help improve net use rates.

Social and behavior change communication for increased net usage and systems for sustained availability of ITNs after campaigns are critical. Studies confirm that communication programs are effective at increasing use of ITNs among targeted populations. The *Malaria BCC Indicator Reference Guide*[46] is a resource to strengthen the evaluation of the effectiveness of malaria SBCC interventions and to measure levels of behavior change for malaria prevention and case management at the country level.

Hang up campaigns

Many PMI-supported countries have supported net hang-up campaigns in the aftermath of mass distribution campaigns to promote correct and consistent use of ITNs, where volunteers go to each house and help to physically hang up all of the campaign nets (sometimes also supplying nails and string). Costs can range from $1 to $1.50 per net hung. To validate PMI's investment in this activity, PMI conducted a study in Uganda to understand the effectiveness of post-campaign, door-to-door hang-up and communication interventions to increase long-lasting insecticide-treated bed net utilization.[47] The results showed no statistical effect of either the routine post campaign visit or the intensive three-month visit or an additional visit at six months in the study setting. While the generalization of these results is limited to areas of similar contexts, the findings were similar to other study results in African settings. Therefore, PMI does not routinely prioritize support for hang-up activities, and will only support such activities as part of mass campaigns on an exceptional basis with strong justification. Community-wide SBCC efforts to promote correct and consistent use of ITNs should be prioritized over any type of door-to-door campaign to educate the population on these issues.

[45] Universal coverage with insecticide-treated nets-applying the revised indicators for ownership and use to the Nigeria 2010 malaria indicator survey data. 2013. Kilian A, et al., Malaria Jour, 12:314.
[46] http://www.rbm.who.int/partnership/wg/wg_communication/docs/Malaria-BCC-Indicators-Reference-Guide.pdf
[47] As of March 17, 2014, the paper with final results is in pre-publication status

WHOPES-Recommended Long-Lasting ITNs (LLINs)

In its most recent report, November 2015, WHO has provided interim or full (phase 3) recommendation for 15 long-lasting ITN products:[48]

- A to Z Textiles' *MiraNet*®
- BASF's *Interceptor*®
- Bayer's *LifeNet*®
- Fujian Yamei Industry's *Yahe* ®
- Life Ideas Textiles' *Panda Net 2.0*®
- Shobika's *Duranet*®
- Sumitomo's *Olyset Net*® and *Olyset Plus*®
- Tana Netting's *Dawaplus* 2.0®
- Vestegaard Frandsen's *PermaNet*®2.0 and *PermaNet*®*3.0*
- *Mainpol GmbH's *SafeNet*®
- *V.K.A. Polymers' *MAGnet* ™
- *Disease Control Technology's *Royal Sentry*®
- *Yorkool's *Yorkool*® *LN*

(*) Denotes a comparator ITN product not procured by PMI (see below)

While these products employ different technical processes for polyester, polyethylene, and polypropylene materials, each has been certified by WHO as being capable of maintaining the full protective effects of an insecticide treated net through a minimum of 20 washes, as described in the WHOPES protocol (http://www.who.int/whopes/guidelines/en/). In line with the 2007 WHO position statement,[49] PMI only supports the purchase of WHOPES-recommended ITNs.

PMI Policy on WHOPES Equivalency Policy

The WHOPES follows an equivalency process that allows new long-lasting ITN products to receive WHOPES recommendation status (interim or full) based on their chemical equivalency to the innovator net product. These "comparator" products are granted WHOPES interim or full recommendation status based only on results from WHOPES Phase 1 testing. In contrast, to achieve interim recommendation status, an innovator long-lasting ITN must have passed both Phases 1 and 2 testing, and to achieve full recommendation it must have passed Phases 1, 2 and 3 testing. There are four comparator long-lasting ITN products that currently have interim or full status based on their chemical equivalency to innovator products that hold those statuses. These comparator products are marked with an asterisk (*) in the list above. After a technical review, PMI has determined that the equivalency status based only on Phase 1 laboratory studies is

[48] http://www.who.int/whopes/Long-lasting_insecticidal_nets_November_2015.pdf?ua=1
[49] http://www.who.int/entity/malaria/publications/atoz/itnspospaperfinal.pdf

insufficient to determine eligibility for PMI procurement because these studies do not determine how the long-lasting ITN product functions in the field where other factors come into play, particularly physical durability and long-term bio-efficacy. **PMI policy does not currently allow for procurement of the comparator nets unless Phase 2 testing has been completed**. (For a full discussion of the policy please see: http://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/itn_procurement_specifications.pdf?sfvrsn=4.)

Cost of ITNs

Cost assumptions for FY 2017 ITN procurements are provided in the **Commodity Procurement and Supply Chain** chapter **(Appendix 1)**. In addition to the cost of the net itself and related procurement costs (freight, insurance, quality assurance, etc.), there are additional costs related to the type of distribution channel used. For mass distribution campaigns, it is also important to budget for specific logistical support to transport the ITNs to the district level and from the district level to the distribution points, conduct post-campaign support activities, targeted SBCC efforts, household registrations, etc. The distribution costs for ITN mass campaigns in five sub-Saharan African countries ranged from $0.38 to $1.83 (median $1.34) per net,[50] but the lowest costs were for integrated campaigns where logistics costs were shared with other interventions. Based on these results, a better estimate of the distribution costs for a free-standing ITN mass campaign is about $1.60. For continuous distribution efforts, countries should budget adequate funds to support logistics of distributing the nets to the districts and points of service on an ongoing/periodic basis, appropriate communication efforts, and appropriate supervision and monitoring efforts. The costs for delivery of ITNs provided free of charge through antenatal clinics in four countries ranged from $1.61 to $2.35 (median about $2.10) per net.[51] In coordination with the NMCP and partners, MOP planning teams should budget for all appropriate costs associated with campaigns and continuous distribution when planning for PMI net procurement(s).

Care of ITNs

Endemic countries and international partners are looking for ways to maintain the average expected life of ITNs, which could result in large savings over time. One possible way to extend the life of ITNs is to improve the household's level of care of ITNs. PMI-funded operational research to understand the knowledge, attitudes, beliefs, and practices that motivate or impede net care and repair behaviors and to use these findings to test the effectiveness of a behavior

[50] Eisele TP, Larsen DA, Walker N, et al. Estimates of child deaths prevented from malaria prevention scale-up in Africa 2001-2010, *Malaria J*, 2012, 11: 93 Additional File 5 accessed at: http://www.malariajournal.com/content/11/1/93
[51] ibid

change communication intervention. Results from the Nigeria[52] and Uganda[53] studies found that exposure to multiple channels of a comprehensive SBCC intervention was associated with improved attitude scores, and with improved net condition at endline. The studies found that while physical repairs themselves were not sufficient to improve net condition, repair attitudes were a critical component of the attitudes that positively affected net condition. Based on these results, PMI will not support stand-alone repair activities (e.g., distribution of ITN repair kits, social mobilization promoting ITN repair efforts, etc.).

PMI will support SBCC activities focused on comprehensive ITN care messages, with primary emphasis on promoting preventive behaviors that protect the net from damage, such as folding or tying the net up every day, keeping children away from the net, avoiding storing food or crops in the same room, and storing the net safely when not in use. A comprehensive promotion of ITN care can include messaging to promote repair of ITNs as a remedial action when holes do appear; however, these messages should remain secondary and serve the larger effort to improve overall care of ITNs at the household level and delay the development of holes for as long as possible.

Reinforcing ITN care behavior should not be a separate activity, as it is easily integrated into existing malaria-related SBCC efforts. The primary messages ("be careful" and "tie it up") can be included simply by adding a radio spot, updating content within job aids, and including the messages during trainings with community health workers already working on malaria. Messages should be included at the time of ITN distribution and communicated continuously to net users. The cost of integrating care messages into larger malaria communication efforts is minimal: these are simple, inexpensive, and feasible actions that can be added into existing platforms and do not require new, stand-alone communication efforts. These studies have shown that they are very likely to result in longer life of nets and better protection of families.

Implication of Pyrethroid Resistance for ITNs

Pyrethroid resistance is a serious threat to ITNs, as no other class of insecticides is currently recommended for use on nets, although a number of products with different active ingredients are currently in the development pipeline. Despite widespread resistance to pyrethroids, there is little epidemiological evidence to date that the public health effectiveness of long-lasting ITNs has been compromised.[54] Nevertheless, PMI is concerned that it is only a matter of time before

[52] Koenker H, Kilian A, Hunter G. Impact of a Behaviour Change Intervention on Long-Lasting Insecticidal Net Care and Repair Behaviour and Net Condition in Nasarawa State, Nigeria. *Malaria J,* 2015, 14:18. Accessed at: http://www.malariajournal.com/content/14/1/18

[53] Helinski M, Namaral G, Koenker H, et al. Impact of a Behaviour Change Communication Programme on Net Durability in Eastern Uganda, *Malaria J*, 2015, 14:366. Accessed at: http://www.malariajournal.com/content/14/1/366

[54] Lindblade K, Mwandama D, Mzilahowa T, et al. A cohort study of the effectiveness of insecticide-treated bed nets to prevent malaria in an area of moderate pyrethroid resistance, Malawi. *Malaria J* 2015, 14:31. http://www.malariajournal.com/content/14/1/3

pyrethroid resistance begins to undermine the gains that have been made in reducing the burden of malaria. The only potential stop-gap solution currently available is to temporarily restore the efficacy of long-lasting ITNs through the use of a pyrethroid + PBO combination net. PBO is a 'synergist' that, despite having no insecticidal activity on its own, enhances the potency of certain insecticides. PBO inhibits the natural defense mechanisms of the insect, the most important being the mixed function oxidase system (MFOs), also known as cytochrome P450 mono-oxidases. The MFO system is the primary route of detoxification in insects, causing the oxidative breakdown of insecticides like pyrethroids. Most pyrethroid-resistant populations of mosquitoes have elevated levels of MFOs.

There are two long-lasting ITN products that may mitigate the impact of cytochrome P450-based metabolic pyrethroid resistance: PermaNet 3.0 and the Olyset Plus. Permanet 3.0 was recognized in 2014 by the Vector Control Advisory Group as a "first in class resistance targeting product".[55] This new class is defined as a "novel intervention or an adaptation of an existing product class that has an overall effect on vectorial capacity and reduces human infection or disease in areas where the local vectors have substantive pyrethroid resistance." These products were developed with a combination of pyrethroid plus PBO, designed to provide effective protection in areas whose vector populations are highly resistant to pyrethroids.

Currently, evidence is lacking on the effectiveness of these nets against pyrethroid resistant mosquitoes under varying resistance intensities. Without this information, it is difficult to target these nets to areas where they would be most effective and to justify their higher cost compared to conventional long-lasting ITNs. Moreover, the performance of the PBO on these products in terms of effective life under field conditions and the effect of these nets on local resistance profiles is unknown.

PMI is currently funding studies to evaluate these products with results expected to be published in early 2016. Also, PMI is working with WHO and the Global Fund to review existing evidence on insecticide resistance to develop normative guidance on better targeting of these products. WHO convened an Expert Review Group in late 2015 to assess the evidence around PBO nets and provide a recommendation for normative guidance to WHO's Malaria Policy Advisory Committee by early 2016. PMI will provide further guidance to countries on PBO nets based on the Evidence Review Group's recommendation (which is expected to be released in early 2016). **At this time, without WHO normative guidance and outside the context of research studies, PMI will not procure these nets to replace standard long-lasting ITN orders for continuous or mass campaign distribution.**

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[55] Report of the Second Meeting of the VCAG, 27 Oct 2014.
http://apps.who.int/iris/bitstream/10665/137318/1/9789241508025_eng.pdf?ua=1

Because of the threat of insecticide resistance, monitoring of vector susceptibility and resistance intensity to various insecticides should be an essential part of every PMI country's vector control strategy. This information will be crucial to better targeting and evaluation of these products in the future. Guidance for entomological and insecticide resistance monitoring are detailed in the **Entomologic Monitoring and Insecticide Resistance** chapter.

Environment risks of ITN Disposal, Misuse, and Repurposing

Disposal

It is estimated that over 750 million ITNs were delivered to sub-Saharan Africa between 2004 and 2014. With an estimated life span of three years, the vast majority of nets delivered before 2012 have likely expired and are no longer viable. The potential environmental impact related to the disposal of these nets has been raised by WHO and other stakeholders in several forums.

In 2014, WHO released recommendations on ITN disposal, based on a three country pilot study. The report recommends:

- Residents should be advised to continue using nets until they have a new ITN to replace it.
- Residents should be advised not to dispose of ITNs in any water body, or use ITNs for fishing.
- NMCPs should only collect ITNs if the communities are covered, and if there is a suitable plan for safe disposal of the collected ITNs.
- Collecting old ITNs should not divert effort from core duties, including maintaining universal coverage.
- If ITNs and packaging are collected, the best option is high-temperature incineration, not burning in open air. If this is not possible, the next best option is burial, away from water sources.
- NMCPs should work with national environment authorities to take WHO recommendations into consideration when formulating local guidance.

The report found that recycling and incineration were not practical or cost-effective in most settings, confirming the results from PMI's experience in piloting a recycling effort in Madagascar in 2010.[56]

[56] In 2010, USAID sponsored a recycling pilot in Madagascar. This looked at several key factors including recovery, transporting, and parameters for converting expired ITNs into a viable alternative product. It was determined that the technology required for this process was not available in Madagascar, and that the cost to ship ITNs back to the US for processing was prohibitively high. Outside of this one recycling pilot, there is no evidence that large quantities of ITNs have ever been collected for disposal, nor has evidence been presented that there is a positive outcome in collecting ITNs for disposal. Most expired ITNs remain at the site and are either repurposed or disposed of at a

Burning is probably the greatest risk posed by uncontrolled disposal of ITNs; however, there are no reports from the field that this is a practice among those who have received ITNs. Ecological concerns have been raised about leaving ITNs with families at their sites, but there is no documented evidence of serious risks with this approach. PMI recommends countries monitor and report any disposal issues that arise, but maintains a "do no harm" approach in light of low risk and lack of appropriate alternatives.

Misuse

Misuse is defined as the use of a viable ITN for purposes other than its intended use as a bednet. Misuse of ITNs is not acceptable under any circumstances and not only defeats the public health purpose of providing protection from malaria, but can also have negative environmental outcomes. The most ecologically damaging misuse of ITNs is for fishing. Pyrethroids can kill fish, especially young fish, aquatic crustaceans, and insects when leached from a viable ITN being used for fishing. The fine mesh of treated or untreated mosquito nets may also cause ecological damage by physically removing many small aquatic animals from an area. This is less of an issue in larger bodies of water but can be a significant problem in small streams and ponds. There are no other known misuses of viable ITNs that pose serious environmental risks. Evidence in the literature indicates that in isolated cases, usually fishing communities, misuse of ITNs can be a problem and efforts should be made to address these situations. However, there is "very little evidence to support claims of widespread misuse across Africa."[57,58]

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household level. Please see: Nelson, Michelle, Ralph Rack, Chris Warren, Gilles Rebour, Zachary Clarke, and Avotiana Rakotomanga. 2011. *LLIN Recycling Pilot project, Report on Phase II in Madagascar.* Arlington, Va.: USAID | DELIVER PROJECT, Task Order 3. AND Nelson, Michelle, and Ralph Rack. 2012. *Madagascar: LLIN Recycling Pilot Project, Report on Phase* III. Arlington, Va.: USAID | DELIVER PROJECT, Task Order 7. Both reports can be downloaded at: http://deliver.jsi.com/dhome/search?p_search_tok=madagascar+recycling&btnG=search

[57] Eisele TP, Thwing J, Keating J. Claims about the Misuse of Insecticide-Treated Mosquito Nets: Are These Evidenced Based? 2011, Plos Med 8(4): E1001019.DOI:10.1371/journal.pmed.1001019

[58] Koenker, H, et al, "What happens to lost nets: a multi-country analysis of reasons for LLIN attrition using 14 household surveys in four countries" 2014, Malaria Journal 13(464) DOI: 10.1186/1475-2875-13-464

Repurposing

Repurposing is defined as the use of expired, non-viable ITNs for purposes other than as a bednet. Because expired ITNs likely have minimal ability to protect against malaria, repurposing is generally not an environmental hazard. There are numerous anecdotal reports on innovative and acceptable uses for expired ITNs. There is only one alternative use that is never acceptable and that is for fishing. Although old nets likely have lower doses of insecticide, it is still recommended that care be taken in repurposing of nets. Old nets should not be used around food storage or in ways that would result in excessive contact with human skin such as bridal veils or for swaddling young infants.

Frequently Asked Questions for ITNs

Q1. What is the difference between conventional ITNs and LLINs?

A. Early versions of insecticide-treated nets – conventional ITNs – were dipped post-production (by the end-user) in a pyrethroid insecticide mixture containing ligands to bind the insecticide to the polyester netting. This process produced nets with an effective life of only about three washes, with reapplication (re-dipping) recommended every six months. With LLINs, pyrethroid insecticides are applied during the manufacturing process, either incorporated into the fibers (polyethylene and polypropylene) or coated on the fibers (polyester). To receive WHOPES recommendation, long-lasting ITNs, must maintain full protective insecticide levels for a minimum of 20 washes. Given the durability of the netting material under field conditions, LLINs are expected to provide up to three years of protection before needing to be replaced. However, field experience has shown that more often netting material deteriorates before the insecticide in the materials falls below minimum protective levels, and that the average lifetime of LLINs may be considerably less than three years. Washing more frequently than is recommended by WHOPES may cause a more rapid loss of insecticide efficacy. Long-lasting ITNs are now the only type of net supported by PMI, and in this guidance document ”ITNs” and “LLINs” are used interchangeable unless noted.

Q2. What is an ITN community effect?

A. Where ITN coverage and use at a community level is sufficiently high, the overall malaria transmission intensity in the community is reduced, resulting in protection for even those not using nets, referred to as a “community effect”. While ITNs offer a degree of personal protection to those sleeping under the net, when ITN coverage rates reach a tipping point in a community, even those residents not sleeping under a net have increased protection from malaria infection. The “community effect” is the result of a reduction in malaria transmission due to reduced

mosquito longevity and the overall mosquito population due to exposure to pyrethroids in ITNs.[59]

The PMI goal for coverage is 85%, but in certain ecological situations (e.g., where vectors prefer to feed indoors on humans and there are few alternate hosts available), modeling indicates that the "threshold" for the community effect may be 35-65% of nightly ITN use by adults and children in the community.[60]

Q3. What are the side effects of insecticides used on ITNs?

A. Pyrethroids are the only insecticides that can be used on mosquito nets due to their extremely low human toxicity (i.e., they are safe enough that a baby sucking on a net would not be harmed). The 'alpha-cyano' pyrethroids, such as deltamethrin, alphacypermethrin, and lambda-cyhalothrin can cause some irritancy on the skin or mucosal membranes when nets are first removed from their protective packaging. Workers assisting with mass campaigns who open and distribute many nets in a short timeframe report skin, eye, and nose irritation. Although this is temporary, they should not continue working directly with the ITNs. Countries may also choose to advise recipients of new ITNs to let the net air out for a day before using. Permethrin does not have the problem of potential irritancy and is therefore the active ingredient in shampoos marketed for lice and flea control, and the pyrethroid used for treating clothes, blankets etc.

Q4. Should people living with HIV/AIDS be targeted for long-lasting ITNs?

A. Yes. Among the major conclusions of a technical consultation on the interactions and implications on malaria and HIV/AIDS, convened by WHO in 2004, are that pregnant women infected with both HIV/AIDS and malaria are at very high risk of anemia and malarial infection of the placenta, and among adult men and non-pregnant women, HIV/AIDS may moderately increase the risk of malaria illness, especially in those with advanced immunosuppression. On the basis of these conclusions, the RBM Partnership recommended that in areas of malaria transmission, people living with HIV/AIDS should be protected by ITNs and HIV-positive pregnant women at risk of malaria should always be protected by ITNs. Some very successful programs have incorporated ITNs into the HIV/AIDS home-based care programs, whereby the home-based care staff or volunteers deliver the ITN and can provide regular follow-up during their subsequent routine visits.

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[59] Hawley WA, Phillips-Howard PA, ter Kuile FO, et al.Community-wide effects of permethrin-treated bed nets on child mortality and malaria morbidity in western Kenya. Am J Trop Med Hyg. 2003 Apr;68(4 Suppl):168-73.
[60] Killeen GF, Smith TA, Ferguson HM, et al. Preventing childhood malaria in Africa by protecting adults from mosquitoes with insecticide-treated net. PloS Medicine (2007) accessed at: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0040229

Q5. What are the environmental procedures and assessments that need to take place in order for ITNs to be procured and distributed with PMI support?

A. Insecticides used in ITN products have been thoroughly evaluated in the *2012 Integrated Vector Management Programs for Malaria Vector Control: Programmatic Environmental Assessment* (PEA). The PEA found that the use of ITNs and long-lasting ITNs remain a valid intervention or malaria vector control. ITNs show a low risk for negatively impacting human and environmental health. The PEA recommends the use of appropriate best management practices to avoid potential human contamination, that monitoring be conducted to identify how the nets are being used, and to include educational programs on appropriate use during distribution efforts. A revised PEA will be released in 2016. The current, full PEA can be downloaded at: http://www.pmi.gov/docs/default-source/default-document-library/implementing-partner-reports/integrated-vector-management-programs-for-malaria-vector-control-programmatic-environmental-assessment---volume-1-of-2-main-document.pdf?sfvrsn=4.

Q6. Can PMI support ITN distribution in emergencies and other special circumstances?

A. Perhaps. From time to time PMI teams may be approached to support procuring ITNs for separate, targeted distribution rather than as part of universal coverage campaigns or routine distributions as programmed in the MOPs, or that are scheduled in national ITN strategic plans. Examples include distribution to refugees, the military, communities affected by outbreaks such as Ebola, and other special populations. In addition, NMCPs and partners may express interest in geographically-focused campaigns that integrate ITN distribution with those of vaccinations and other services. All have substantial logistical, funding, policy and strategic implications that could impact – positively or adversely – attaining both NMCP and PMI objectives. The PMI Headquarters ITN Team is available to advise on these and other special circumstances that may arise.

Durability Monitoring

Introduction

LLIN monitoring aims to provide programs with information needed to optimize their procurement, delivery and effectiveness. Monitoring allows programs to identify products that perform below expectations; it also provides useful feedback to manufacturers in their efforts to improve their products. While a rule of thumb that nets should be replaced every three years is commonly followed, field studies have shown that the durability of LLINs varies within and among countries, and that the durability of different types of nets may also vary. This variation is attributed to various behavioral, mechanical, and chemical elements so country-specific information is thus useful for guiding procurement and programmatic decisions made by NMCPs and PMI.

Similar to monitoring of drug efficacy and insecticide sensitivity, LLIN monitoring must compromise between cost and optimal sampling. The diversity of LLIN types, environmental circumstances, and cultural practices make exhaustive sampling impractical; however, it is possible and cost-effective to obtain representative data on the major types of LLINs distributed. This document provides guidance on how monitoring can be done. It also aims to provide a framework to decide whether monitoring should be carried out and under what circumstances it might be terminated. Programmatic context drives the decision making process; it does not matter whether PMI, the Global Fund, or other funds have been used to purchase the nets.

LLIN monitoring measures the effect of normal daily use on four outcomes: (1) **attrition** (survivorship), as measured by the loss of nets from households; (2) **physical durability**, as measured by the number and size of holes in the net; (3) **insecticide effectiveness**, as measured directly but imprecisely by bioassay; and (4) **insecticide content analysis**, as measured accurately by chromatography. These are best monitored in a prospective design linked to a mass LLIN distribution campaign. In the following, we provide a decision matrix for deciding whether to carry out LLIN monitoring and provide guidance for sample sizes for each outcome.

Should LLIN monitoring be carried out?

Factors affecting whether LLIN monitoring might be undertaken include:

1. **Stage of malaria control**. LLIN monitoring is most valuable for countries whose programs are in control phase and distribute large of numbers of LLINs. It is less useful for a program in pre-elimination or elimination phase which distributes fewer numbers of LLINs.

2. **Size and diversity of the country**. The larger the country and the more diverse it is culturally and environmentally, the more useful LLIN monitoring is likely to be. A small country with limited diversity might carry out monitoring in one site, while a larger country with greater environmental or cultural diversity might monitor LLINs at two sites. Monitoring at more than two sites is not recommended.

3. **Numbers of types of LLINs distributed**. Programs that rely heavily on one brand or type of LLIN might carry out durability monitoring on that brand only, while a country distributing large numbers of several types of nets might wish to carry out durability monitoring on the two major types of nets used. Monitoring more than two net types concurrently is not recommended.

4. **Availability of data**. Countries with data available on the durability of specific brands of nets distributed in the country do not need to carry out further monitoring on those

brands. Countries with no data should consider carrying out LLIN monitoring. Programs that distribute nets that have not previously been subjected to routine monitoring in other countries should also be given priority. This is particularly true for nets that are recommended under a WHOPES extension of specifications[61] as these nets have not undergone the extensive Phase 2 and 3 testing to which other nets have been subjected; it is also true for next generation nets for which no durability data yet exist.

5. **Programmatic context**. Programs have multiple priorities. It is possible that other priorities such as diagnosis, treatment, or surveillance might take precedence, depending upon country context. Initiation of a mass LLIN distribution campaign is, in contrast, an opportunity to begin prospective monitoring should other factors support this.

Clearly, the above factors are best weighed by PMI country teams in consultation with NMCPs, with a view towards extracting maximally useful data with the least expenditure. Some extreme cases have clear outcomes. A small country with existing data on the type or types of LLIN to be distributed in the future can discontinue monitoring. A country that is distributing small numbers of LLINs in the context of malaria elimination has no urgent need to carry out LLIN monitoring, even if data on LLIN durability are unavailable. In contrast, a large country distributing large numbers of several types of LLINs with no country-specific data should make LLIN monitoring a priority. A country introducing a new type of LLIN into its program should also begin monitoring its durability. Most countries will fall between these extremes and should exercise judgement in deciding upon whether or not to initiate monitoring.

If LLIN monitoring is done, which outcomes should be measured and with what sample size?

LLIN durability monitoring consists of four outcomes: attrition, physical integrity, insecticidal activity and insecticide content. Depending upon the country context, it may be necessary to limit which outcomes are measured. At a minimum, all countries should have the capacity to measure attrition and physical integrity. These outcomes do not require any special equipment or expertise. Further, recent evaluations suggest that these factors may be the most important limiting factor in LLIN durability. Attrition and physical durability can be reasonably measured in a sample of 250 marked nets followed longitudinally and examined yearly for three years. With this sample size, using 15 clusters of 10 households each, countries will be able to detect approximately 20% variation in performance among products over a three year period, equivalent to approximately plus/minus 6-7 months of median net lifespan.

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[61] As of July 2015, this includes the following WHOPES recommended LLIN brands: Dawa Plus 2.0, MiraNet, Panda Net 2.0, Yahe. http://www.who.int/whopes/Long-lasting_insecticidal_nets_September_2015.pdf?ua=1 (last accessed Sept 30, 2015)

Insecticidal activity is measured by exposing LLINs to susceptible mosquitoes in WHO cones. Because the purpose of the activity is to measure insecticidal activity, any susceptible species of mosquito may be used for the bioassay. This activity requires specialized facilities and staff, in particular an insectary with a susceptible colony of mosquitoes and lab staff with the ability to consistently generate large numbers of mosquitoes of uniform quality required for bioassays. If an insectary is not available, net samples may be sent to an outside laboratory for analysis. Measurement of insecticidal activity should be done in a separate cohort of nets, whereby 30 nets are taken from the field for laboratory testing each year for three years. The nets taken from the field will need to be replaced by new nets.

The measurement of insecticidal content is a supplementary tool for the monitoring of insecticidal activity that may be done on the same cohort of nets sampled for bioassays. Content testing should not be done independently of bioassays. Determination of insecticidal content can be used to confirm the bioassays and estimate insecticide retention rates across different settings and in different LLIN products. However, measurement of insecticidal content requires highly specialized capacity that is likely limited or absent in nearly all PMI-supported countries. Therefore, this must be done either at CDC or at a WHO collaborating center where the cost of analysis is approximately $150-$350 per sample. Furthermore, in some cases, there is a poor correlation between insecticidal content and insecticidal activity, particularly for some LLINs made of polyethylene with insecticide directly incorporated into the fiber. We do not generally recommend carrying out content testing for nets types which incorporate insecticide in solution in the net fiber.[62]

Measurement of insecticidal content is done by PMI at baseline for all PMI-procured LLINs. The Global Fund has put in a place an analogous program so there is no need for PMI to fund baseline measurement of insecticide content in Global Fund-procured nets. Insecticidal content testing may be done on samples of the same 30 nets taken from the field for bioassays. If bioassays are being performed, the marginal cost of performing insecticidal content analysis is determined by the cost of the laboratory analysis; for 30 samples this cost will range from $4,500–$10,500. Such analysis should be given priority where there are no existing data or where new compounds or new net technologies are in use. It may also be useful to carry out content testing on an ad hoc basis should bioassay data demonstrate a loss of effectiveness.

[62] As of September 2 2015, this includes the following WHOPES recommended LLIN brands: Duranet ®, LifeNet ®, MagNetTM, Olyset Net®, Olyset Plus®, Royal Sentry®, MiraNet®, Panda Net 2.0®. http://www.who.int/whopes/Long-lasting_insecticidal_nets_September_2015.pdf?ua=1 (last accessed Sept 30, 2015)

Interpretation and use of the results of LLIN monitoring

WHOPES has provided clear cut-off points for WHO cone tests. Nets are considered optimally effective if they cause >80% mortality or >95% knockdown in the WHO cone test while nets are considered minimally effective if they cause >50% mortality or >75% knockdown. If less than 80% of nets are minimally effective at any given time point, the LLIN product should be replaced.

Criteria for attrition and physical durability are less established but recent guidelines have been presented by the WHO Vector Control Advisory Group and the WHO Malaria Policy Advisory Committee. PMI recommends that nets be considered in need of replacement if they have at least $1000cm^2$ of damage (regardless of assumptions of shape of the hole). Population level survivorship curves can then be fitted to estimate an optimal replacement cycle.

Results of LLIN monitoring can be used:

- To determine the median LLIN life in a country and understand factors affecting attrition and LLIN performance
- To inform improved procurement practices to ensure that LLINs bought provide as optimal performance as can be expected
- To inform countries on how to develop their LLIN distribution strategies to ensure nets are available when needed, depending on median life
- To inform countries to develop effective SBCC messages on the care of LLINs
- To provide information to WHOPES and manufacturers on the durability of different LLINs under different conditions to improve products and their specifications

LLIN durability operational research

There may be occasions where PMI country teams seek additional data points to answer an expanded set of programmatic and/or operational questions related to the national LLIN program. Expanding beyond the parameters outlined in these guidelines will likely shift this investment from a standard monitoring activity to one more closely aligned with operational research. In those circumstances, these guidelines are no longer applicable and PMI country teams must develop and submit a concept note to the PMI Headquarters Operational Research Committee to explain, justify, and seek approval for the proposed operational research study.

Indoor Residual Spraying

New/Key Messages in the FY 2017 Technical Guidance

- PMI is participating in a UNITAID Next Generation Indoor Residual Spraying (NGenIRS) Project to subsidize the uptake of long-lasting, non-pyrethroid insecticides for IRS. Five countries will participate in Year 1, with additional countries added in subsequent years. Implementation guidance for participating countries is included below.

Introduction

Indoor residual spraying is the organized spraying of an insecticide on the inside walls of houses prior to peak malaria transmission. It is designed to interrupt malaria transmission by either killing adult female mosquitoes when they enter houses and rest on the walls after feeding or by repelling mosquitoes from entering houses. Indoor spraying has helped to greatly reduce or eliminate malaria from many areas of the world, particularly where the mosquito vectors feed and rest indoors and where malaria is seasonally transmitted. As a best practice, PMI recommends that IRS campaigns should occur just before the peak of the transmission season, in order to provide the highest impact.

Successful IRS depends on the use of an insecticide that kills the local malaria vector(s) and the quality of spraying of the IRS operation. Unfortunately, IRS successes are now being jeopardized by the spread and intensification of insecticide resistance. According to WHO, mosquito resistance to at least one class of insecticides has been reported from 64 countries with ongoing malaria transmission. PMI's own entomological data shows evidence of insecticide resistance to one or more classes of insecticides in all 19 PMI-supported countries in Africa. While the majority of PMI-supported countries relied on pyrethroids for IRS in the early years of PMI, because of documented pyrethroid resistance, only one out of twelve countries plans to use pyrethroids in 2015.

UNITAID IRS Project - NGenIRS

In an effort to mitigate insecticide resistance, PMI is partnering with the Innovative Vector Control Consortium, the Global Fund, Abt Associates, and PATH Malaria Control and Elimination Partnership in Africa, on the UNITAID-funded Next Generation Indoor Residual Spraying (NGenIRS) Project. The overall aim of NGenIRS is to accelerate and expand access to and adoption of new, third generation of IRS (3GIRS) formulations (long-lasting non-pyrethroid insecticide formulations) that overcome insecticide resistance and increase the effective lifetime

of IRS products (only one third generation IRS insecticide formulation is available presently – Syngenta's Actellic CS). UNITAID is supporting the NGenIRS Project because it is a market-shaping intervention that aims to grow and stabilize the market for 3GIRS. UNITAID will provide a 35% subsidy on long-lasting non-pyrethroids directly to the manufacturer, effectively decreasing the price of 3GIRS formulations. As more countries join the project, the increased market volume and stability will decrease the price of 3GIRS, so that the subsidy will no longer be needed. The creation of a larger, more stable market for 3GIRS will benefit all partners by increasing IRS coverage while providing incentives for manufacturers to develop new, long-lasting insecticides. The following elements are included:

- Leveraging co-funding to grow the marketplace and coverage 5-10 fold
- Strengthening, integrating, and supporting county capacity to forecast global demand
- Negotiating price reductions to reflect this larger, more stable and competitive market
- Increasing the numbers of suppliers and variety of products with different active ingredients
- Creating and disseminating the evidence base on impact and cost effectiveness

This Project, covering 2016-2019, begins with five countries in Year 1 (Mozambique, Mali, Ghana, Ethiopia, and Zambia), and will increase steadily to reach 16 countries by Year 4. Criteria for inclusion as a Year 1 country included:

- Low income countries with a high malaria disease burden
- Existing investment in IRS from a major donor and/or the NMCP
- Documented insecticide resistance to pyrethroids
- Willingness and capacity to register 3GIRS products in a timely fashion
- Coverage and willingness to deploy 3GIRS, however limited by budget/commodity costs
- M&E capability to gather evidence

Country selection is jointly made by project stakeholders, including country teams, NMCPs, and PMI Headquarters. The selection for Year 2 countries will take place in the spring of 2016.

Insecticide Selection

The choice of which insecticide class (or compound) to use in a particular setting should be made with expert consultation (PMI Headquarters IRS Team), implementing partners, and in-country technical working groups) during the planning period for spraying and **at least six months before the spray campaign** to allow adequate time for procurement, delivery and receipt of insecticide. PMI has specified the following factors that should be considered in the choice of insecticide class: vector resistance, duration of efficacy, risk to human health and environment

(i.e. livestock, agricultural trade, etc.), and cost. All decisions about the choice of insecticide should be done in consultation with the NMCP.

The four classes of insecticides currently recommended by WHO for IRS (**Figure 1**) are all neurotoxins that paralyze and subsequently kill the insect. The oldest of these, the organochlorine class to which DDT belongs, came into widespread use in the 1940s. The mode of action of the organochlorines, like that of the pyrethroid class developed in the 1970s and 80s, is on the insect neuron sodium channel, keeping it open and therefore preventing the nerve impulse to recharge. The two other classes, the carbamates and the organophosphates, inhibit acetylcholinesterase, an enzyme in insects and humans that terminates the action of the excitatory neurotransmitter (acetylcholine) at nerve synapses. Carbamates bind loosely and reversibly to acetylcholinesterase, whereas the organophosphates bind more strongly. A potential new class of public health pesticide, the pyrroles, is currently registered by the U.S. Environmental Protection Agency (U.S. EPA) for some indoor uses (e.g., commercial kitchens). Pyrroles act by disrupting mitochondrial ATP, leading to cellular death and eventual insect mortality. One member of this class, chlorfenapyr, is being evaluated by WHOPES for use on ITNs and as an IRS insecticide.

Figure 1. WHO Recommended Insecticides for Indoor Residual Spraying Against Malaria vectors

Insecticide compounds and formulations[1]	Class group[2]	Dosage (g a.i./m²)	Mode of action	Duration of effective action (months)
DDT WP	OC	1-2	contact	>6
Malathion WP	OP	2	contact	2–3
Fenitrothion WP	OP	2	contact & airborne	3–6
Pirimiphos-methyl WP, EC	OP	1-2	contact & airborne	2–3
Pirimiphos-methyl CS	OP	1	contact & airborne	4–6
Bendiocarb WP, WP-SB	C	0.1–0.4	contact & airborne	2–6
Propoxur WP	C	1–2	contact & airborne	3–6
Alpha-cypermethrin WP, SC	PY	0.02–0.03	contact	4–6
Alpha-cypermethrin WG-SB	PY	0.02–0.03	contact	up to 4
Bifenthrin WP	PY	0.025–0.05	contact	3–6
Cyfluthrin WP	PY	0.02–0.05	contact	3–6
Deltamethrin SC-PE	PY	0.02–0.025	contact	6
Deltamethrin WP, WG, WG-SB	PY	0.02–0.025	contact	3–6
Etofenprox WP	PY	0.1–0.3	contact	3–6
Lambda-cyhalothrin WP, CS	PY	0.02–0.03	contact	3–6

Chlorfenapyr 240 SC: The current assessments of Chlorfenapyr SC (class group: pyrrole) are available in the report of the 16th WHOPES Working Group meeting, 22–30 July 2013 and the report of the 17th WHOPES Working Group meeting, 15–19 September 2014 (both reports available at: http://who.int/whopes/resources/en/).

Note: WHO recommendations on the use of pesticides in public health are valid ONLY if linked to WHO specifications for their quality control. WHO specifications for public health pesticides are available on the WHO homepage on the Internet at http://www.who.int/whopes/quality/en/.

[1] CS = capsule suspension; EC = emulsifiable concentrate; SC = suspension concentrate; SC-PE = polymer enhanced suspension concentrate; WG = water dispersible granules; WG-SB = water dispersible granules in sealed water soluble bags; WP = wettable powder; WP-SB = wettable powder in sealed water soluble bags.

[2] OC = organochlorines; OP = organophosphates; C = carbamates; PY = pyrethroids.

The WHOPES-specified duration of effective action in the table above corresponds to results from WHOPES supported trials. However, PMI's operational experience has demonstrated effective action for the longer-lasting pyrethroids of 6-10 months and for the longer-lasting OP (pirimiphos-methyl CS) of at least 6 months on cement, mud, and wood surfaces. Likewise, operational experience to date with bendiocarb in most cases has not demonstrated effective action beyond 3-4 months, with residual activity of only 2-3 months on mud surfaces reported in five countries.

In addition, it should be noted that not all of the chemicals listed are currently being produced by WHO pre-qualified manufacturers. In fact, only one each of the carbamate and the organophosphate classes are produced by WHO pre-qualified manufacturers (bendiocarb and pirimiphos-methyl, respectfully). **PMI can only procure insecticides from WHO-pre-qualified manufacturers**.

Since questions remain regarding how successful insecticide rotations will be in slowing the selection of resistant vectors, countries that choose to conduct preemptive rotations should closely monitor and evaluate the effects of insecticide rotation on insecticide resistance profiles and implementation costs. Country teams should engage PMI Headquarters IRS Team if/when their country counterparts begin to consider pre-emptive rotation of insecticide in order to appropriately consider the need for monitoring and support.

Key Issues

The IRS technical guidance below is organized by key issues, and addresses how best to implement IRS in the most cost-effective manner in different epidemiological settings. These issues are intertwined and should be considered together. Additional technical and programmatic resources regarding IRS can be found on the PMI website. Another excellent source of information on IRS strategy, management, and operational issues such as the safe use of insecticides and spray application guidelines, is the recently published (June 2015) WHO *Manual on Indoor Residual Spraying* (http://www.who.int/malaria/publications/atoz/9789241508940/en/).

Key issue 1: IRS in various epidemiological settings

- Historically, PMI prioritized support for IRS in areas with seasonal malaria, but with longer lasting insecticides available, PMI also supports IRS in perennial transmission settings as a means to rapidly reduce malaria transmission.
- PMI does not support IRS as an epidemic prevention measure in areas that may experience a malaria outbreak, followed by long periods without transmission. PMI also does not support IRS as an epidemic response measure. In most cases the logistics and lead time for IRS is too long to allow for rapid response, and often epidemics are over before IRS can be implemented.
- PMI does not typically support IRS in urban settings. However, IRS may be justified once local transmission is confirmed with entomological data and if there are unique circumstances (e.g., delayed ITN distribution, sudden population shift, or hotspot identified) that can justify IRS, and if urban housing conditions allow for anticipated access with high levels of acceptance among urban community dwellers. The PMI Headquarters IRS Team must be consulted in advance of including urban settings within spray targets.

- When country teams are selecting new spray areas, for example because a decision has been made to expand or retarget the program, epidemiological data should be taken into consideration and the PMI Headquarters IRS Team should be consulted.

Key issue 2: Targeting IRS and blanket versus focal application of IRS

IRS programs should aim for 100% coverage of all eligible structures in the area to be sprayed, although WHO guidelines state that coverage above 80% is sufficient to produce a community effect. After an area is selected for spraying, there are two ways to implement IRS: blanket spraying and focal spraying. Whereas blanket spraying is defined as the spraying of all houses within a targeted area (e.g., entire provinces or districts), focal spraying is defined as the selection of discrete geographic areas within an area targeted for IRS activities, based on eco-epidemiologic parameters (e.g., communes). Focal IRS requires precise environmental, epidemiological, and entomological information on households within an area. The goal of focal IRS is to cover epidemiological "hotspots," which can be defined as a town, village, or geographic area that experiences regular increases in confirmed malaria cases or transmission activity in comparison to surrounding areas. This could be due to the proximity of mosquito breeding sites, variations in housing structure, particular resident behaviors, etc. Therefore, the scale of selection is much finer than that determined by an administrative or political boundary, while also being independent of such boundaries.

- IRS should be targeted based on malaria disease burden and/or community parasite prevalence, malaria seasonality/epidemiological setting, population density, vector behavior and resistance status, and the presence of other interventions, particularly ITNs. Stratification of the country can facilitate the decision-making process and assist countries in determining areas suitable for spraying.
- While focal IRS should theoretically decrease cost while maintaining impact, implementing it requires significantly more data collection, analysis, planning, and logistics than blanket spraying. Focal spraying would only be appropriate in countries where epidemiological data is sufficiently granular to accurately target sub-district areas for spraying. Inaccurate targeting of focal IRS can waste significant resources and leave high-transmission areas unprotected.
- If a country has already decided to re-evaluate the scope of its IRS program (i.e., shift from blanket spraying to focal spraying), care must be taken to ensure that newly targeted spray locations are selected in an evidence-based manner and that the localities targeted for IRS with focal spraying are large enough to achieve some level of public health impact. The PMI Headquarters IRS Team should be consulted to help with these decisions.
- In 2015, PMI began conducting operational research to assess the effectiveness and cost-implications of focal spraying. Once data are available, recommendations will be

provided to countries regarding focal spraying. In the meantime, countries that have not already initiated focal spraying should not plan to do so given the uncertainties.

Key issue 3: How long to spray and withdrawal of IRS

- IRS should only be implemented as part of a long-term vector control or malaria elimination strategy.
- When new spray areas are being considered, areas that require only one spray round per year to cover majority of the transmission season should be prioritized.
- When existing spray areas are being considered:
  - In many instances, twice-yearly spraying with a shorter-lasting insecticide may technically be the best option for IRS; however, given the cost increases associated with spraying twice per year, careful deliberations and consultation with the PMI Headquarters IRS Team are needed if countries propose to do so.
  - If the decision is made to change to more than one round of spraying per year, country teams should provide justification for why spraying twice a year is needed (e.g., provide evidence of length of the transmission season, document attempts to reach high coverage or use of ITNs in the IRS areas, and document anticipated efficacy of the insecticide of choice).
- If IRS is withdrawn, it should be in the context of a malaria elimination plan or as part of a malaria control program using a "knock-down/keep-down" strategy, ensuring universal ITN coverage. If countries are discussing withdrawal of IRS in an area, the PMI Headquarters Vector Monitoring and Control Team should be consulted.
- If IRS is the main form of vector control in an area, it should continue to be implemented even if transmission drops.

If IRS is to be withdrawn because of resource constraints or a shift in a country's IRS targeting strategy, countries should ensure clear SBCC messaging, high ITN coverage and use, strengthen malaria case detection and response systems, and closely monitor ACT and RDT stocks. It is prudent to expect and plan for an increase in malaria cases following the withdrawal of IRS. Additional commodities may be needed in the former IRS targeted areas, and entomological monitoring should be continued to monitor the impact of withdrawal on the vector population. The country team needs to consult with the PMI Headquarters IRS Team, and collaborate to submit adequate documentation to PMI leadership to justify the change in strategy. As with any change in strategic shift of PMI's support to country efforts, advance approval from PMI leadership, including the U.S. Global Malaria Coordinator, is needed.

Key issue 4: Costs of IRS implementation

According to the PMI AIRS Project cost analysis of IRS programs in 2014,[63] in the majority of PMI-supported countries insecticide costs average 30% of the IRS budget, ranging from 4% to 52%, depending on the insecticide class used. Note that shipping costs for organophosphates can be high (~$9/bottle) if using air shipment (as opposed to sea shipment), since the insecticide is liquid and shipped in large, heavy bottles. Although most of the costs for IRS currently fall under training, short-term labor, transportation, and warehousing, the transition away from pyrethroids and carbamates to longer lasting organophosphates will increase the insecticide proportion of total IRS costs.

- Currently there is not enough evidence to make statements about the relative cost-effectiveness of IRS versus LLINs, given the variations of costs between countries, differing efficacy periods, variation of the programmatic impact of resistance on the interventions, and LLIN durability.
- For FY 2017 MOP planning and beyond, PMI country teams, together with NMCPs, should consider IRS programs in the context of the current resource allocations for vector control interventions from all sources, given the malaria burden, insecticide resistance profile, and actual program expenditures in each country, and make changes in upcoming years where necessary.

Key Issue 5: Insecticide Resistance: Implications for IRS

- PMI must continue to support monitoring of insecticide resistance to inform the selection of insecticides for IRS. PMI supports NMCP efforts to compile national insecticide resistance profiles for this purpose. Please refer to the **Entomologic Monitoring and Insecticide Resistance** chapter for further details.
- Insecticide selections for PMI-supported IRS should continue to be informed by evidence/experience within each country, and if changes in insecticide class are made, the effect on mosquito densities and resistance should be monitored.

Key Issue 6: Monitoring and Evaluation of IRS

- All PMI-supported vector control programs should collect entomological data for data based decision-making, and for inclusion in the PMI/headquarters entomology database. See the **Entomologic Monitoring and Insecticide Resistance** chapter for suggested indicators.
- PMI country teams are encouraged to support routine epidemiologic monitoring, including some measure of disease burden, in areas with PMI-supported IRS activities as

[63] Accessible at http://www.pmi.gov/docs/default-source/default-document-library/implementing-partner-reports/africa-indoor-residual-spraying-project-pmi-irs-country-programs-2014-comparative-cost-analysis.pdf?sfvrsn=4.

a means of tracking malaria trends that will help guide policy decisions (e.g., scaling down, suspending spraying, or moving from blanket to targeted spraying).

- Given the logistic issues around conducting high-quality community parasitemia surveys, in most countries PMI recommends the use of existing routine health facility data for epidemiologic surveillance in IRS areas. The PMI Headquarters IRS and SM&E teams are collaborating to identify the best ways (and implementing partners) to collect epidemiological data in order to better inform each country's IRS decision-making. Please consult with these teams for specifics about your country situation.
- Questions about the timing of spraying, whether a single round of spraying per year is sufficient to cover the entire transmission season, and/or the need to change from one insecticide or formulation to another are probably best answered by a review of routine entomologic data from the area being sprayed.
- PMI supports the spraying of sleeping structures, and generally does not support IRS in non-sleeping spaces, such as latrines, fowl runs, grain storage or animal shelters. If a country's national policy is to spray non-sleeping spaces in their IRS program, and the country would like PMI to support this, sufficient entomological evidence, including molecular identification of malaria vectors in these non-sleeping structures, must be documented in order to justify the added cost of extending spraying to these additional structures with PMI resources. Please engage the PMI Headquarters Vector Monitoring and Control Team for further clarification.
- Countries that are confronted with potential IRS-related OR questions should engage the PMI Headquarters IRS and OR Teams to determine the best way forward.

Key issue 7: Capacity building for IRS implementation and evidence-based decision making

- The capacity for entomological and epidemiological monitoring should be established in PMI-supported countries to enable ongoing improvement in IRS targeting and implementation.
- PMI promotes the transfer of technical capacity to national governments so that they are able to assume greater responsibility for planning, implementing, and monitoring IRS activities.
- Providing direct funding to national governments to support IRS activities can be considered, provided the country has the appropriate technical capacity, environmental oversight, and the proper programmatic and fiduciary risk assessments are completed.

Frequently Asked Questions for IRS

Q1. What is PMI's role in ensuring the quality of insecticides used in IRS?

A. As noted earlier, PMI procures insecticides from manufacturers who are pre-qualified by WHOPES. Typically, insecticides will arrive in country with quality assurance documents from the manufacturer. However, to ensure due diligence, PMI requires IRS partners (central or bilateral) to conduct independent, pre-shipment quality control evaluations. (For countries under the central IRS mechanism, quality testing occurs as part of the procurement protocols.) In countries where PMI conducts IRS but the insecticide was not been procured by PMI, quality assurance testing must still be undertaken by PMI prior to use. Quality control testing of insecticide can be conducted at a number of qualified laboratories; please discuss with the PMI Headquarters IRS Technical Team for more information.

Q2. Is there any level of resistance that would cause us to stop IRS?

A. If resistance were detected to all available IRS insecticides, we would discontinue IRS. At present, there are only a few reports from West Africa where the vectors are resistant to all four classes of insecticide (but not necessarily all active ingredients in each class), and new classes of insecticide for IRS are currently undergoing WHOPES review. Therefore, we should choose an insecticide that works, not just for transmission reduction, but also as a strategy to help manage resistance, remembering that the ITNs themselves can be selecting for resistance.

Q3. Does PMI use DDT in its spray programs?

A. In select countries, PMI has supported IRS with DDT since 2006, but the emergence of high levels of DDT resistance has limited its use, and no PMI-supported IRS program has used DDT since 2012. Furthermore, there are issues regarding the supply of quality DDT. PMI will continue to support the use of DDT where there is an approved supplemental environmental assessment (SEA) in place and when appropriate given susceptibility profiles, ensuring always that appropriate safeguards are in place to prevent leakage into the agricultural sector and mechanisms for safe disposal of unused DDT and DDT-contaminated materials exist. **These additional safeguards are costly, and the supplemental environmental assessments for DDT should be initiated at least one year prior to use and require yearly revisions.** Any country using DDT for IRS should have signed and be in compliance with the Stockholm Convention for use of DDT, including the requirement of prior notification of intent to use.

Information on the Stockholm Convention can be found at: http://chm.pops.int/Home/tabid/2121/mctl/ViewDetails/EventModID/7595/EventID/447/xmid/7598/Default.aspx. For more information on the use of DDT in IRS programs, refer to the WHO

position statement revised in 2011, located at: http://www.who.int/malaria/publications/atoz/who_htm_gmp_2011/en/.

Q4. Who is responsible for monitoring human and environmental safety measures for IRS?

A. It is the shared responsibility of in-country PMI team members (particularly the Activity Manager of the IRS partner), the Mission Environmental Officer, and the IRS Contracting Officer's Representative (COR) team 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
- Strict insecticide sachet accounting methods are in place to prevent leakage
- IRS contractor(s) complete environmental compliance visits, and include findings in End of Spray Reports

A best management practices manual was developed in 2010 and revised in 2015 to assist PMI managers and IRS implementing partners in monitoring compliance efforts. The *PMI Best Management Practices for IRS* contains checklists for field evaluations and can be found at: http://pmi.gov/docs/default-source/default-document-library/tools-curricula/best-practices-indoor-residual-spraying-feb-2015.pdf?sfvrsn=4. In addition, PMI through the PMI AIRS project has developed several supervisory tools and checklists which are available at: http://www.africairs.net/wp-content/uploads/2012/08/AIRS-Supervisory-Toolkit.pdf.

Q5. How do I comply with USG Regulation 216 if asked to support non-PMI financed IRS operations?

A. USAID has historically interpreted "the procurement or use of pesticides" clause under Reg. 216 to mean both direct and indirect forms of support (e.g., disposal of pesticides, provision of fuel to transport pesticides, technical assistance to pesticide management, etc.). This clause is of particular importance for PMI because (1) as host-country capacity grows for IRS, PMI's role will likely shrink, and (2) as more countries prioritize IRS as a key component of malaria control, funds from other donors, the private sector, and NGOs will be used for IRS, and PMI may be called upon to play a more limited role, such as provision of technical assistance and supervision, etc.

In all cases, PMI-supported countries must document the specific actions a USAID Mission/PMI program is proposing to support in the form of a new SEA or an amendment to the existing SEA. The SEA or SEA amendment should be shared with the IRS COR team, Mission Environmental Officer, and Global Health Bureau Environmental Officer, who will collectively review and

provide required clearances. Because countries need to allow time for completion and approval of the more time-consuming SEAs, below are illustrative lists of actions that must be included in a SEA or SEA amendment:

- Procurement, transport, storage, loaning, direct application, or disposal of insecticide
- Loaning of spray pumps or IRS related equipment (i.e., progressive rinse barrels)
- Provision of direct supervision
- Providing payment for spray personnel or fuel to transport insecticide
- Procurement of personal protective equipment
- Hosting/co-hosting training for spray operators, trainers, supervisors, environmental compliance inspectors, IEC mobilizers, and other technicians

Please contact the IRS COR Team for country-specific scenarios.

Malaria in Pregnancy

New/Key Messages in FY 2017 Technical Guidance

- WHO recommends intermittent preventive treatment in pregnancy with SP (IPTp-SP) at each ANC visit starting in the 2nd trimester for all women not on cotrimoxazole, provided there has been at least one month since the last dose of SP.
- Based on data from several, recently completed studies, WHO does not recommend Intermittent Screening and Treatment during pregnancy (ISTp).
- WHO recommends 0.4 mg daily folic acid supplementation in pregnant women; ideally this should be administered as a combination iron/folate tablet (60 mg iron and 0.4mg of folate).
- The primary indicator for IPTp-SP recommended by RBM's Monitoring and Evaluation Reference Group is IPTp3. However, PMI will continue to monitor IPTp2 as its primary indicator and IPTp3 as an additional indicator.[64]
- PMI country teams are encouraged to explore innovative strategies for scaling-up coverage of IPTp and addressing missed opportunities.

Introduction

Each year, approximately 125.2 million women living in malaria-endemic countries,[65] including 30 million in Africa, become pregnant. For these women, malaria is a threat to both themselves and to their babies, with an estimated 10,000 maternal and up to 200,000 newborn deaths each year as a result of malaria in pregnancy. Pregnant women, particularly those in their first or second pregnancies, are particularly vulnerable to malaria as pregnancy reduces a woman's immunity to malaria, making her more susceptible to malaria infection and increasing the risk of illness, severe anemia, and death. For the unborn child, maternal malaria increases the risk of miscarriage, stillbirth, premature delivery, and low birth weight – a leading cause of child mortality.[66]

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[64] Due to the revised WHO policy of giving IPTp at every ANC visit after quickening, the RBM MERG has recommended tracking percentage of women receiving the 3rd dose (IPTp3), which corresponds to the FANC approach. However, PMI has historically tracked the 2nd dose, and will continue to do so in order to continue monitoring trends over time; PMI will continue to measure success as the proportion of women who receive 2 doses, assuming that it will be some years before there is significant uptake of 3 doses. PMI will also begin to track the 3rd and 4th dose of IPTp as countries start implementing the new policy.

[65] Dellicour S, Tatem AJ, Guerra CA, Snow RW, ter Kuile FO (2010) Quantifying the Number of Pregnancies at Risk of Malaria in 2007: A Demographic Study. PLoS Med 7(1): e1000221. doi:10.1371/journal.pmed.1000221

[66] http://www.who.int/features/2003/04b/en ; http://www.who.int/malaria/high_risk_groups/pregnancy/en/index.html

The impact of malaria infection on the health of the pregnant woman and her developing fetus depends to a large extent on the level of malaria transmission in the region in which she lives. In low-transmission areas, women usually present with symptomatic malaria, which can result in severe illness for the mother as well as the potential for premature delivery or miscarriage. In these areas, WHO recommends the use of ITN by all pregnant women and prompt diagnosis and treatment with an effective antimalarial. Intermittent preventive treatment in pregnancy (IPTp) is not recommended for pregnant women living in areas with low levels of malaria transmission, such as in Asia or selected areas of Africa (e.g., Ethiopia).

In contrast, women living in areas of sub-Saharan Africa with moderate to high levels of malaria transmission may have asymptomatic infections during pregnancy, resulting in maternal anemia, which can have severe consequences for the fetus and newborn. Maternal anemia and the presence of parasites in the placenta impair fetal nutrition, contributing to a range of negative pregnancy outcomes including low-birth weight.

In areas with moderate to high levels of malaria transmission, WHO recommends a three-pronged approach to reduce the burden of malaria infection among pregnant women:

- Intermittent preventive treatment of malaria during pregnancy
- Insecticide-treated nets
- Effective case management of malarial illnesses and anemia

PMI supports this approach for malaria in pregnancy implemented through the focused antenatal care service delivery platform. As such, PMI supports collaboration by both NMCPs and Reproductive/Maternal Health Programs on improving the delivery and uptake of malaria in pregnancy (MIP) interventions, particularly through a national technical advisory body, such as an MIP working group. Coordination with other infectious disease programs (including HIV) are also important considerations for MIP services provided to pregnant women. For example, HIV infection lessens a pregnant woman's ability to control malaria infections and placental infection with malaria parasites doubles the risk of vertical transmission of HIV.[4]

Intermittent Preventive Treatment in Pregnancy

IPTp is the periodic dosing of a pregnant woman with a curative treatment of an antimalarial, regardless of the presence of parasitemia, since placental infections may not be detected through standard methods. Currently, the only recommended regimen by WHO is sulfadoxine-pyrimethamine (SP), which has been shown to be safe and effective for use in pregnancy. The purpose is to clear (or substantially lower) the parasites from the placenta and to provide protection against new infections during the course of the pregnancy. This strategy has proven to

be effective in preventing parasitemia and anemia in the mother, and in increasing the birth weight, and thus the chances of survival, for the newborn.[67]

Since more than 70% of pregnant women in Africa attend ANC once during their pregnancy, and the vast majority of these women attend at least twice, the provision of IPTp during ANC visits should be an effective way to ensure that a majority of pregnant women receive a minimum of two doses of IPTp during pregnancy. PMI country teams should consider all possible efforts to increase uptake of IPTp with SP at ANC in areas with moderate to high transmission in Africa. IPTp should be incorporated into the routine ANC visit, and by definition, should be provided to asymptomatic women without testing for malaria.

In October 2012, WHO revised its policy recommendations on IPTp-SP to call for administration of **IPTp-SP at each scheduled antenatal care visit** starting as early as possible in the second trimester, provided that there has been an interval of approximately one month since the last dose of SP. [68,69,70] This change was made as a result of recent research demonstrating that providing IPTp at least three times during the course of pregnancy is more effective at preventing the adverse effects of malaria in pregnancy than providing only two doses of IPTp.[71,72,73, 74] For a woman to get the maximum benefit from IPTp, SP should be administered routinely at every scheduled ANC visit starting in the second trimester (13 weeks).

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[67] ter Kuile, F. O., A. M. van Eijk, et al. (2007). "Effect of Sulfadoxine-Pyrimethamine Resistance on the Efficacy of Intermittent Preventive Therapy for Malaria Control During Pregnancy." JAMA **297**(23): 2603-2616.
[68] WHO Malaria Policy Advisory Committee and Secretariat (2012). "Malaria Policy Advisory Committee to the WHO: conclusions and recommendations of September 2012 meeting." Malaria Journal **11**(1): 424.
[69] http://www.who.int/entity/malaria/iptp_sp_updated_policy_recommendation_en_102012.pdf
[70] http://www.who.int/malaria/mpac/sep2012/iptp_sp_erg_meeting_report_july2012.pdf
[71] Filler, S. J., P. Kazembe, et al. (2006). "Randomized Trial of 2-Dose versus Monthly Sulfadoxine-Pyrimethamine Intermittent Preventive Treatment for Malaria in HIV-Positive and HIV-Negative Pregnant Women in Malawi." J Infect Dis **194**(3): 286-293.
[72] Kayentao K, et al, 2013. Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa: Systematic review and meta-analysis. JAMA 309: 594-604.
[73] Diakite, O. S. M., K. Kayentao, et al. (2011). "Superiority of 3 Over 2 Doses of Intermittent Preventive Treatment With Sulfadoxine-Pyrimethamine for the Prevention of Malaria During Pregnancy in Mali: A Randomized Controlled Trial." Clin Infect Dis **53**(3): 215-223.
[74] Kayentao K, et al, 2013. Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa: Systematic review and meta-analysis. JAMA 309: 594-604.

WHO Policy Recommendation (October 2012)

- In areas of moderate-to-high malaria transmission, IPTp with SP is recommended for all pregnant women at each scheduled antenatal care visit. WHO recommends a schedule of four antenatal care visits.
- The first IPTp-SP dose should be administered as early as possible during the second trimester of gestation.
- Each SP dose should be given at least one month apart.
- The last dose of IPTp with SP can be administered up to the time of delivery, without safety concerns.
- Ideally, IPTp should be administered as directly observed therapy (DOT).
- SP can be given either on an empty stomach or with food.
- Folic acid at a daily dose equal or above 5 mg should not be given together with SP as this counteracts its efficacy as an antimalarial.
- SP should not be administered to women receiving cotrimoxazole prophylaxis.

Each dose of IPTp consists of three tablets of 500 mg sulfadoxine/ 25 mg pyrimethamine for a total dose of 1500 mg sulfadoxine and 75 mg pyrimethamine. All three tablets should be provided together, preferably under DOT at ANC, and may be given on an empty stomach. Co-administration of SP with other sulfa drugs, such as cotrimoxazole (Bactrim), is contra-indicated, as this will increase the risk of severe adverse events.

The Focused Antenatal Care approach, recommended by WHO, stresses four ANC visits during a pregnancy with three of these visits in the second and third trimesters. If a woman makes more than three ANC visits more than a month apart after quickening, she should receive more doses of IPTp, **with the objective of ensuring that at least three doses are received during her pregnancy**. There is no evidence of a negative health impact for either the woman or baby associated with receiving more than three doses of IPTp when doses are administered at monthly intervals.

Current WHO recommendations are to give IPTp up to the time of delivery; there is no need to withhold SP in the month prior to delivery. The previous recommendation to avoid the use of SP in the last four weeks of pregnancy was based on the theoretical risk that sulfonamides could increase the risk of kernicterus (a form of brain damage caused by excessive jaundice or hyperbilirubinemia) in the infant by displacing unconjugated bilirubin (the result of breaking down hemoglobin due to red blood cell turnover) from albumin (the major protein in the blood). However, after more than a decade of use, there is **no** evidence for this.

In all cases where PMI is procuring SP, only those drug products that are either produced in facilities in compliance with current Good Manufacturing Practices (GMP) as evaluated using

International Conference on Harmonization, WHO, or stringent regulatory authority (SRA) guidelines, *or* approved for marketing by an SRA[75] can be procured. In cases where countries are procuring SP themselves (i.e., not PMI procured), either from a local manufacturing facility or internationally but from a source where the quality standards and certification are unknown, teams should consider periodic testing of drug quality to ensure that high quality drugs are being used. In the case, however, where PMI funds will be used to support the storage, distribution, and/or usage of locally-sourced SP that has not been procured through PMI directly, the full consignment will be subject to 100% batch testing before release. This testing is important because although SP is produced locally in many countries, not all of these products are produced in facilities that are GMP compliant. Adherence to GMP helps ensure products manufacturers at the site in question are not adulterated or misbranded in any way. In a drug quality survey conducted by WHO, 33 out of 127 (26%) samples of SP (from 25 batches, produced by 18 different manufacturers) were found non-compliant in tests of the content of active ingredients,[76] and in one study in Kenya 45% of SP was found to be substandard.[77] Depending on the manufacturer, SP has a reported shelf life of between 36 and 48 months.

With increasing demand and long supply timelines, PMI supported a market analysis review[78] of SP in 2014 to better understand the global market situation. In 2012, the revised WHO IPTp policy recommendations and WHO's recommendation for Seasonal Malaria Chemoprevention (SMC) with a combination of SP and amodiaquine triggered increased global demand for SP. The report found several primary and secondary manufacturers of SP with varying production capacity; only one manufacturer is currently WHO pre-qualified. In addition, importation issues and registration policies were cited as key challenges to ensuring access to SP in African countries. The variety of SP presentations (i.e. bottles, blisters) has added an additional obstacle to the in-country registration processes, providing little incentive for local producers to register. The report concluded that there is enough production to cover the current needs for 2015; however the complexity surrounding multiple presentations of SP used in PMI-supported countries as well as the challenging situation with registration, puts the global community at risk for the SP supply. PMI-supported countries should plan on longer lead times (6-12 months) for SP commodity orders from quality-assured manufactures.

In areas where IPTp-SP is currently being implemented, and transmission of malaria has been reduced substantially, IPTp should be continued; at this time, it is not clear at what level of

[75] This could include, for example, the US FDA-approved product, Fansidar. In such cases, no quality testing is necessary as the US FDA qualifies as a stringent regulatory authority. For a complete list of SRAs, see the International Conference on Harmonization website at http://www.ich.org/.
[76] WHO, Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa. Quality Assurance and Safety: Medicines Essential Medicines and Pharmaceutical Policies. January 2011.
[77] Amin A, et al. The quality of sulfadoxine-pyrimethamine and amodiaquine products in the Kenyan retail sector. J Clin Pharm Ther, 30:6 (2005).
[78] USAID DELIVER Project, Supply Market Review of Sulfadoxine-pyrimethamine. September 2014.

transmission reduction IPTp should be abandoned as a strategy, and no alternate strategy has been demonstrated to be more effective or more cost-effective. Caution should be exercised in recommending the cessation of IPTp as a strategy, as there are not yet sufficient data from countries where transmission has fallen to show that such gains are long-standing rather than transient.

Although in some areas, particularly in East Africa, high levels of SP resistance have been documented, rendering SP ineffective as therapy for acute malaria infection, the available data suggest that there is still a benefit of giving IPTp-SP, and WHO continues to recommend its use, irrespective of SP resistance. Currently, there are no approved preventative treatment alternatives to IPTp-SP. If, in future, there is a recommendation to switch to an alternative drug, this will likely utilize the same delivery mechanism as IPTp-SP, and it will be easier to replace SP with the new drug on an existing platform rather than stopping and restarting an IPTp program. At the present time, there is not enough evidence to recommend a wide scale policy change in favor of IPTp with dihydroartemisinin-piperaquine (DP), and WHO is recommending additional research to better understand the impact, safety, and operational feasibility associated with IPTp-DP, which would need to be delivered as a treatment course over three days rather than as a single dose at each ANC. PMI will support a study to further assess IPTp with DP in Malawi.

Intermittent screening and treatment in pregnancy (ISTp), which involves screening with an RDT at each ANC visit and treating only women who test positive, has been evaluated in both East and West Africa, and ISTp was not superior to IPTp-SP even in areas with significant SP resistance. ISTp was associated with more maternal clinical malaria episodes, and was more costly than IPTp-SP, and therefore is not being recommended by WHO for use in any settings.

Opportunities for Community-Based Programming

Although community-based delivery of IPTp with SP has not been approved by WHO, and WHO recommends that IPTp be delivered at routine ANC visits, WHO does support exploring partnerships to deliver some components of the proposed malaria prevention and control package to pregnant women. As such, "community health workers may be effective at promoting the use of ANC services and ITNs and, with appropriate training and logistic support, could deliver IPT."[79]

Five studies from four countries (Nigeria, Uganda, Malawi, and Burkina Faso), all conducted prior to the current WHO recommendations for IPTp-SP to be delivered at each ANC visit starting in the second trimester, explored community delivery of IPTp-SP and all showed an increase in IPTp-SP uptake. Only two studies had a standard form of community health workers

[79] WHO Regional Office for Africa: A Strategic Framework for Malaria Prevention and Control During Pregnancy in the African Region (2004).

(CHWs) who were integrated with the local health services and were trained not only to deliver IPTp-SP, but also to refer women to ANC.[80,81] These two (Nigeria and Uganda) had positive effects on ANC attendance. Two other studies (Uganda and Malawi) trained a variety of community based agents to deliver IPTp-SP, but did not set out to increase ANC attendance, and in fact did not result in increased ANC visits.[82,83] The fifth study (Burkina Faso) did not include community IPTp-SP delivery but used female CHWs to encourage both ANC attendance and IPTp-SP uptake through ANC.[84] This resulted in increase of both ANC attendance and IPTp-SP uptake. The key lessons are that community MIP interventions work best if volunteers are specifically taught to focus on both ANC and IPTp-SP. One option that has been shown to be effective in improving IPTp uptake and ANC coverage is to promote IPTp and ANC attendance at the community-level to ensure that women visit the ANC to receive their IPTp doses.

Few studies have assessed the effects of community level delivery of IPTp-SP. These studies have shown mixed results with regard to ANC attendance. As we do not want to promote a policy to improve IPTp at the expense of ANC attendance, additional research is needed to assess whether delivery of IPTp-SP at the community level is cost-effective and can be achieved without compromising ANC attendance. PMI is funding a study in Burkina Faso to assess the effects of community level delivery of IPTp on both IPTp uptake and ANC attendance. If additional countries wish to consider this option, it would need to be assessed with an OR study before moving to wide scale implementation. Countries interested in exploring community-based distribution of IPTp-SP should discuss this with the PMI Headquarters MIP Team. An alternate implementation approach to increase uptake of IPTp for countries to consider would be to expand their facility-based ANC outreach services to include IPTp (along with delivery and promotion of the full ANC package) as a means of reaching pregnant women in remote, rural areas.

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[80] Okeibunor JC, Orji BC, Brieger W, Ishola G, Otolorin EO, Rawlins B, Ndekhedehe EU, Onyeneho N, and Fink G. Preventing malaria in pregnancy through community-directed interventions: evidence from Akwa Ibom State, Nigeria. Malaria Journal 2011; 10:227 http://www.malariajournal.com/content/10/1/227/abstract.

[81] Richard Ndyomugyenyi, Ephraim Tukesiga, James Katamanywa. Intermittent preventive treatment of malaria in pregnancy (IPTp): participation of community-directed distributors of ivermectin for onchocerciasis improves IPTp access in Ugandan rural communities. Transactions of the Royal Society of Tropical Medicine and Hygiene (2009) 103, 1221-1228.

[82] Anthony K. Mbonye, Pascal Magnussen and I. B. Bygbjerg. Intermittent preventive treatment of malaria in pregnancy: the effect of new delivery approaches on access and compliance rates in Uganda. Tropical Medicine and International Health 2007; 12(4): 519–531.

[83] K. P. Msyamboza, E. J. Savage, P. N. Kazembe, S. Gies, G. Kalanda, U. D'Alessandro and B. J. Brabin. Community-based distribution of sulfadoxine-pyrimethamine for intermittent preventive treatment of malaria during pregnancy improved coverage but reduced antenatal attendance in southern Malawi. Tropical Medicine and International Health 2009; 14(2): 183–189.

[84] Sabine Gies, Sheick O. Coulibaly, Clotilde Ky, Florence T. Ouattara, Bernard J. Brabin, and Umberto D'Alessandro. Community-Based Promotional Campaign to Improve Uptake of Intermittent Preventive Antimalarial Treatment in Pregnancy in Burkina Faso. Am. J. Trop. Med. Hyg., 80(3), 2009, pp. 460–469.

Insecticide-Treated Mosquito Nets

Use of ITNs during pregnancy is a key component of PMI's malaria in pregnancy strategy. In areas with moderate to high levels of transmission, the use of ITNs during pregnancy provides significant protection against malarial infection, illness, maternal anemia, and low birth weight.[85] The provision of ITNs to pregnant women is part of the essential package of ANC and FANC services. ITNs should be provided to pregnant women as early as possible in pregnancy and their use should be encouraged for women throughout pregnancy and during the postpartum period. ITNs and IRS are the only interventions that protect women early in pregnancy, during the first trimester. Ideally, all women of childbearing age should sleep under an ITN, as this will ensure protection even before the woman realizes that she is pregnant. PMI supports universal coverage of ITNs to ensure women of reproductive age sleep under ITNs early in their pregnancy. **With continuing support for universal ITN coverage campaigns and maintaining high ITN ownership, countries should not lose sight of the importance of providing ITNs to pregnant women at first ANC visit as part of the routine health services.** Although mass campaigns are critical to ensure universal coverage is achieved, when planning a campaign, please attempt to ensure sufficient ITNs are available such that ITNs are not removed from the ANC clinics resulting in a prolonged period of unavailability following the campaign. The RBM Malaria in Pregnancy and Vector Control Working Groups and the Alliance for Malaria Prevention have published a joint statement detailing the importance of maintaining LLIN coverage of vulnerable populations via ANC and EPI distribution.[86]

Case Management of Malaria in Pregnancy

Prompt treatment with a safe and effective antimalarial drug is a fundamental component of the WHO-RBM's strategy to control malaria. Antimalarial treatment shortens the duration of illness, and reduces the frequency of complications and the risk of death for the mother and fetus. This is particularly important in pregnant women, due to their increased risk of developing severe disease. Essential elements of the ANC package in malaria endemic regions should, therefore, include malaria diagnosis and treatment with antimalarial drugs that have an adequate safety and efficacy profile for use in pregnancy.

Women who present at routine ANC with fever, malaise, or other symptoms consistent with malaria should be tested by blood smear or rapid diagnostic test (RDT) whenever possible. If a pregnant woman is found to have malaria, she should be treated as outlined below. There is no contra-indication to the co-administration of SP with either quinine or artemisinin-based combination therapies (ACTs), thus IPTp may be administered or not. In all instances, she

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[85] Gamble, C., Ekwaru JP, ter Kuile FO (2006). "Gamble C, Ekwaru JP, ter Kuile FO. Insecticide-treated nets for preventing malaria in pregnancy." Cochrane Database of Systematic Reviews **CD003755**.
[86] http://www.rollbackmalaria.org/files/files/partnership/4_FLLIN_E.PDF

should be instructed to return for IPTp in one month. If a woman is tested and found to be negative, then she should be given IPTp as usual and followed-up as per country protocol.

For uncomplicated malaria, WHO recommends that women in the first trimester should be treated with oral quinine for seven days (with or without clindamycin) as there is still insufficient safety data on ACTs in the first trimester to recommend ACTs as first-line treatment. Only if there are no other efficacious antimalarial treatments available should ACTs be used for treating uncomplicated first trimester malaria infections. In the second and third trimesters, ACTs are the preferred therapy. Quinine is associated with an increased risk of hypoglycemia in late pregnancy, and it should be used only if efficacious alternatives are not available. Primaquine and tetracycline should not be used in pregnancy.

For treatment of severe malaria in pregnancy, parenteral antimalarials should be given without delay; maternal mortality in severe malaria is approximately 50%, which is higher than in non-pregnant adults. Parenteral artesunate is preferred in the second and third trimesters while either parenteral quinine or parenteral artesunate are acceptable choices in the first trimester (the increased risk of death outweighs the uncertainties over safety).[87]

Treatment of Malaria in Pregnancy

	1st trimester	**2nd or 3rd trimester**
Uncomplicated malaria	Oral quinine for seven days (with or without clindamycin)	ACT*
Severe malaria	IV/IM artesunate or IV/IM quinine	IV/IM artesunate (preferred) or IV/IM quinine if artesunate not available

***** HIV infected individuals on zidovudine or efavirenz should avoid ACT regimens that contain amodiaquine.

HIV-Infected Women

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-infected. 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 first and second pregnancies, in the presence of HIV infection, the risk associated with placental malaria is independent of the number of pregnancies. Given this increased risk, emphasis should be placed on ensuring that HIV-infected women sleep under ITNs every night.

[87] WHO, 2012. Management of severe malaria: a practical handbook – 3rd ed.

Intermittent preventive treatment is recommended for HIV-infected pregnant women living in areas with high levels of transmission only when they are not receiving daily trimethoprim-sulfamethoxazole (cotrimoxazole) prophylaxis, because co-administration of these drugs increases the risk of sulfa-related adverse effects, including Stevens-Johnson Syndrome (a severe skin reaction). In addition, daily cotrimoxazole provides a similar protective effect to IPTp if doses are not missed.[88] HIV-infected women who are not taking cotrimoxazole prophylaxis should receive a minimum of three doses of IPTp with SP during pregnancy, in order to obtain protection similar to that received with two doses in women not infected with HIV.

Given that many HIV-positive women will not be eligible for IPTp due to concurrent cotrimoxazole prophylaxis, it is imperative that HIV-positive women receive an ITN and are encouraged to sleep under the net throughout their pregnancy.

Case management of malaria in pregnancy in HIV-positive individuals is the same as in uninfected individuals, with the exception that amodiaquine-containing ACT regimens should be avoided in patients on zidovudine or efavirenz.

Prevention of Anemia in Pregnancy

Folic acid supplementation in pregnancy is important to prevent neural tube defects in the developing fetus as well as to prevent megaloblastic anemia in the mother. The recommended dose of folic acid for use in pregnancy is 0.4 mg/day or 400 micrograms per day, which is adequate to prevent neural tube defects in the infant.[89] In many African countries, the higher (5 mg) dosage, which is used to treat megaloblastic anemia (anemia resulting from folic acid deficiency, which is rare in pregnancy), is predominantly available. However, this higher dose should not be used in conjunction with IPTp, as it has been shown to decrease the efficacy of SP.[90] In contrast, the 0.4 mg daily dose did not interfere with SP efficacy. In countries where doses of folic acid greater than 0.4 mg/day are used for supplementation in pregnancy, PMI teams should work with the MOH to procure (or consider procuring) low-dose folic acid (or iron and folate combination tablets, with 60 mg iron and 0.4mg of folate), which is recommended by WHO for use in pregnancy.

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[88] Kapito-Tembo et al., Marked reduction in prevalence of malaria parasitemia and anemia in HIV-infected pregnant women taking cotrimoxazole with or without sulfadoxine-pyrimethamine intermittent preventive therapy during pregnancy in Malawi. J Infect Dis. 2011 Feb 15;203(4):464-72.
[89] http://www.who.int/maternal_child_adolescent/documents/924159084x/en/index.html
[90] Ouma P, et al. (2006) A randomized controlled trial of folate supplementation when treating malaria in pregnancy with sulfadoxine-pyrimethamine. PLoS Clin Trials 1(6): e28.

Improving Program Implementation for IPTp

A number of challenges to IPTp scale up have been observed in PMI-supported countries. These include issues concerning central and peripheral level stock-outs of SP, inconsistent malaria and maternal health guidance on IPTp administration, confusion among providers about timing and dosages, and lack of coordination between Reproductive/Maternal Health and NMCPs of their responsibilities for program implementation.

PMI country teams are encouraged to:

- Identify and assess potential issues and challenges to IPTp scale-up
- Foster coordination between Maternal Health Programs and NMCPs, with establishment of a national MIP working group or task force
- Review the current policy in country and work with the MOH, Reproductive Health, and NMCP to update the policy to conform to the revised WHO guidelines
- Update the HMIS and ANC registers to facilitate collection of data regarding the additional doses of SP
- Disseminate revised guidelines widely, and ensure that they are available to health providers at the facility level (e.g., a simple memo from District Medical Officer followed by a supervisory visit may be an effective means to improve IPTp uptake)
- Develop an action plan for IPTp training and supervision of health providers
- Support SP supply chain management and logistics and procure SP in case of gaps
- Explore innovative means to reach out to CHWs, including the use of cell phone messaging
- Consider support for electronic based supervision and reporting forms to assess health worker performance

In addition, PMI teams are encouraged to reach out to other donors and partners such as the U.S. Peace Corps to help facilitate MIP activities including IPTp. For example, Peace Corps Volunteers can assist facility based health workers and community health workers to increase IPTp uptake through targeted SBCC strategies including mobilizing community members through household visits, organizing women's and other community group discussions, focus group discussions, etc. Peace Corps Volunteers could also be trained to do rapid MIP/IPTp assessments in communities where IPTp uptake is particularly low to identify some of the major bottlenecks.

Focused Antenatal Care

In 2001, WHO issued guidance on a new model of ANC called goal-oriented or focused antenatal care (FANC) for implementation in developing countries.[91] FANC is a package of essential evidence-based interventions provided to pregnant women at each of the recommended four antenatal care visits. The essential interventions include identification and management of obstetric complications such as preeclampsia, tetanus toxoid immunization, IPTp, and identification and management of infections including HIV, syphilis, and other sexually transmitted infections. FANC is also an opportunity to promote the use of skilled attendance at birth and healthy behaviors, such as breastfeeding, early postnatal care, and planning for optimal pregnancy spacing. In many countries, ITNs are delivered to pregnant women through FANC. PMI supports FANC programs in many of the focus countries. WHO's Department of Reproductive Health and Research is currently embarking on revisions to the ANC guidelines and working closely with WHO's Global Malaria Program to ensure consistency with MIP and IPTp policy recommendations. The new ANC guidelines are expected to be released in 2016.

Additional Resources

- WHO-Roll Back Malaria website: http://mosquito.who.int
- The updated WHO IPTp-SP policy and full meeting report (July 2012): http://www.who.int/malaria/mpac/sep2012/iptp_sp_erg_meeting_report_july2012.pdf.
- The full report from the Malaria Policy Action Committee meeting: http://www.malariajournal.com/content/11/1/424
- WHO updated policy brief published in April 2013: http://www.who.int/malaria/publications/atoz/policy_brief_iptp_sp_policy_recommendation/en/.
- The report from the Expert Review Group meeting: http://www.who.int/malaria/mpac/mpac_sep13_erg_ipt_malaria_pregnancy_report.pdf
- *The epidemiology of malaria in pregnancy* (by Desai M, ter Kuile FO, et al) and other articles in the Lancet supplement (volume 7), February 2007.
- 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.

[91] Villar, J. et al. 2001. "WHO antenatal care randomized trial for the evaluation of a new model of routine antenatal care," *The Lancet* 357: 1565-1570.

Frequently Asked Questions for MIP

Q1. If SP is no longer effective in children, why are we giving it to pregnant women?

A. The spread of resistance of *P. falciparum* to SP in eastern and southern Africa has raised concerns about the efficacy of SP for IPTp. However, even in areas where SP is not an effective therapy in children, it remains effective as IPTp. It is thought that pregnant woman's pre-existing immunity amplifies the effectiveness of SP in IPTp, whereas young children have no such immunity.[92] IPTp is thought to work both by clearing existing asymptomatic placental malaria infections as well as preventing new infections for several weeks (due to the long half-life of SP). Even in areas of high level resistance to SP, this combination has been shown to provide a benefit against the adverse effects of malaria.

Q2. What are the key findings from recent efficacy studies of IPTp with SP?

A. Some recent studies present mixed findings on the efficacy of IPTp with SP. There is evidence of decreasing efficacy of SP in Eastern Africa, specifically in studies from Tanzania and Malawi suggesting that SP may no longer be of benefit in specific regions of the respective countries.[93,94,95] Of particular concern are several studies in areas where the dihydropteroate synthase (*dhps*) A581G mutation has been identified on a background of the dihydrofolate reductase (*dhfr*) /*dhps* quintuple mutant, resulting in a "sextuple mutant." These include a recent paper by Minja et al showing decreased birth-weight in infants of mothers infected with the sextuple mutant.[96] However, the extent of this mutant remains limited, and data from areas without the sextuple mutant (even with high prevalence of the quintuple mutant) suggest that IPTp continues to provide benefit.[97] In a study in Mozambique, Menendez et al. found a protective effect of SP against neonatal death despite a lack of protection from low birth weight or placental infection by histology, suggesting that there may be additional mechanisms through

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[92] ter Kuile FO, et al: Effect of Sulfadoxine-Pyrimethamine Resistance on the Efficacy of Intermittent Preventive Therapy for Malaria Control During Pregnancy. *JAMA* 2007, 297:2603-2616.
[93] Harrington WE, et al: Intermittent Treatment to Prevent Pregnancy Malaria Does Not Confer Benefit in an Area of Widespread Drug Resistance. *Clin Infect Dis* 2011, 53:224-230.
[94] Feng G, et al: Decreasing burden of malaria in pregnancy in Malawian women and its relationship to use of intermittent preventive therapy or bed nets. *PLoS ONE* 2010, 5:e12012.
[95] Harrington WE, et al: Competitive facilitation of drug-resistant *Plasmodium falciparum* malaria parasites in pregnant women who receive preventive treatment. *Proc Natl Acad Sci U S A* 2009, 106:9027-9032.
[96] Minja D, et al., 2013. Infections with Plasmodium falciparum sextuple dihydrofolate reductase/dihydropteroate synthetase allelic haplotypes during pregnancy are associated with decreased birth weight in Korogwe, Tanzania. Emerg Inf Dis. 19.
[97] Kayentao K, et al, 2013. Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in africa: Systematic review and meta-analysis. JAMA 309: 594-604.

which SP provides protection.[98,99] Studies in areas with lower levels of SP resistance (West Africa) have found that IPTp with SP remains effective.[100,101] In addition, a recent meta-analysis of national survey data has shown that SP provides protection in a programmatic context.[102] Similarly, a meta-analysis of data from eight delivery cross-sectional studies in six countries with varying degrees of resistance found no correlation between the effect of IPTp-SP and resistance strata.[103] Consequently, PMI recommends that we continue IPTp with SP until such time as there is clear evidence that it is no longer effective or an effective alternative is recommended. The updated WHO policy recommendations are based on the recent evidence and seek to reinforce the importance and appropriateness of SP for IPTp.

Q3. How can one be assured that a woman is in the second trimester?

A. The second trimester starts at the beginning of the 13th week of pregnancy. This can be determined by one or more of the following:

- Counting weeks from the first day of the last menstrual period
- Palpation of the uterine fundus: once the fundus can be palpated, the woman is definitely in the 2nd trimester, although an unskilled provider may not be able to palpate the fundus as early as 13 weeks
- Quickening, which is defined as when the mother first feels fetal movements, and usually occurs at approximately 20 weeks gestation in the first pregnancy, and earlier (between 15-20 weeks) in subsequent pregnancies (given that this is well into the 2nd trimester, it is preferred that other methods be used to determine gestational age/ whether the woman is in the 2nd trimester)

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[98] Menendez, C., A. Bardaji, et al. (2010). "Malaria Prevention with IPTp during Pregnancy Reduces Neonatal Mortality." PLoS ONE **5**(2): e9438.

[99] Menéndez, C., A. Bardají, et al. (2008). "A Randomized Placebo-Controlled Trial of Intermittent Preventive Treatment in Pregnant Women in the Context of Insecticide Treated Nets Delivered through the Antenatal Clinic." PLoS ONE **3**(4): e1934.

[100] Maiga OM, et al: Superiority of 3 Over 2 Doses of Intermittent Preventive Treatment With Sulfadoxine-Pyrimethamine for the Prevention of Malaria During Pregnancy in Mali: A Randomized Controlled Trial. *Clin Infect Dis* 2011, 53:215-223

[101] Likwela JL, et al. Sulfadoxine-pyrimethamine resistance and intermittent preventive treatment during pregnancy: a retrospective analysis of birth weight data in the Democratic Republic of Congo (DRC). Trop Med Int Health. 2011

[102] Eisele, TP, Larsen DA, et al. (2012). Malaria prevention in pregnancy, birthweight, and neonatal mortality: a meta-analysis of 32 national cross-sectional datasets in Africa. Lancet Inf Dis 12:(12):942-949.

[103] Desai M, Gutman J, et al. Impact of Sulfadoxine-Pyrimethamine Resistance on Effectiveness of Intermittent Preventive Therapy for Malaria in Pregnancy at Clearing Infections and Preventing Low Birth Weight. Clin Infect Dis. 2015 Oct 20. pii: civ881.

Other Preventive Approaches

New/Key Messages in FY 2017 Technical Guidance

- Seasonal Malaria Chemoprevention (SMC) has been shown to be an effective strategy in reducing morbidity and mortality in applicable countries of the Sahel and feasible to implement on existing integrated community case management platforms.
- RTS,S vaccine received a positive recommendation by the European Medicines Agency in July 2015. Subsequently, WHO's Strategic Advisory Group of Experts and Malaria Policy Advisory Committee recommended that several large-scale pilot projects (Phase IV research trials in operational conditions) be carried out in Africa to collect further information on safety and feasibility.
- WHO's Malaria Policy Advisory Committee has issued new recommendations on mass drug administration (MDA) and mass screen and treat (MSAT) strategies. MSAT, using currently available diagnostic tools, was not shown to be effective in interrupting transmission and PMI does not recommend it as an intervention for transmission reduction.
- WHO also recommends that MDA could be considered in elimination settings where coverage of control interventions is fully scaled-up and where importation of malaria cases is infrequent. PMI is not currently supporting MDA implementation activities and recommends that MDA only be undertaken with PMI support in the context of operational research, with direct engagement with PMI Headquarters Case Management Team and Pre-Elimination Working Group, at this point in time.

Introduction

Although much progress has been made with the scale-up of the four core PMI interventions, additional tools are being implemented or evaluated to either reduce malaria morbidity and mortality in high transmission settings or to interrupt malaria transmission in low transmission settings. This chapter will describe these ancillary interventions— the intended role, targeted settings, and level of current evidence. **These are not exclusive to pre-elimination settings and in fact are mostly intended to reduce morbidity in high transmission settings.**

In recent years, WHO has approved new approaches involving anti-malarial medication for prevention (e.g., seasonal malaria chemoprevention or intermittent preventive treatment in infants) to further reduce morbidity and mortality in target groups in high transmission areas. In addition, the RTS,S vaccine is being considered as an additional tool to reduce morbidity and mortality in children in high transmission areas.

To accelerate the pathway to elimination or to interrupt transmission, other tools (e.g., MDA and MSAT) are being evaluated in various transmission settings currently. The evidence to date was recently reviewed by WHO. No matter the transmission setting, all of these ancillary approaches are intended as additional targeted activities and are not a substitute for a robust malaria control program based on vector control and strong case management practices. **For countries considering implementing any of these interventions, please consult with the PMI Headquarters Case Management Team or the PMI Headquarters Pre-Elimination Working Group.**

Seasonal Malaria Chemoprevention

WHO issued a recommendation for the implementation of SMC in March 2012. Seasonal malaria chemoprevention, formerly known as intermittent preventive treatment for children, is the administration of treatment doses of longer-acting antimalarial medications at monthly intervals in areas of exclusively seasonal transmission with the aim of completely treating any existing infections and maintaining protective drug concentrations in the blood throughout a complete transmission season. The current WHO recommendations consist of a treatment dose of amodiaquine plus sulfadoxine-pyrimethamine (AQ+SP) given to children between 3 and 59 months of age at monthly intervals during the malaria transmission season, up to a maximum of four doses. This approach is only recommended for geographic regions where the malaria transmission season is short. Seasonal malaria chemoprevention also is not recommended for areas where high-levels of resistance to either SP or AQ have been demonstrated. Based on these criteria, implementation of this strategy is only recommended in countries or portions of countries in the Sahel region of West Africa. The following PMI-supported countries meet the criteria for implementing SMC: Senegal, Mali, Burkina Faso, and the northern areas of Ghana, Benin, and Nigeria. Seasonal malaria chemoprevention is not recommended in the seasonal transmission belt in Southern Africa, because intense SP resistance has been well documented in the area, and sufficient data on the safety and efficacy of alternative drugs for SMC programs are lacking.

A number of technical and logistical considerations exist when supporting an SMC program. One of the primary issues is having the necessary quantities of quality-assured SP+AQ available in time for the malaria transmission season. In the past, SP and AQ were purchased separately, and required cutting and packaging to prepare doses, especially for children under one year of age who require smaller doses. In 2014, one approved manufacturer received approval from the WHO Prequalification Program, with one co-blister presentation of SP+AQ, facilitating PMI's ability to procure a quality-assured product. However, lead times are long (approximately10 months) and countries considering supporting drug procurement for SMC campaigns should place orders as early as possible to ensure the drugs arrive in country in time for the malaria transmission season, taking into consideration customs clearance, the possible need for drug

registration waivers, and transport/distribution for pre-positioning at the intended point-of-care distribution locations. All PMI country teams planning to support SMC now or in the future should work closely with the PMI Headquarters Commodity Procurement and Supply Chain Team to ensure sufficient supplies of drugs will be available when needed. See the **Commodity Procurement and Supply Chain Management** chapter for additional information.

In addition, the use of AS-AQ as a first-line malaria treatment is not recommended for SMC areas because AQ is used for SMC, so countries implementing SMC where AS-AQ is the first-line treatment must ensure a sufficient supply of a non-amodiaquine-based ACT (i.e., AL or DHA-Piperaquine) for first line treatment either nationwide or in SMC areas. It is also recommended that countries do specific quantification for RDTs and ACTs needs during the SMC distribution rounds as part of the logistics planning, as the additional testing of febrile children during these rounds might result in a slight temporary increase in the needs for ACTs and RDTs.

Seasonal malaria chemoprevention programs should ideally be built on an existing CHW or iCCM programs, when available. Community health workers are often best placed to identify the children who qualify for SMC, to distribute the medications, and to follow-up to ensure adherence to dosing regimens throughout the rainy season. Preliminary results from the PMI-funded pilot implementation and evaluation of SMC in Senegal and Mali showed substantial reductions in malaria-associated morbidity and mortality and also demonstrated the feasibility of implementing through existing iCCM platforms. Teams in relevant countries are encouraged to consult with the PMI Headquarters Case Management Team to determine whether and how to support country-level SMC strategies.

Additional information on the WHO policy recommendation can be found at:
http://www.who.int/malaria/publications/atoz/smc_policy_recommendation_en_032012.pdf
A field guide for SMC implementation from WHO is available here:
http://www.who.int/malaria/publications/atoz/9789241504737/en/

Intermittent Preventive Treatment in Infants

In 2010, WHO issued guidance on the use of SP for intermittent preventive treatment in infants (IPTi). Intermittent preventive treatment in infants consists of the administration of a full treatment dose of SP to infants less than one year of age, living in areas at high risk of malaria, concurrently with the routine immunization schedule. The routine EPI scheduling varies by country but usually includes doses at 10 weeks and 14 weeks (with DPT vaccinations), and 9 months of age (with measles vaccination). IPTi has been approved by WHO for use in areas of moderate to high malaria transmission, where transmission occurs year-round, and where parasite resistance to SP is not high, which can be defined as areas that have less than 50% prevalence of *pfdhps* 540 mutations associated with resistance in the *P. falciparum* parasite. This

strategy may be implemented at the regional or district level when the extent of SP resistance is not known at the national level.

In reality, most countries lack information on the prevalence of this mutation at the population level, making this strategy difficult to implement. To date, NMCPs have not prioritized IPTi for PMI support in any country. Any requests from NMCPs to support such a program must be discussed with the PMI Headquarters Case Management Team.

Additional information on the WHO policy recommendation can be found at:
http://www.who.int/malaria/news/WHO_policy_recommendation_IPTi_032010.pdf

Malaria Vaccine

Research and development to produce a malaria vaccine has been ongoing for decades. The RTS,S/AS01 malaria vaccine was tested in 11 sites in seven African countries with different transmission intensities. The vaccine was tested in two age-categories: children first vaccinated at 5-17 months of age, and young infants first vaccinated at 6-12 weeks of age. After approximately four years of follow-up, vaccine efficacy against clinical malaria in children was 36% and 28%, and against severe malaria was 32% and 1.1% when administered with and without a booster dose, respectively. In young infants, the vaccine efficacy against clinical malaria was lower at 26% with the booster dose and 18% without; no efficacy against severe malaria was shown. Despite moderate to low efficacy, impact, measured as number of cases averted, was high; 1,774 cases of clinical malaria were averted per 1,000 children vaccinated with booster, and 1,363 without. In young infants, 983 and 558 cases of clinical malaria were averted per 1,000 vaccinated with and without the booster, respectively. Two important safety signals were noted; an increase in meningitis and febrile seizures in RTS,S/AS01 vaccinated children compared with controls.

The RTS,S/AS01 vaccine was reviewed by the European Medicines Agency in July 2015 and received a positive scientific opinion. Subsequently, a joint meeting of the WHO's Strategic Advisory Group of Experts and Malaria Policy Advisory Committee recommended to WHO that a large-scale Phase IV pilot implementation in operational context in 3-5 targeted countries in Africa be carried out to assess the feasibility of implementation of the vaccine in children 5-17 months of age. They also recommended collection of additional information on adverse events. WHO has now adopted the Strategic Advisory Group of Experts/Malaria Policy Advisory Committee recommendations, and is working with partners to plan the recommended trials, some of which may be carried out in PMI-supported countries. Although PMI will not be providing direct support for the implementation of these pilots, PMI may have an important role in supporting scale-up and maintenance of coverage of vector control and case management interventions in the areas targeted by these pilots. PMI Resident Advisors in the targeted countries should participate in country-level discussions to ensure coordination of these trials

with PMI's implementation activities. PMI leadership will keep the field informed regarding discussions with GlaxoSmithKline, Global Fund, GAVI, and other donors regarding plans for the vaccine pilot projects. It is not anticipated, though, that PMI will have additional funding, beyond what is already provided to countries, to support implementation of this vaccine.

Mass Drug Administration

Mass Drug Administration is defined as the practice of treating a targeted population in a defined geographic area for malaria, irrespective of the presence of symptoms and without diagnostic testing. As malaria control programs aspire to elimination, there has been a resurgent interest in MDA as a tool to eliminate the remaining parasite reservoir in a given geographic area. Mass drug administration was a strategy used with mixed results during the eradication era of the mid-20th century. In some regions, such as the USSR and China, it was used for malaria control, parasite elimination, and epidemic response. In combination with vector control measures MDA helped to eliminate malaria in select settings (e.g., small islands or highland settings).

Based on those eradication era experiences, WHO had discouraged MDA for routine malaria control because of its limited sustained impact on transmission and the high potential for the development of drug resistance. However, when artemisinin resistance was first detected in Southeast Asia, MDA was revived as a potential approach to eliminate the resistant strains of the parasite in limited geographic settings and targeted populations. In 2010, WHO convened an expert group to review the evidence for the use of MDA in the artemisinin-resistance containment project in Southeast Asia. The WHO Technical Experts Group concluded that there was no evidence of long-term benefits for MDA in large population groups. More recently, a Cochrane review and an independent review of the data commissioned by the Gates Foundation provided more detailed conclusions on the use of MDA. These two reviews found that while MDA can be successful at reducing parasite prevalence, once the activity is stopped, there is a strong tendency for malaria to rebound to previous transmission levels especially in higher transmission settings.

There were some limited examples of success, especially against *P. vivax* in seasonal transmission settings and small, isolated populations (such as on islands). However, many questions regarding the effective use and long-term effectiveness of MDA still remain, including which drug regimens to use and for what duration, which populations to target, how best to achieve high coverage, and what combination of co- interventions is necessary for MDA to be effective.

In addition, in the context of the 2014 Ebola outbreak in West Africa, MDA was used as a strategy to reduce the prevalence of malaria in selected urban areas. Temporarily reducing the burden of malaria on the health facilities allowed health workers to focus efforts on establishing critical Ebola diagnostic and treatment protocols.

Other partners, particularly the Gates Foundation and the Global Fund, are currently funding pilot studies in the Greater Mekong Subregion and other areas to assess the effectiveness of MDA, particularly in the context of elimination efforts. The underlying assumption of these efforts is that subpatent parasitemias contribute substantially to malaria transmission and therefore must be treated if malaria is to be eliminated. Preliminary results vary across the different study settings in the Mekong and appear to be related to coverage and ongoing importation of malaria infections from outside the targeted area. In addition, preliminary results from southern Zambia showed marked reductions in malaria prevalence and incidence across both control and MDA arms following universal coverage ITN distributions, variable IRS, and effective community case management. In addition, focal MDA was not as effective as MDA.

In 2015, WHO convened an Evidence Review Group to review of all available evidence on MDA and presented their draft recommendations to the Malaria Policy Advisory Committee. In December 2015, WHO issued its recommendations stating that: *"Use of MDA for the elimination of P. falciparum malaria can be considered in areas approaching interruption of transmission where there is good access to treatment, effective implementation of vector control and surveillance, and a minimal risk of re-introduction of infection."* The goal in this setting is to eliminate all remaining parasite carriers and fully interrupt transmission. WHO also recommends that MDA could be considered in the context of epidemics or complex emergencies to transiently reduce malaria prevalence and reduce the risk of severe disease and death, thereby reducing the burden on the health system.

PMI is not currently supporting MDA implementation activities and recommends that MDA only be undertaken with PMI support in the context of operational research at this point in time. PMI will be supporting operational research around targeted MDA in response to index cases in the elimination settings of Madagascar. Any country teams considering supporting an MDA program should consult with the PMI Headquarters Pre-Elimination Working Group and Case Management Teams.

Further information on the Cochrane and University of California San Francisco reviews can be found here:

- http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008846.pub2/full
- http://globalhealthsciences.ucsf.edu/sites/default/files/content/ghg/mei-review-of-mda-and-primaquine.pdf

Mass Screen and Treat

Mass screen and treat refers to screening all people in a population with a malaria diagnostic test and providing treatment to those with a positive test result. The aim of this type of program is to reduce the parasite reservoir and decrease malaria transmission. By systematically testing a population and treating all positive cases, including asymptomatic infections, the hope is that the reservoir of parasites will be diminished beyond that which is possible by traditional case management.

At present, malaria RDTs are the only feasible option for conducting MSaT. However, the currently available RDTs are not sensitive enough to detect very low density parasitemias, which can comprise up to 50% of malaria infections found in a population. Work to develop more field-friendly molecular tests and more sensitive RDTs are on-going. There is increasing evidence from Burkina Faso and Zambia, and from a PMI-supported study in Kenya, that MSaT with RDTs are insufficient to eliminate the human infection reservoir.

Although the final Malaria Policy Advisory Group recommendations are pending, it will likely not recommend the use of MSAT or focused screening and treatment to reduce malaria burden or interrupt malaria transmission. PMI is not currently supporting MSaT activities; however, it may consider its use in the context of operational research once a more sensitive point-of-care diagnostics become available. Any country teams considering supporting an MSaT program should consult with the PMI Headquarters Pre-Elimination Working Group and Case Management Teams.

Case Management

New/Key Messages in FY 2017 Technical Guidance

- PMI continues to prioritize scaling up diagnostic testing with both microscopy and RDTs at facility and community levels, including through iCCM.
- Scaling up of case management must be closely linked with communications and social and behavior change activities focused on changing the expectations and practices of patients, caregivers, and healthcare providers.
- In countries where strengthening of case management in the private sector is prioritized, a non-PMI source of commodities (such as Global Fund) should be sought. PMI does not subsidize commodities for the private sector or allow PMI-procured commodities to be sold for profit.
- Parenteral artesunate is recommended as the first-line treatment for severe malaria diagnosed in all populations, including women in all trimesters of pregnancy. However, challenges in cost, procurement, and implementation must be carefully considered prior to rollout.
- Monitoring of molecular markers of artemisinin resistance is now included as part of routine therapeutic efficacy monitoring.
- Because drying out of buffer ampules in individual test kits remains a problem, PMI no longer procures individual RDT kits.
- Multi-species RDTs will only be procured in countries with co-endemic *P. vivax* (Ethiopia, Madagascar, and Greater Mekong Subregion). Multi-antigen RDTs for *P. falciparum* will not be procured.
- Information on single, low-dose primaquine and other topics related to case management in pre-elimination settings can be found in the new **Pre-Elimination** chapter.

Introduction

A comprehensive program for malaria case management should support interventions to strengthen and expand:

- Diagnostic testing for malaria, including both quality-assured and quality-controlled microscopy and RDTs
- Prompt and effective case management of fever, including adherence to diagnostic test results, management of uncomplicated malaria and severe disease (including in pregnant women), iCCM of pneumonia, diarrhea, and malaria in children
- Introduction and scaling-up of fever case management, including malaria diagnostic testing, in the private sector, where appropriate
- Monitoring the therapeutic efficacy of first-line antimalarial treatments

- Systems for forecasting, procuring, storing, distributing, and monitoring the quality of essential drugs and diagnostics

Diagnostic Testing

In 2010, WHO's revised treatment guidelines changed its recommendations on malaria diagnosis, calling for all patients with suspected malaria to undergo quality-assured diagnostic testing, with either microscopy or RDTs, and for treatment decisions to be based on test results. Diagnosis based on clinical signs and symptoms alone should only be used when diagnostic testing is unavailable.

Diagnostic confirmation by microscopy is obtained by identification of malaria parasites on thick and thin blood films. Thick blood films are more sensitive in detecting and quantifying malaria parasites because the blood is more concentrated allowing for a greater volume of blood to be examined. Thin smears are particularly helpful for malaria speciation. However, speciation can also be done with thick smears, and in cases where only materials for thick smears are available, microscopists may be more comfortable using this modality for all applications (detection, quantification, and speciation). Microscopy results are dependent on the competence and performance of laboratory technicians in preparing, staining, and reading blood slides, as well as the quality of the reagents and equipment.

Malaria RDTs detect parasite antigens, specifically histidine-rich protein 2 (HRP-2), *Plasmodium* lactate dehydrogenase (pLDH), or aldolase. RDTs may remain positive for up to two weeks or more after clearance of parasitemia (particularly those RDTs based on the HRP-2 antigen) and are not designed for determining the density of parasitemia, which is used for monitoring response to treatment. Also, RDTs are less sensitive for non-falciparum malaria species.

Consistent with WHO recommendations, PMI has prioritized scaling up diagnostic testing for malaria with both microscopy and RDTs in all focus countries with the goals that all persons with suspected malaria are tested and only those with a positive test are treated for malaria. This requires that quality-assured diagnostic testing for malaria be available at all levels of the health care system, including at the community level, at all times. In most countries, microscopy is only available at hospital level and at larger health centers. In contrast, RDTs are being used at all levels. Each country must decide which of these two tests should be used at which points-of-care and for what indications. Microscopy, though, should be available in settings where severe malaria patients are treated (i.e., referral facilities). In contrast, RDTs would be the best option in settings where a laboratory is not available (e.g., at the community level).

Case Management

Treatment of uncomplicated malaria

PMI supports WHO revised guidance recommending that patients with parasitologically confirmed malaria (or suspected malaria, if diagnostic testing is not available) should be categorized as having either uncomplicated or severe disease for the purposes of prescribing treatment. Uncomplicated malaria is defined as symptomatic malaria without signs of severity or evidence of vital organ dysfunction (see severe malaria below).

For uncomplicated malaria, WHO recommends ACTs as the first-line treatment of choice.[104] ACTs partner an artemisinin drug (e.g., artesunate, artemether, dihydroartemisinin) with a second antimalarial that has a longer half-life. Artemisinins rapidly reduce parasite density in the blood and control fever. Side effects are uncommon, and serious or life-threatening adverse drug reactions are exceedingly rare. When combined with a second antimalarial, such as mefloquine, SP, amodiaquine, lumefantrine, or piperaquine, a 3-day course is usually curative. Monotherapy with artemisinin compounds is not recommended by WHO or PMI, except for initial or pre-referral treatments of severe malaria with non-oral (i.e., intravenous or intramuscular, or rectal if pre-referral) artesunate, which is followed by a full course of ACT.

Five ACTs are recommended by WHO as first-line treatment of uncomplicated malaria:

1. Artemether-lumefantrine
2. Artesunate-amodiaquine
3. SP-artesunate
4. Mefloquine-artesunate
5. Dihydroartemisinin-piperaquine

The determination of the recommended first-line ACT should be based on the known therapeutic efficacy in the respective country. In areas where either amodiaquine or SP has been used extensively as monotherapy leading to the development of resistance to these drugs, combinations of either drug with artesunate may not be ideal choices for first-line treatment. Mefloquine-artesunate is recommended only for areas of multi-drug resistance (i.e., parts of Southeast Asia and South America). Other ACTs such as artemether-lumefantrine and artesunate-amodiaquine are generally better tolerated and are available in sub-Saharan Africa. As mentioned before, oral monotherapy, including with artemisinin drugs, is not recommended because of the likelihood of promoting the spread and intensification of drug resistance and has been banned by many countries.

[104] http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf?ua=1&ua=1

Treatment of severe malaria

Severe malaria is characterized by fever plus one or more of the following symptoms or findings: prostration, impaired consciousness or coma, multiple convulsions (more than two within 24 hours), circulatory shock, pulmonary edema, acute respiratory distress syndrome, abnormal bleeding, jaundice, severe anemia, acute renal failure, disseminated intravascular coagulation, acidosis, hemoglobinuria, hypoglycemia, hyperlactatemia, and/or parasitemia greater than 5%.

Severe malaria is a medical emergency and should be managed with the immediate initiation of appropriate parenteral treatment. Based on evidence from a large, multi-center, randomized trial, WHO modified their treatment guidelines for severe malaria in 2011 **to recommend parenteral artesunate as the first-line treatment in children and adults, including pregnant women in all trimesters; if parenteral artesunate or artemether is not readily available, parenteral quinine should be used**.[105] Management of patients with severe malaria also includes ancillary treatments to deal with complications, which could include intravenous hydration without a bolus, transfusion, and glucose supplementation.

In response to a few published case reports and case series of delayed hemolytic anemia following treatment with parenteral (i.e., intravenous and intramuscular) artesunate,[106] [107] [108] some of which required blood transfusions, an expert meeting was convened by Medicines for Malaria Venture and WHO in March 2013 to review the evidence. The conclusion was that the benefits of parenteral artesunate far outweigh the risks, including delayed hemolytic anemia,[109,110] and WHO continues to recommend parenteral artesunate for the treatment of severe malaria. Patients initiating parenteral treatment can be switched to a full-course of oral ACTs after 24 hours if parasitemia density is <1% and the patient is able to tolerate oral therapy.

PMI strongly recommends supporting the training of clinicians to counsel patients who receive parenteral artesunate on the potential side effects at a minimum and the preference for patient follow-up visits within 30 days of completing treatment. Notably, WHO's *Management of*

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[105] Arjen M Dondorp et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. The Lancet. Volume 376, Issue 9753, 13e 376, Issue 9753w.sciencedirect.7.

[106] Zoller T, Junghanss T, Kapaun A, et al. Intravenous artesunate for severe malaria in travelers, Europe. Emerg Infect Dis 2011;17:771–7.

[107] Kreeftmeijer-Vegter AR, van Genderen PJ, Visser LG, et al. Treatment outcome of intravenous artesunate in patients with severe malaria in the Netherlands and Belgium. Malar J 2012;11:102.

[108] Rolling T, Schmiedel S, Wichmann D, et al. Post-treatment haemolysis in severe imported malaria after intravenous artesunate: case report of three patients with hyperparasitaemia. Malar J 2012;11:169.

[109] Jauréguiberry S, Ndour PA, Roussel C, et al. Postartesunate delayed hemolysis is a predictable event related to the livesaving effect of artemisinins. Blood 2014;124:167–75.

[110] Paczkowski MM, Landman KL, Arguin PM; CDC. Update on cases of delayed hemolysis after parenteral aretesunate therapy for malaria - United Sates, 2008 and 2013. MMWR Morb Mortal Wkly Rep. 2014 Aug 29:63(34):753-5.

Severe Malaria - A practical Handbook recommends follow-up to monitor hemoglobin recovery on days 7, 14, and 28 after discharge for treatment of severe malaria.[111] Although this may be difficult for recovering patients living in rural locations where hemoglobin cannot be monitored, clinical signs of anemia and general status can be monitored instead.

In addition, WHO recommends that pharmacovigilance systems be strengthened as part of the overall effort to monitor the use of parenteral artesunate. Although PMI welcomes the efforts of WHO and other partners to strengthen these systems, PMI does not prioritize support for pharmacovigilance activities because of the number of other groups already working on these efforts and the well-established safety of ACTs.

WHO-prequalified parenteral artesunate

Currently, there is one WHO-prequalified parenteral artesunate product (Guilin's IV artesunate), and it is significantly more costly than parenteral quinine. Therefore, decisions about when to procure the product, how to properly implement and scale up parenteral artesunate, logistics around a smooth transition from quinine to artesunate, and the respective use of these two severe disease treatments, must be carefully planned. Of the three WHO-prequalified parenteral artesunate preparations – 30 mg, 60 mg, and 120 mg vials – **only the 60 mg formulation is currently available from the manufacturer for procurement**. It is not known at this time when the two additional preparations will be available. Increased global demand has contributed to extremely lengthy lead times (up to 12 months or more). In addition, like other severe malaria treatments, dosing is weight-based, which has made the quantification of actual needs challenging. Finally, registration hurdles at the country level have further complicated the successful launch and roll-out. Because of these challenges, country teams are asked to reach out to the PMI Headquarters Case Management and PMI Headquarters Commodity Procurement and Supply Chain Teams early when considering procurement of injectable artesunate.

Severe malaria at peripheral/community level

Management of severe malaria cases at peripheral facilities and at community level, where facilities are not equipped to manage such cases, should focus on rapid referral to an appropriate health facility and provision of pre-referral treatment (administration of an antimalarial at a lower-level facility in order to reduce disease severity until the patient can receive parenteral therapy at a higher-level facility). In order of preference, intramuscular artesunate, artemether, or quinine are all options for pre-referral treatment. If intramuscular treatments are not available or if the provider is not capable of safely administering injections, rectal artesunate is recommended as pre-referral treatment in children under six years of age.[112] Rectal artesunate is currently being

[111] Management of severe malaria: a practical handbook, 3rd edition. (http://www.who.int/malaria/publications/atoz/9789241548526/en/)
[112] Guidelines for the treatment of malaria: 3rd edition. WHO 2015 (http://www.who.int/malaria/publications/atoz/9789241549127/en/)

rolled out in a number of PMI-supported countries. As more information from these rollouts becomes available, lessons from the field will be shared. Some challenges have already been anticipated and realized, including difficulties in ensuring the completion of referral. Lack of follow up to the referred level of care can result in the return of severe disease and, in some cases, death. Therefore, the importance of completing timely referral following initial treatment should be strongly emphasized during training of health care workers and in communication with patients. In addition, the message that pre-referral treatment alone is not a substitute for management of severe malaria at a referral center should be included in the counselling by health worker and SBCC materials.

Treatment of malaria in pregnancy

Malaria infection in pregnant women is associated with high risks of spontaneous abortion, stillbirth, premature delivery, low-birth weight, congenital infection, and/or neonatal death. In high-transmission areas, malaria parasitemia in a pregnant woman is usually asymptomatic. Treatment of pregnant women also has challenges because some malaria drugs carry a risk of teratogenicity during the first trimester of pregnancy. Because women may not know or declare their pregnancy status during the first trimester, all women of child-bearing age should be asked about the possibility of being pregnant before treatment is started.

For uncomplicated malaria diagnosed in a pregnant woman during her first trimester, oral quinine plus clindamycin or oral quinine monotherapy for seven days is recommended. A number of recent studies have indicated that ACTs in the first trimester do not present a cause of concern in terms of miscarriage or low birth weight outcomes. However, there is insufficient data to make a determination regarding other outcomes and thus WHO continues to recommend that ACTs should be given during the first trimester only if quinine is not available. Pregnant woman in their second or third trimester should be treated with the same first-line ACT as their non-pregnant counterparts. The use of primaquine or doxycycline/tetracycline is contraindicated during pregnancy.

WHO recommends parenteral artesunate as the first-line treatment for severe malaria in a pregnant woman during all trimesters, with parenteral quinine as an alternative, because the benefits of parenteral artesunate in preventing maternal deaths far outweighs any potential teratogenic effects of use during the first trimester.

A job aid for case management of malaria in pregnancy, developed with PMI partners, is available at http://reprolineplus.org/resources/treatment-uncomplicated-malaria-among-women-reproductive-age and can be adapted by countries for use. Further information can also be found in the **MIP** chapter.

Integrated Community Case Management

A number of studies have demonstrated that malaria diagnosis and treatment can be provided to children less than five years of age through community-based agents. WHO and UNICEF now recommend implementation of iCCM for sick children less than five years of age as an essential method for improving access to malaria diagnosis and treatment. The iCCM approach provides diagnosis and treatment of pneumonia, diarrhea, and malaria (including the use of RDTs) through community health workers or health extension workers using standard algorithms. Such iCCM programs also provide a platform for facilitating referral of severe illness, including use of pre-referral rectal artesunate.

Each PMI country must tailor its iCCM program to meet country needs which include decisions on location of CHWs, whether CHWs will be paid (salary/stipend or other compensation) or volunteer, and what age groups the CHWs will serve. Because access to adequate diagnosis and treatment may be difficult in many rural areas of sub-Saharan Africa, PMI encourages all focus countries to develop policies and support scaling-up of iCCM programs that include diagnosis with RDTs and treatment of malaria. Where possible, PMI strongly encourages the development of a systematic approach to the collection and processing of all testing and treatment data gathered through iCCM efforts. Data from iCCM efforts will strengthen malaria surveillance systems and complement the routine data collected from health facilities.

PMI funding for iCCM

PMI funding can be used to support integrated platform costs which include trainings; revising and/or printing training manuals, updated guidelines, and job aides; and integrated supervision visits. The 'integrated' piece of community case management means not just that the program aims to diagnosis and treat three main causes of childhood fever but that programming should be co-supported and co-funded by maternal and child health or community health partners.

PMI funding can only be used to procure malaria commodities, therefore funding for pneumonia and diarrhea medications must be provided by other sources. PMI does not support salaries, salary top-ups, or stipends (other than stipends associated with program costs such as training and associated travel); please review the section below called "**Incentives and Retention Strategies for CHWs**".

More information on iCCM, including information on training, iCCM indicators, and the latest research, can be found at: www.ccmcentral.org.

Diagnosis and Treatment in the Private Sector

In many PMI-supported countries, a large proportion of malaria cases are diagnosed and treated in the private sector. The private sector often includes non-profit and faith-based clinics and hospitals, for-profit facilities and providers, licensed retail outlets (including pharmacies and drug shops), and informal providers (both at fixed sites and mobile). Appropriate use of diagnostics and treatment in this sector has the potential for significant impact on malaria control and prevention.

PMI encourages all focus country teams to work with NMCPs to assess whether intervention in the private sector should be prioritized. The first step in such assessment is to clearly define which types of providers should be targeted. In most countries, non-profit and faith-based facilities already receive support and oversight from the MOH, essentially functioning like an extension of the public health system. Other private providers may or may not be overseen by Pharmacy Boards or drug regulatory authorities, depending on the country. Most commonly, the target of so-called private sector interventions are registered private, for-profit facilities and providers, and/or private retail outlets, but this will vary by country. Irrespective of which private sector partners are engaged, a system of accountability for commodity supplies, quality services, biosafety, and data reporting to assess effectiveness is critical to the success of such a program. In most cases, introducing such services into the private sector will require changes to regulations related to the performance of diagnostic testing, biosafety, and diagnostic and prescribing practices. Engaging in the private sector will also have implications for training and supervision that need to be budgeted for.

As in the public sector, PMI supports WHO guidance that all suspected malaria cases presenting at private sector outlets should undergo diagnostic testing with either RDTs or microscopy prior to receiving treatment. **PMI does not support private sector interventions that focus solely on providing malaria treatment in the absence of diagnostic testing.**

Many of the challenges with providing comprehensive malaria case management services in the public sector are amplified in the private sector. Ensuring that only high quality RDTs and ACTs are available may require better monitoring and enforcement by drug regulatory authorities, intervention with importers and wholesalers, and subsidies that reduce financial barriers to retailers and consumers. Structures may also be lacking to provide appropriate training and supervision of private providers, as well as case reporting and monitoring and evaluation of program effectiveness.

There may be opportunities, though, to partner with existing private sector structures, including pharmacy and/or medical societies or associations or common wholesalers or supply networks, to identify target providers. These groups may serve as platforms to support training and

supervision. Such networks also may play a central role in the supply of quality-assured commodities to private outlets.

Unlike the public sector, where diagnosis and treatment are often provided for free or at low cost, any private sector strategy must have a clear plan on appropriate pricing of diagnostic testing and treatment that takes into account the consumer's willingness to pay, the need of retailers and suppliers to make a reasonable profit, and the market prices of non-recommended treatments. The easy availability of alternative treatments for non-malaria fevers (e.g., antibiotics and antipyretics, such as paracetamol) must be considered, as it has been shown that inappropriate use of malaria treatment can be reduced if alternative treatments are available. **Commodities procured and donated by PMI (ACTs and RDTs) cannot be sold for profit. Therefore all PMI commodities must be provided free of charge to patients/beneficiaries.** Thus, when working with the private for-profit sector, teams are encouraged to seek support for procurement of RDTs and ACTs from other donors that provide subsidies and allow for sale of commodities, such as the Global Fund.

In addition, any private sector intervention must be accompanied by good training, supervision, and appropriate social and behavior change and communications activities. It should be recognized that, with the introduction of diagnostic testing, appropriate messaging becomes far more complex. Simply instructing consumers to seek treatment for fever is no longer sufficient. Rather, those with fever must be encouraged to get tested, to take treatment only if the test is positive, and to look for other causes of fever if they test negative. PMI is supporting a limited number of projects (e.g., Cambodia, Ethiopia, Nigeria) to gather more information and evidence on best practices for working with the private sector. The results of these projects will be disseminated once available.

Given these many complexities, countries are encouraged to seek the guidance of the PMI Headquarters Case Management Team early in the planning phase for such private sector interventions.

Surveillance of Antimalarial Drug Efficacy

In Southeast Asia, artemisinin resistance — which manifests as delayed clearance of parasitemia and is associated with mutations to the K-13 gene — has now been reported from multiple areas throughout the Greater Mekong Subregion.[113] Fortunately, there is no clinical evidence of similar resistance outside of the Mekong. For *P. vivax*, resistance to chloroquine is an increasing public health problem in Indonesia and Papua New Guinea. Cases of chloroquine-resistant *P. vivax* have been reported from other regions, but only in small numbers or sporadic cases.

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[113] Ashley EA et al. Spread of artemisinin resistance in Plasmodium falciparum malaria. *N Engl J Med.* 2014 Jul 31;371(5):411-23

PMI recommends that all focus countries/programs establish and maintain routine, periodic monitoring of the therapeutic efficacy of their first-line (and if possible, second-line) malaria treatment in line with WHO recommendations.[114] WHO recommends that the efficacy monitoring be conducted once every 24 months at four to eight sites per country. To help sustain the capacity of national testing teams, many NMCPs conduct such monitoring at half the sites one year and the other half the following year. The maximum cost to conduct such surveillance should be up to $75,000 per site per year, with the potential for exceptions based on justification. Second-line treatments can also be included in the testing. The WHO standard protocol is not designed for the evaluation of new or experimental medicines.

The purpose of antimalarial drug efficacy surveillance is to allow ministries of health to develop or update national treatment strategies and policies, and facilitate a timely change to a new first-line antimalarial, if necessary. PMI need not financially support the full cost of all *in vivo* studies, as many countries will have other sources of funding for these studies. In those cases, PMI can provide technical assistance when needed to ensure that these data are of high quality, and interpreted and used appropriately. To facilitate high quality data collection in therapeutic efficacy studies (TES) that are PMI-funded or not, PMI is piloting a quality assurance (QA)/quality control (QC) checklist and protocol for assuring high quality data collection. The PMI Headquarters team is currently working with country teams that have TES planned in FY 2016 to implement the pilot. The goal is a simple, rapid QA tool that can be implemented in TES across PMI-supported countries, and thereby assure some consistency of data quality across countries.

PMI should work with NMCPs to ensure the sharing of drug efficacy data with WHO, RBM, and international consortia focusing on antimalarial drug resistance.

Monitoring Molecular Markers of Artemisinin Resistance

Introduction

Recent studies have identified[115] and validated[12] a strong association between prolonged parasite clearance and point mutations in the propeller region of the *P. falciparum* kelch protein on chromosome 13 (K13). Although several distinct point mutations in the K13 propeller region have been detected in African parasites, they have not been associated with prolonged clearance or treatment failures.

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[114] http://whqlibdoc.who.int/publications/2009/9789241597531_eng.pdf
[115] Ariey F et al. A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria. 2014. *Nature*. 505(7481):50-5.

The PMI Antimalarial Resistance Monitoring in Africa (PARMA) Network has been established to determine when artemisinin resistance-conferring mutations in the K13 gene arise or appear in Africa. Activities of the network will supplement countries' routine drug efficacy monitoring efforts by characterizing molecular markers that may help to improve surveillance. Sample collection will begin in FY 2015 in a subset of countries with broader rollout continuing into FY 2016. Expenses related to the additional cost associated with this effort, such as cost of international shipment and K13 testing itself, will be covered by headquarters. There should not be a significant increase in workload for countries, as samples will be collected concomitantly with already scheduled TES blood draws. Guidance will be updated on an annual basis as more information on resistance markers becomes available. In the meantime, the PMI Headquarters PARMA Team will work with individual RAs to assess the current status of in-country efficacy testing and how best to utilize this additional resource.

Sampling framework

Because data on the presence or prevalence of K13 mutations cannot be interpreted without accompanying clinical phenotypes, PMI recommends that K13 testing be conducted **within the context of TESs**. Activities to genotype K13 outside the scope of TESs are considered operational research and require concept note and protocol approval by the OR working group. This pertains mostly to the Mekong region where extensive efforts for K13 monitoring are in place.

Dried blood spot samples for K13 genotyping will be collected on filter paper following the WHO protocol for sample collection for recrudescence/reinfection genotyping. Blood spots should be collected on day 0 and on every subsequent day of follow-up. Spots already being collected for testing recrudescence versus reinfection should provide sufficient material for both K13 and recrudescence/reinfection genotyping. Detailed protocols for collection, labelling, storage, and shipment of specimens are in place and can be shared with the relevant TES points of contact.

K13 genotyping methodology and analysis

Because there is a diversity of point mutations within the K13 propeller region and it is not yet known which point mutations may be relevant for artemisinin resistance, WHO and PMI recommend sequencing the entire propeller region of the kelch gene. This activity will be carried out by the molecular laboratory at the CDC Malaria Branch in Atlanta, or, in some cases, by laboratories in country that are already conducting K13 testing. All K13 data generated at the CDC laboratory will be analyzed and shared with in-country staff and partners, as well as with WHO and the Worldwide Antimalarial Resistance Network. The PMI Headquarters PARMA Team will work with field teams to ensure that protocols and transfer of samples conform to all U.S. and international ethical standards.

Forecasting, Procuring, Distributing, and Monitoring the Quality of Drugs and Diagnostics

Forecasting

Forecasting requirements for ACTs and RDTs must be done in tandem and informed by available country data. Although accurate consumption data is best used for this purpose, in many PMI-supported countries these data are not available or they are of poor quality. In such situations, forecasts can be developed using morbidity data. RBM, with the support of PMI, has detailed guidance on the quantification of ACTs and RDTs that should assist countries in developing more accurate estimates of country needs.[116, 117] Because many countries are now scaling up RDT use in peripheral health facilities and at the community level, it is critical to take into account the country's policies on diagnostic testing, in particular where and in what situations microscopy and/or RDTs are to be used, when quantifying these requirements. Refer to the **Commodity Procurement and Supply Chain Management** chapter for further information on quantification.

RDT selection

WHO, in collaboration with the Foundation for Innovative New Diagnostics (FIND) and CDC, has conducted five rounds of standardized product testing and prepared an information note on criteria for selecting appropriate tests.[118] In addition, an interactive web-based tool is available to assist countries in choosing RDTs based on preferred characteristics. As there are currently more than 200 different brands of RDT kits available on the market, the choice of the appropriate RDT test kit should be decided by each country based on their specific needs. These tests are relatively easy to use following only a few hours of appropriate, high-quality training, but ongoing supportive supervision is necessary. RDTs come in a number of formats, including strips, cards, and cassettes. In general, the cassette format has been demonstrated to be easier to use than other formats. Different RDT kits have different accessory components, including different blood handling devices, and somewhat different procedures (e.g., different numbers of drops of buffer, different incubation times). It is preferable to procure only one format of test in a country to reduce confusion and the need to re-train health workers in multiple formats. In general, the shelf-life of RDTs is approximately 24 months from the date of manufacture. If more than one RDT brand with different characteristics is used in a country, it is important that adequate

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[116] Good practices for selecting and procuring rapid diagnostic tests for malaria: http://www.who.int/malaria/publications/atoz/9789241501125/en/index.html

[117] Manual for quantification of malaria commodities: Rapid diagnostic tests and Artemisinin-based combination therapy for first-line treatment of *Plasmodium falciparum* malaria http://www.msh.org/projects/sps/SPS-Documents/loader.cfm?csModule=security/getfile&pageid=61711

[118] Information note on recommended selection criteria for procurement of malaria rapid diagnostic tests (RDTs): http://www.who.int/malaria/diagnosis_treatment/diagnosis/RDT_selection_criteria.pdf

information is provided to health workers about how the tests differ. Where relevant, PMI RAs and country teams should work closely with the NMCP and other donors to harmonize procurement and avoid potential implementation problems with multiple RDT brands.

All RDTs procured by PMI undergo pre-shipment lot testing to assess their quality prior to delivery. Extensive experience from multiple countries and results from lot testing indicate that RDTs are much more stable to temperature and humidity than originally thought. PMI has rarely identified RDTs of poor quality before or after distribution. For information on post-deployment lot testing, please see Priority Area #4 below ("Quality assurance of diagnostic testing"). Recently, reports have been received on nine different kits from three manufacturers with individual buffer ampules whose fluid had dried out. All of these kits were individual kit formats (i.e., the test strip, buffer and testing accessories were individually packaged as opposed to bulk preparations). Although new plastics have been tested to prevent drying out of buffer in individual ampules, problems have remained. Therefore, PMI will not procure individual test kits until this problem has been fully addressed and WHO approves their use.

It is important to provide training and capacity building among healthcare practitioners and staff to collect an appropriate blood sample, conduct the test, and be able to identify tests with problems that affect performance. RDTs are not designed to determine the density of parasitemia, which is required for monitoring the response to treatment for severe malaria. As with microscopy, testing also produces biohazardous waste that must be properly disposed in accordance with national guidelines. For information on temperature monitoring to ensure RDT stability, please see Priority Area #4 below.

Multi-species and multi-antigen tests

Some NMCPs in PMI-supported countries have indicated an interest in procuring RDTs that detect both *P. falciparum* and other Plasmodium species, so-called multi-species RDTs. Many of these RDTs have been shown to accurately detect both *P. falciparum* and *P. vivax* and are recommended by WHO for use in "Zone 2" countries with significant falciparum and vivax malaria, including Ethiopia, Madagascar, and the Greater Mekong Subregion.[15] The remaining PMI-supported countries are classified as "Zone 1" (*P. falciparum*-predominant), where WHO recommends that single-species tests be used. A growing number of Zone 1 countries have requested that PMI procure multi-species RDTs, with a rationale that NMCPs also want the capacity to diagnose non-falciparum species (which in such settings would be largely *P. malariae*). However, a limited number of studies have shown that the accuracy of RDTs to detect *P. malariae* is rather poor, which is at least partly explained by the very low parasite density of most *P. malariae* infections.

Beyond the technical aspects on which WHO bases these recommendations, there also are programmatic considerations that further strengthen this guidance. Single species RDTs are

simpler to interpret (as there is only one test line and one control line) and they are less costly. The unit cost of multi-species RDTs is up to 30% greater than single-species RDTs.
Based on the WHO guidance, reviewing species prevalence data from selected countries, and assessing the cost implications of procuring single vs. multi-species RDTs, **PMI no longer supports procuring multi-species RDTs in countries that WHO classifies as Zone 1 (*P. falciparum*-predominant)**. **All PMI-supported countries in Africa (with the exception of Madagascar and Ethiopia) should be procuring single-species *P. falciparum* RDTs.** This decision is based on the following considerations:

- WHO guidance, as outlined above
- The poor performance of RDTs at detecting *P. malariae* infection
- The availability in all countries of malaria microscopy that could be used in cases where non-falciparum infections are suspected
- Analysis of available data on species prevalence in selected countries, demonstrating that the relative prevalence of non-falciparum infections of less than 5% and that most *P. malariae* infections are detected in patients with concurrent *P. falciparum* infection (further noting that mixed Pf/Pm infections are treated with ACTs, exactly as one would treat Pf-only infection)
- The significant cost savings from procuring single-species RDTs, rather than multi-species tests, which could be used to increase the number of RDTs procured or to direct to other priorities, as determined by each PMI country team

Exceptions to this guidance will be granted if credible evidence can be provided to PMI leadership that demonstrates ongoing local transmission of *P. vivax* infections of significant prevalence (at least 5% relative prevalence).

Single-species tests that detect two *P. falciparum* antigens (HRP2 and LDH) are now available. These tests are difficult to interpret in the case of conflicting results and do not provide a diagnostic advantage in detecting symptomatic malaria. **Therefore, PMI will not procure multi-antigen RDTs for *P. falciparum*.**

Quality monitoring of drugs

Quality monitoring of drugs available in public and private sector outlets has been supported by PMI in many focus countries. These programs monitor the quality and availability of antimalarial drugs using tools such as market surveys and mystery shopper assessments. PMI, through its implementing partners, collects readily available public and private sector antimalarial products and sends them for quantitative analysis at qualified laboratories to determine content and quality. Drug registration processes also are evaluated. These activities help national drug regulatory authorities on multiple levels, including improving and strengthening technical capacity and overall quality assurance.

In more rural settings, semi-quantitative mobile devices are sometimes used, including pilot activities with the U.S. FDA to help evaluate hand held anti-counterfeiting devices. Recently evaluated in Ghana, the CD3 handheld counterfeit detecting device from the US FDA demonstrated its effectiveness to detect counterfeited products in a field setting. When compared to other known mobile technologies (e.g., Mini-lab, hand held Raman devices), it showed comparable, but not superior, results, but unlike the Mini-lab, CD3 requires a more sophisticated infrastructure in terms of technologic and human resources capacity. Use of the CD3 requires significant support from malaria control programs and regulatory authorities, coordinated training and follow-up supervision to ensure appropriate use, etc. Therefore, use of the CD3 device as part of more comprehensive anti-counterfeiting programs and an overall QA/QC strategy may be considered alongside technologies like the Mini-lab, but only in the context of the specific country setting. **One-time or inconsistent investments in these activities is not recommended.** PMI strives to strengthen existing quality control measures, thereby helping develop more robust quality assurance programs overall. When part of a larger strategic plan and longer-term strategy where the primary objective is to build a robust national-level quality assurance program, country teams are encouraged to invest in drug quality monitoring programs and should take into consideration, information from various PMI or USAID Global Health tools, such as the Pharmaceutical management system strengthening tool, data from end-use verification surveys, and supply and logistics internal control evaluation tool (if available).

For more information on drug quality, please refer to the **Commodity Procurement and Supply Chain Management** chapter.

Pharmacovigilance

Pharmacovigilance activities aim to detect, assess, understand, and prevent adverse effects of medications, which are different from known, expected side effects identified in human subjects during the clinical trial evaluation of the drug. ACTs have already been extensively evaluated for side effects through large clinical trials. Experiences to date demonstrate that adverse reactions to the use of ACTs are infrequent and rarely severe (although sparse data are available from HIV-infected patients receiving antiretroviral medications). A global ACT pharmacovigilance network and a global registry for ACT-exposed pregnant women are being supported by the Bill and Melinda Gates Foundation. **For these reasons, PMI typically does not prioritize PMI funding support for pharmacovigilance programs for ACTs.**

Priority Areas for PMI Support

A successful malaria case management program consists of several distinct, but interrelated activities that should be implemented in concert.

1. **Appropriate policies and guidelines**: WHO has published detailed guidance for laboratory procedures for malaria diagnosis and on the programmatic elements of a malaria diagnostics program, which should assist the development of national policies and guidelines.[119, 120, 121] These documents also provide specific guidance on the type of test (microscopy or RDT) that is appropriate at different levels of care, how to select an appropriate RDT for specific epidemiologic contexts, and which RDT kits are recommended for use.

   Policies and guidelines on the clinical management of fever and malaria should be periodically reviewed, revised, and harmonized with WHO recommendations[122] and other relevant clinical policies and guidelines (e.g., integrated management of childhood illness guidelines). These policies and guidelines should provide specific recommendations on when a diagnostic test is indicated and how the results of testing should guide treatment decisions. If diagnostic testing is to be carried out by non-laboratory personnel or volunteers, clinical guidelines should incorporate or reference standard operating procedures and job aides on performing the test and guidance on handling and disposal of blood and biohazardous materials.

   Policies on drug treatment for malaria should periodically be reviewed to ensure they are in line with WHO recommendations. They also should be informed by the results of the latest therapeutic efficacy studies and other relevant investigations (e.g., acceptability studies). In particular, policies regarding treatment of severe malaria should be aligned with the updated recommendations issued by WHO in April 2011.[123] In countries with co-endemic vivax malaria, treatment strategies should be species-specific for the treatment of uncomplicated malaria and for malaria in pregnant women with a strategy for preventing relapses. Such guidance should clearly articulate when treatment is to be provided, at what level of care, what facilities and supportive services are required, and

[119] WHO Malaria Diagnosis website: http://www.who.int/malaria/areas/diagnosis/en/
[120] Universal Access To Malaria Diagnostic Testing: An operational manual 2011: http://www.who.int/malaria/publications/atoz/9789241502092/en/index.html
[121] Malaria Rapid Diagnostic Test Performance- Results of WHO product testing of malaria RDTs: Round 3 (2010-2011): http://www.who.int/malaria/publications/atoz/9789241502566/en/
[122] Malaria case management: operations manual: http://www.who.int/malaria/publications/atoz/9789241598088/en/index.html
[123] Guidelines for the treatment of malaria, 2nd edition – Rev. 1 (Updated guidance on severe disease management) http://www.who.int/malaria/publications/atoz/mal_treatchild_revised.pdf

when referral is indicated. Policies and guidelines also should clearly articulate what is and what is not permissible for both diagnosis and treatment at community level and in the private sector and the qualifications and training required for CHWs and private providers.

Regulations and/or laws governing who is permitted to perform a diagnostic test and dispense antimalarial drugs and antibiotics may need adjustments. For example, the task of performing RDTs in health facilities may be shifted to hospital or clinic assistants who may not be authorized or trained to conduct these tests. In the private sector, the most common sources of malaria treatment may be drug dispensers, who may be restricted from performing diagnostic tests or dispensing drugs without a prescription. In some countries, this may require changes in legislation.

2. **Training and supervision of laboratory staff:** In most countries, training and supervision of laboratory personnel will be delivered as an integrated package. It is the responsibility of the NMCP, the National Reference Laboratory, and/or the Laboratory Department of the MOH to ensure that training materials reflect the current state-of-the-art, that the trainers and supervisors have the appropriate level of skill in the performance of malaria microscopy and RDTs, and that supervisory checklists and laboratory records collect all necessary information, including any data required for appropriate monitoring.

   PMI can play a critical role in providing technical assistance to these efforts. Capacity also should be available to conduct refresher training in both RDTs and microscopy when supervision identifies deficiencies in health worker performance of the test. Training and supervision materials, standard operating procedures (SOPs), and bench aids developed by PMI through the IMaD Project (http://www.mcdinternational.org/training.html) which can be tailored to country context, are available in English, French and Portuguese upon request from PMI headquarters. The CDC malaria diagnostics bench aids and SOPs are available on the CDC DPDx website (http://dpd.cdc.gov/dpdx/Default.htm). In addition, a CDC-developed malaria microscopy training CD-ROM (in English) can be obtained from WHO Global Malaria Programme at:
   http://www.who.int/malaria/areas/diagnosis/microscopy_cd_rom/en/

3. **Training and supervision of clinical staff:** Training curricula for clinicians and community health workers should be periodically revised to align with the country's most updated malaria case management policies and guidelines, including integrated management of childhood illness (IMCI) guidelines. Whenever feasible, clinical training on malaria case management should be incorporated into training on the management of childhood illness. In addition, experience suggests that coordinated training of clinical and laboratory staff, in those facilities with laboratories, improves clinicians' understanding and interpretation of the results of diagnostic testing. After training,

periodic supportive supervision of clinicians and community health workers will be required. When possible, such supervision should be built into existing functional supervisory mechanisms, be guided by structured checklists, and focus on real-time problem-solving. Generic training and supervision materials and checklists for facility-based clinicians are available upon request from PMI headquarters staff. A tool kit for iCCM is available on the CCM Central website (www.ccmcentral.org).

4. **Quality assurance (QA) of diagnostic testing:** Development of a QA system is an essential component of a comprehensive diagnostics program. WHO has developed detailed guidelines on quality control of malaria microscopy,[124] which involves collection of a subset of slides from clinical specimens and re-examination of those slides by expert microscopists, which depending on country situation can be performed during a supervision visit or in a national, regional, or district reference laboratory. PMI supports the development or purchase of validated malaria reference slide sets with known species and parasitemia density that can be used for training and quality assurance. On average, the development of a national archive of malaria microscopy slides costs $100,000, including costs associated with seeking ethical approvals, training, sample collection, validation, and supplies. Because multiple slides are produced during the activity, providing a wide and redundant range of parasitemia and species combinations (as applicable), this is largely a one-time expenditure for countries. The PMI central supply chain partner procures RDTs that are lot-tested by WHO/FIND before they are distributed in country. For RDTs not procured by PMI, lot testing is available free-of-charge from WHO/FIND. Instructions on how to submit RDTs for lot testing can be found on the FIND website (www.finddiagnostics.org).

   At this time, methods for quality control of RDTs at the point of service are somewhat limited. Facility- and community-level QA/QC should include, at a minimum, regular supervision at least every six months with observation of healthcare workers' performance of RDTs using a standardized checklist. Laminated cards with pictures of positive, negative, and invalid RDT results also have been used to test health workers' skill at interpreting test results. Positive control wells (PCWs) with positive control antigens that enable end-users to determine whether the RDT kit they are using is performing properly are now available from a limited number of manufacturers for a limited set of products. WHO is in the process of developing guidance on how these PCWs should be used and by whom. Further guidance on the appropriate piloting/use of PCWs will be issued once they are available for procurement and will likely only be in place prior to FY 2018 MOP planning.

[124] Malaria microscopy quality assurance manual - version 1: http://www.who.int/malaria/publications/atoz/mmicroscopy_qam/en/index.html

Post-deployment monitoring of RDT kit performance can be conducted in cases where poor storage conditions are known or suspected to be poor. In PMI's experience, RDTs have remained stable even at high temperatures and humidity, and post-deployment tests are only rarely warranted. In these cases, testing should be performed no sooner than 12 months post-deployment. Samples of test kits should be sent to WHO-approved laboratories for further lot testing and will be done at no cost beyond the cost of shipping the test kits. WHO and PMI do not recommend routinely comparing microscopy to RDT performance, as they measure different evidence of infection (RDTs detect antigen, microscopy detects actual parasites). Such a comparative assessment, though, may be useful as a first step in an investigation of suspected poor quality RDTs.

WHO is currently updating its guidelines for QA of malaria microscopy, which should be published in early 2016. Following the publication of this document, WHO will be developing a guidance on QA of RDTs. Revised guidance on quality monitoring of RDTs at the point of care are expected to be included in this guidance. PMI will disseminate updated guidelines as soon as they are available.

RDTs require proper transport and storage to avoid damage that may be caused by extreme heat and humidity. USAID's Central Malaria Commodities Procurement and Supply Chain Project has published a guide on the transport and storage of RDTs.[125] This document includes guidance on how to maintain and monitor adequate storage temperatures (usually below 30°C) in storage and health facilities.

5. **Equipment and supplies:** For microscopy, lists of necessary supplies and specifications for microscopes are widely available through WHO, CDC, and from PMI headquarters upon request. The choice of RDT will be made by each NMCP, based on their specific needs, and should be informed by the WHO-FIND RDT product testing program and the most recent version of the Information note on criteria for RDT selection.[17]

   For both RDTs and microscopy, it is essential that proper supplies for blood sampling and for the safe disposal of biohazardous materials – including latex gloves, sharps boxes, and cleaning materials – are also available wherever testing is done. In addition, supplies for maintaining and monitoring proper storage temperature, such as thermometers, may be needed. In most countries, procurement of laboratory supplies is handled by the same authorities that handle pharmaceuticals. In others, the central laboratory or individual regional or district authorities may handle procurement and/or

[125] Transporting, storing, and handling malaria rapid diagnostic tests at central and peripheral storage facilities: http://deliver.jsi.com/dlvr_content/resources/allpubs/guidelines/TranStorRDT_Central.pdf

distribution. In many cases, local quality-assured sources of these supplies may be procured more quickly and at lower cost than through the PMI central supply chain partner.

Correct quantification of requirements for ACTs, RDTs, and laboratory supplies has been a significant challenge in all PMI-supported countries because of the lack of complete and accurate consumption data for these products. See the "Forecasting, Procuring, Distributing, and Monitoring the Quality of Drugs and Diagnostics" section above for further information on quantification tools. Support already is provided to all PMI-supported for improving the capacities of the NMCPs and other key stakeholders in the quantification of requirements for these commodities. PMI Headquarters is currently working with key implementing partners (including the central malaria commodities procurement and supply chain partner and SIAPS) to support the roll-out of this updated guidance on ACT and RDT quantification. Guidance on quantification can be found in the **Commodity Procurement and Supply Chain Management** chapter.

6. **Communications and behavior change:** Historically in sub-Saharan Africa, almost everyone who presented to a health facility with fever was treated for malaria and mothers were encouraged to seek malaria treatment whenever their child had a febrile illness. Scale-up of diagnostic testing, therefore, poses a major communications and behavior change challenge, particularly for health workers but also for caretakers of sick children who have a negative test and do not receive treatment for malaria. Diagnostic testing must be closely linked with communications and behavior change activities focused on changing the expectations and practices of patients and caregivers. In addition, the availability of poor quality, counterfeit, and inappropriate drugs (including artemisinin monotherapy and older treatments, such as chloroquine) requires that behavior change and communications messages and activities also focus on promoting use and adherence to recommended quality-assured ACTs.

7. **Incentives and Retention Strategies for CHWs:** This remains a controversial area, although there is a growing consensus that some incentives are needed to retain CHWs. Incentives can range from needed supplies and equipment, such as flashlights, bicycles, and funds for travel, to stipends or salaries. Each country will decide, based on all relevant factors, what is the best approach for their community workers. There is a growing body of experience in a number of countries with the use of various types of incentives. In general, PMI does not provide support for monetary incentives for CHWs beyond reimbursement of travel or other expenses. Support for other incentives (e.g., bicycles, flashlights, etc.) may be appropriate in some situations and settings.

Frequently Asked Questions for Diagnostic Testing

Q1. What can be done to improve the accuracy of malaria diagnosis?

A. For both RDTs and microscopy, a QA system should be established to monitor accuracy of test performance. The QA system should include, but not be limited to, appropriate training, regular supervision to monitor adherence to standard operating procedures and test performance, and proficiency testing. Procurement of quality tests, supplies and reagents, and storage temperature monitoring should be part of a comprehensive QA system.

Q2. Are RDTs cost effective for case management?

A. Yes. Most RDTs cost between $0.40 and $0.60 per test, which is less than the cost of a pediatric dose of ACT. Studies have demonstrated that the use of RDTs is comparable, equal to, or more cost-effective than treating all persons with fever, particularly in settings where malaria burden is decreasing because of the success of other control interventions. However, cost-effectiveness should not be the only consideration for the introduction of RDTs in moderate- to high- prevalence settings. The improvements in malaria surveillance, appropriate diagnosis and treatment of individual patients, and the related reduction in drug pressure on antimalarials (which may slow the spread of drug resistance) are equally important reasons for use of RDTs in those settings.

Q3. How can countries encourage the use of diagnostic test results for treatment decisions?

A. With both RDTs and malaria microscopy, several studies have demonstrated that clinicians may not always accept negative test results when those results do not agree with their clinical impression of the cause of a patient's illness. Recent evaluations, though, demonstrate that good training, supervision, and the use of job aids, plus training and equipping providers to manage non-malaria fevers, improves health workers' adherence to the test results. Implementation of a strong quality assurance plan also improves clinician acceptance and use of test results. Interestingly, CHWs tend to adhere to test results much more frequently than higher-level health workers. This is probably because CHWs training and supervision is heavily focused on adherence to established case management algorithms.

Q4. For countries with co-endemic *P. vivax,* how and when should one test for glucose-6-phosphate dehydrogenase deficiency?

A. Glucose-6-phosphate dehydrogenase (G6PD) deficiency, an X-linked disorder, is the most common enzymatic disorder of red blood cells in humans, affecting more than 400 million people worldwide. The prevalence of G6PD mutations is highest in populations residing in regions that are historically malaria endemic. Individuals with severe G6PD deficiency cannot

tolerate the oxidative stress caused by 8-aminoquinoline drugs, such as primaquine, and tafenoquine. Prior to primaquine administration, which is currently the only drug available for radical cure of *P. vivax* hypnozoites, patients need to undergo G6PD testing.

In most clinical settings, including the United States, a qualitative method (most often the fluorescent spot test), is used to guide primaquine administration, but requires additional equipment and training and is not suitable for point-of-care use. Two products are currently marketed for point-of-care use, BinaxNOW® G6PD and the CareStart™ G6PD deficiency screening test. The BinaxNow G6PD test is U.S. FDA approved, but has not been used widely due to its requirement for venous blood collection, strict temperature range of 18ºC to 25ºC, and high cost of around $25 per test. The CareStart G6PD deficiency screening test is a qualitative enzyme chromatographic test where a color change to purple denotes normal and no color change indicates deficiency. It should be noted that this test could not be used to guide tafenoquine therapy as a quantitative G6PD test is likely needed. The CareStart RDT, which uses blood from a finger prick, has been evaluated in Cambodia, Indonesia, and Haiti, and has shown test performance comparable to the fluorescent spot test in study settings. Further evaluations under more routine healthcare settings are required to help inform how this RDT may guide primaquine radical cure. PMI Cambodia is currently conducting one such OR study to assess the validity and feasibility of using the CareStart RDT at health facility and community level to guide primaquine administration for both *P. falciparum* transmission-blocking (single, low dose) and *P. vivax* radical cure. Results are expected in late 2016.

The CareStart RDT is marketed at $1.50 per test and comes in a box of 25 tests that has a shelf-life of 1 year. PMI procurement of this RDT is limited at this time by the lack of WHO pre-qualification or established QA procedures. Programs interested in incorporating G6PD testing into their vivax case management should consult the PMI Headquarters Case Management Tea and PMI Headquarters Commodity Procurement and Supply Chain Teams prior to implementation.

Q5. Should special measures be taken for malaria diagnosis in Ebola-affected countries?

A. One challenge posed by Ebola-virus disease (EVD) is its similar clinical presentation to malaria, as both initially manifest with fever, malaise, and body pain. Another challenge is its transmissibility, making patient care—including the collection of blood for malaria testing—a possibly dangerous undertaking. However, the importance of differentiating between these two diseases is crucial, as hospitalizing malaria-infected patients alongside those with EVD not only utilizes scarce resources and personnel, but also exposes malaria mono-infected patients to infection with the Ebola virus.

Case management of malaria in areas with active EVD includes a few changes to the normal approach:

- The use of enhanced personal protective equipment when performing any blood test: this includes double gloves, a face shield, and a disposable gown if the patient does not have vomiting, diarrhea, or bleeding; or double gloves, an impermeable gown, boots, head cover, and a face shield (goggles or medical mask also acceptable) if the patient has vomiting, diarrhea, or bleeding
- Administration of presumptive malaria treatment in patients with undifferentiated febrile disease and foregoing RDTs when the aforementioned personal protective equipment is not available or in rural settings where CHWs work

In order to harmonize approaches throughout the most affected regions, WHO developed guidelines for the malaria control in Ebola-affected countries.[126] In addition to diagnosis, the guidelines also address other malaria interventions applicable to EVD-affected areas, including mass drug administration and the distribution of ITNs.

Frequently Asked Questions for Malaria Treatment

Q1. What new drugs are expected to be introduced or are in the pipeline for the treatment of malaria?

A. **Artesunate-Pyronaridine** (AS-PYR): Developed under Medicines for Malaria Venture in partnership with Shin Poong Pharmaceutical Company, this drug combination was approved by the European Medicines Agency in February 2012 and added to the WHO prequalification list of approved medicines in May 2012. Marketed as Pyramax®, it is another fixed-dose combination, once-daily, three-day treatment regimen demonstrating efficacy against both *P. vivax* (blood stage only) and *P. falciparum*. AS-PYR is available in tablet form for dosing individuals 15 kg or greater (180 mg pyronaridine/60 mg artesunate), and in a granularized formulation for children weighing 5 kg to 14 kg (60 mg pyronaridine/20 mg artesunate). It is also expected to have a relatively longer shelf-life (i.e., greater than 24 months, which is the typical shelf-life for most ACTs). It is registered in Vietnam and Cambodia, in countries with areas of low malaria transmission where there is reported artemisinin resistance and diminished efficacy of other ACTs. A recently completed clinical trial of AS-PYR in Cambodia did not show high (<90%) efficacy and AS-PYR will not be considered as an option for case management in settings of ACT resistance.

[126] WHO Guidance on temporary malaria control measures in Ebola-affected countries, 2014 (http://apps.who.int/iris/bitstream/10665/141493/1/WHO_HTM_GMP_2014.10_eng.pdf)

Three other drugs are in the testing phase and are not yet ready for consideration for FY 2017 MOP planning:

- ***Tafenoquine*** *(Phase 3):* Tafenoquine, in development by Medicines for Malaria Vencture in partnership with GSK, is being investigated for the treatment and radical cure of *P. vivax* (relapsing) malaria. In December 2013, the U.S. FDA granted Breakthrough Therapy Designation for tafenoquine, a designation aimed at accelerating the development and review times of drugs for serious or life-threatening conditions. Phase III trials are underway. Medicines from the 8-aminoquinoline class, including tafenoquine and primaquine, are associated with hemolytic anemia in individuals with inherited glucose-6-phosphate dehydrogenase (G6PD) deficiency. See Q4 under the diagnostics FAQ for more information on point-of-care tests to identify individuals with G6PD deficiency and ensure well-tolerated and effective use of medicines for radical cure of patients infected with *P. vivax*.
- ***OZ439*** *(Phase 2)**:*** While OZ439, a fully synthetic peroxide drug, is thought to act against the parasite in the same way as the artemisinins, its structural properties and *in vitro* data suggest that OZ439 is effective against artemisinin resistant strains of malaria. Phase II trials have been successfully completed and Phase IIb combination trials with piperaquine and with ferroquine are underway. If successful, these combinations could be approved by a strict regulatory authority in 2016 or 2017.
- ***KAE609*** *(Phase 2):* KAE609 is a novel, synthetic antimalarial molecule belonging to the spiroindolone class, which has demonstrated an adequate pharmacokinetic and safety profile in humans. As a result, KAE609 was the first molecule with a novel mechanism of action to successfully complete Phase IIa studies for malaria in the last 20 years. Phase IIb combination trials are expected to begin soon.

Q2. What is the role of single, low-dose primaquine for *P. falciparum*?

A. Please see the **Pre-Elimination** chapter ("**Case Management**" section) for guidance on single, low-dose primaquine.

Health Systems Strengthening

New/Key Messages in the FY 2017 Technical Guidance

- Health Systems Strengthening is one of five strategic focus areas outlined in the *PMI Strategy 2015-2010*.
- Peace Corps and Field Epidemiology and Laboratory Training Program (FELTP) information should be included under this chapter.
- Clarified guidance for PMI support to strengthen capacity of NMCPs is now included.
- Inclusion of a table cross referencing HSS activities with technical areas is now required in the MOP.

Introduction

Building capacity and health systems is identified in the *PMI Strategy 2015-2020* as a core area of strategic focus, which states that successful country-owned and country-lead malaria control programs are only possible when country programs possess appropriately-skilled human resources and the necessary infrastructure to plan, implement, and monitor progress of their malaria control activities. Therefore, it is within PMI's mandate to build capacity to enable countries to implement their own programs rather than building parallel or stand-alone systems, including engaging communities to participate in malaria control, and addressing gaps in country health systems in the key areas of supply chain management, training and supervision of health workers, health financing systems, and monitoring and disease surveillance systems.

Investments in HSS from PMI have focused strongly on:

- Strengthening quantification methods and supply chains for drugs and other essential malaria commodities
- Expanding the availability of key health services by building networks of trained community health workers
- Improving the quality of facility based health services, including capacity for effective malaria diagnosis and treatment
- Improving the quality of clinical laboratory services
- Establishing and building skilled capacity for entomologic monitoring
- Streamlining and expanding routine health information systems to ensure collection, transmission, analysis, and dissemination of critical malaria indicators
- Strengthening the capacity of NMCPs and local government entities to plan and oversee malaria control activities

PMI's support for HSS is aligned with USAID's *Vision for Health Systems Strengthening 2015-2019*,[127] which is organized along the six priorities listed in the table below. Examples of PMI support that align with each HSS priority also are provided.

WHO Health Systems Strengthening Building Blocks[128]	USAID Vision for Health Systems Strengthening 2015-2019 (which is aligned closely with WHO HSS building blocks)	Examples of PMI Specific Support for HSS[129]
Health Services	Focus on access to effective, safe, and high quality public and private sector services by those who need them, when, and where they are needed, with maximum efficiency and patient choice.	• Training and supervision of health workers, including private sector providers • Support for CHW/iCCM programs • Strengthening of QA systems
Health Workforce	Focus on enabling partner countries to have technically competent, well-deployed health workforces that provide essential services in accordance with standards in a timely, patient-centered manner.	• Seconding staff to NMCPs to fill technical or managerial gaps (e.g., entomology, M&E) • Short-course training in program management for NMCP staff
Health Information	Support countries to collect, analyze, disseminate, and use timely and high quality health information.	• Strengthening HMIS and surveillance systems • Training in data for decision-making
Essential Medical Products, Vaccines, and Technologies	Promotes sustained access to and make appropriate use of essential medical products that are safe, effective, and of assured quality.	• Strengthening of commodity forecasting and supply chain systems • Drug quality monitoring

[127] For more information on the USAID Vision for Health Systems Strengthening 2015-2019, visit https://www.usaid.gov/what-we-do/global-health/health-systems/usaids-vision-health-systems-strengthening

[128] For more information about the WHO HSS Building Blocks, visit http://www.wpro.who.int/health_services/health_systems_framework/en/

[129] PMI will not support the following: the hiring of public sector staff; the topping up of government salaries; construction or major renovation of buildings; or contributions to sector-wide approaches (donor common basket funding).

Health Finance	Promotes countries to mobilize sufficient resources to pay for health needs, effectively pool resources to foster efficiency, and purchase packages of high quality, high impact services.	• Support for targeted efforts to incorporate malaria targets into performance-based financing and health insurance schemes.
Leadership and Governance	Invests in health governance in countries with significant barriers to the delivery of high quality and equitable health services to promote robust oversight, regulations, and accountability for health activities and health results in the public and private sectors.	• Strengthening national coordinating and regulatory bodies to direct and manage malaria resources, develop guidelines, and improve quality of services.

PMI funding can be utilized to support activities that contribute to the six HSS priorities, but such activities must directly address key barriers to achieving PMI goals and objectives. As with any proposed MOP activity, HSS activity descriptions should clearly describe the intended contribution to malaria control efforts. As with all intervention areas, HSS activities should be tailored to the specific country and operating context. Activities supported with PMI funding related to health financing must be directly related to an improvement in the countries' malaria control program strategy and goals, and must be integrated with other funding streams. Activities supported with PMI funding related to leadership and governance must be directly related to an improvement in the countries' malaria program.

Health systems strengthening activities that are specific to a particular technical/intervention area should be described in detail in the appropriate section of the MOP (i.e., within IRS, case management, etc.). Health systems strengthening related activities that are described in other technical areas should be briefly cross-referenced in this section within the HSS table provided in the FY 2017 MOP template.

In addition, there may be cross-cutting HSS activities, including health systems financing-related activities that will be described exclusively in the HSS section. For such activities, please describe in detail any health systems strengthening activities and capacity building activities that are not described in other sections of the MOP. These will include but are not limited to:

- Broad/cross-cutting activities aimed at integration with other health programs
- Promotion of partnerships to advance malaria control, such as PMI partnership in country with Peace Corps and private sector actors
- Training and capacity strengthening activities with NMCPs and other local government entities including Field Epidemiology and Laboratory Training Program (FELTP) activities

- Where applicable, PMI support for health finance activities that directly contributes to improvements in malaria outcomes
- Where applicable, PMI support for leadership and governance activities

Integration with Other Health Programs

Where possible, PMI should look for opportunities to integrate malaria activities with other USG-supported health and development programs in country. The *PMI Strategy 2015-2020* clearly articulates the importance of integration: "Whenever feasible and technically indicated, increase the level of integration of malaria activities with maternal and child health, HIV and AIDS, tuberculosis, neglected tropical disease activities, and the U.S. Government Global Health Security activities".

Support for integrated service delivery should be described in the appropriate section of the MOP; for example, a description of an iCCM program will be included under the case management section, but also referenced in the HSS section. The HSS section provides an opportunity to describe the benefits to the health system of PMI's integrated approach for a specific activity, as opposed to the PMI-specific goals to be achieved that will be described in the other appropriate technical section of the MOP. It is expected that many systems strengthening efforts, particularly those focused on health financing, leadership and governance, and work force management, will be integrated across several health elements. Integrated programs should benefit all groups involved through improved coordination, increased cost-effectiveness, reduction of management workload, leveraging of resources, etc., while ensuring or enhancing achievement of malaria control objectives. Integrated activities should also be in line with PMI's basic principles.

In proposing integrated activities, PMI should ensure that:

- Funding sources other than just PMI are contributing to the proposed integrated activity
- PMI implementing partners for these integrated activities have one or more staff members with expertise planning and implementing the malaria control interventions for which they are responsible
- Malaria-specific objectives and targets are included in the M&E plan for the activity and within the partner's overall project scope of work and annual work plans
- Partners are able to account for PMI funding and measure and report on PMI objectives and targets separately from other non-malaria activities
- PMI staff review and concur with annual work plans and participate in monitoring for these mechanisms

Promotion of Partnerships to Advance Malaria Control

Achieving PMI goals at the country-level can best be served by close partnerships with civil society organizations, including non-governmental organizations (NGOs), community-based organizations (CBOs), and faith-based organizations (FBOs), and private and public sector entities, including academic institutions. Non-governmental organizations have significantly contributed to PMI's successes to date and it is expected that they will continue to be strong partners in PMI efforts in the future. Partnership activities aimed at advancing malaria control objectives, including those that leverage public-private partnership, as well as those that link with education, agriculture, commerce etc., should be described or cross-referenced in the HSS section of the MOP**.** PMI-supported activities to promote partnership, such as capacity building of new partners or support for coordination of malaria partners (including PMI support for national malaria coordination committees) should be described in the HSS section of the MOP.

Peace Corps

Background

With over 3,000 Peace Corps Volunteers (PCVs) in Africa, the Peace Corps (PC) is well positioned to assist in the collective efforts of the USG to reduce the burden of malaria in sub-Saharan Africa. The Peace Corps labels their overall malaria program efforts across all of their endemic countries in Africa as their *Stomping Out Malaria in Africa Initiative* – in short, referred to as STOMP. In 2011, PMI teamed up with PC to harness its reach and capacity in the fight against malaria in countries in sub-Saharan African where PMI and PC have a common presence. Funding for this is provided via a USAID small provision assistance grant, which supplements the Peace Corps' own appropriations.

In countries where there is PC-PMI collaboration, the expectation is that activities will be part and parcel to the larger malaria control effort led by the NMCP and the PMI platform will be used for coordinating such collaboration. Consultation between staff from the PC and PMI should occur prior to beginning any activity that is not already part of the national strategy and will ensure that efforts are complementary and technically sound. Collaborative activities currently underway in 14 countries.

The PMI-PC collaboration includes two potential areas for PMI financial support funded through the MOP process: (1) funding for up to three PC Malaria Volunteers (MVs), and (2) funding to allow for malaria community projects funded through small grants with a maximum of $10,000 per year.

1. **Funding PC MVs**: PMI country teams planning to support 1 – 3 PC MVs should budget approximately $10,000 per malaria volunteer per year. There are two potential

mechanisms to support PC MVs: (a) the USAID-Peace Corps Interagency Agreement (SPA Agreement) managed by USAID/Washington, or (b) through a bilateral PMI implementing partner (appropriate when the PC MV's scope of work involves secondment to the implementing partner). The $10,000 covers housing, operational support (e.g., laptop computer), basic work supplies, work related travel, etc. Regardless of which mechanism is selected for PC MV support, the MOP should specify this support clearly in a line item in Table 2.

2. **Funding Malaria Community Projects through SPA Grants**: PMI country teams planning to make funding available for access by PCVs to support malaria community projects through a small grants process should budget $10,000 per year (assuming previous year's small grants pipeline has been spent down). The mechanism to support malaria community projects through small grants is the USAID-Peace Corps Interagency Agreement managed by USAID/Washington.

PCVs can access small grants through USAID Mission Program Office awards. PMI-funded malaria specific SPA projects range from less than $100 to $500. Funded activities typically include training or local community mobilization activities, such as a student song contest about malaria, painting a malaria mural at the health facility or school, Grass Roots Soccer games about malaria, etc. The PMI in-country team should participate in the application review and award process to ensure that proposed projects align with PMI and NMCP priorities. This will also enable the PMI team to follow the implementation of the projects and the use of these funds.

Additional information – PC Malaria Volunteers

Peace Corps Malaria Volunteers MVs are experienced PCVs either serving a third year in their initial country of assignment, or PC Response Volunteers (PCRVs) who have already completed their initial two years of service and who have applied for another short-term assignment. A PCRV usually completed their initial service in a different country from their response assignment and may or may not have contiguous timing with their initial service. Peace Corps MVs are expected to work closely with PMI in-country staff and the NMCP as well as, collaboratively with other malaria partners active in the country to support national malaria control efforts. Peace Corps MVs also play a coordination and mobilization role for malaria activities carried out by PCVs posted throughout the PC MV's country (including non-health sector PCVs).

The PMI-PC collaboration provides PMI and the NMCP with a network of volunteers experienced in community-level work, communities gain valuable malaria technical expertise, and the PC MVs and the larger network of PCVs working throughout the country acquire

valuable first-hand technical and operational skills. (See more at: http://stompoutmalaria.org/ and http://www.peacecorps.gov/learn/whatvol/malariaday/).

Examples of areas where PC MVs and/or PCVs have contributed include:

- Assisting with the organization and monitoring of bednet distribution campaigns at the district and community levels
- Helping PMI implementing partners with malaria interventions, such as preparing communities for indoor residual spraying or organizing and conducting training programs on community-based case management
- Designing and conducting SBCC interventions, including working with community groups and local organizations
- Advising communities on malaria surveillance and monitoring and evaluation, including analysis and mapping of malaria data
- Supporting the logistics and implementation of priority operations research projects
- Documenting and sharing operational and community-based best practices within and across countries

PMI's country level collaboration with PCVs must be aimed at building local capacity of host country counterparts. Peace Corps Volunteer presence in communities can extend the reach of NMCP and PMI staff and implementing partners. However, PMI funding should not be used to train PCVs to carry out malaria control work without a plan for how that training will be transferred to members of PCVs' local communities to carry out malaria activities after the volunteer is gone.

Training/country orientation

Peace Corps conducts a comprehensive ten day Malaria "Boot Camp" training in Senegal that provide MVs – those supported by PMI and those supported by PC directly - with a basic understanding of malaria disease, key program interventions, and how MVs/PCVs can support national strategies at a grassroots level. This training is organized and funded by PC, not by PMI funding. However PMI staff are routinely invited to participate in specific sessions of the training, either in person (Senegal-based PMI team members) or virtually (Headquarters-based PMI staff, including the U.S. Global Malaria Coordinator). The PMI in-country team is encouraged to collaborate with the NMCP and partners to coordinate country specific training for the new PC MVs to orient them, at minimum, to the NMCP Strategy, current status of malaria control nationally and sub-nationally, key country challenges, and priority activities.

Supervision, communication, and assessment

Peace Corps MVs work under the administrative supervision of the PC country office. PMI in-country staff, designated NMCP staff, and implementing partner staff should work together to identify the MV's day to day supervisor/mentor. If an implementing partner will be supervising a MV, then this responsibility should be indicated in the implementing partner's work plan. The MVs will develop their work plans with their supervisor, and ultimately seek PMI and PC approval of their work plan activities. During field trips, PMI in-country staff, in coordination with the PC country office, are also encouraged to visit MVs and other PCVs involved with malaria activities to provide opportunity for support, guidance, and mentorship. PMI staff and MVs should have at least quarterly updates, in-person or by phone, to ensure that volunteer activities are consistent with national guidelines, and that the MVs have the support and guidance they need.

Each MV will complete a report at the end of service that summarizes their accomplishments (e.g., malaria activities they supported, etc.) as they relate to supporting the NMCP/PMI's efforts. These reports should include indicators from the work plan and will be made widely available to the full PMI interagency team.

Pre-service and in-service training

In addition to working with the PC MVs, the PMI in-country team often participates in PC pre-service, in-service, and even close-of-service training (to provide career guidance). Generic training materials are available to be adapted to specific country needs.

Training and Capacity Strengthening of NMCPs and Other Local Government Entities

Capacity strengthening activities with national malaria control programs and other local government entities should be described in detail in the health systems strengthening section. Training activities for NMCP staff that do not appear within the technical interventions sections of the MOP, including FELTP, should also be included in the HSS section.

As a part of efforts to strengthen national capacity in malaria control, PMI will provide support to short-term training of NMCP permanent staff in areas that will directly benefit the NMCP. Since other donors and international organizations (e.g., Global Fund, World Bank, WHO, etc.) also provide funding for such training, PMI-supported efforts should be coordinated with those of other groups. Priority should be given to in-country training opportunities, followed by regional training programs, as workers will be absent from their jobs for shorter periods of time. Only under exceptional circumstances will training in Europe or the United States be considered and only when justification for this training is provided.

Direct support to NMCPs and local government entities must be in accordance with USAID regulations and procurement guidelines regarding grants to governments. Where used, direct grants to the Ministry of Health, NMCPs, or other local government entities may include support for financial management and tracking of the funds provided. Technical assistance and support to Ministry of Health, NMCPs, or other local government entities to build their capacity can be part of the scope of work requested of PMI implementing partners.

PMI supports and encourages NMCP staff to benefit from training opportunities and to participate in international conferences, particularly as presenters (oral or poster). Financial support for this engagement should be carefully reviewed by the PMI team to ensure that both the participants and the events are appropriate, that funds from other sources are leveraged if possible, and that outcomes of the participation are expected to benefit to the country program. Funding to respond to these opportunities may be programmed in the MOP as a component within HSS activities designed to build NMCP capacity, and/or within interventions related to a specific technical area. Malaria Operational Plans should not include a single budget line item for support for international travel for NMCP staff.

Tracking of HSS Inputs Throughout PMI Technical Areas

PMI documents investments made to strengthen health systems throughout a country's portfolio, including system strengthening activities that have a primary goal in another technical area. For example, case management activities may include investments to improve human resources for health care. As mentioned above, these activities are therefore described and justified in the appropriate technical section, but should also be referenced within the HSS section in order for these important investments to be documented. For this reason, the inclusion of the HSS table cross referencing HSS activities from other technical areas is now required in the MOP.

Field Epidemiology and Laboratory Training Program

PMI supports efforts to initiate and strengthen local epidemiologic and laboratory data collection, management, analysis, and dissemination capacity in PMI-supported countries. As one approach to strengthening the long-term capacity of this health system component, country teams may consider supporting training through the CDC FELTP. The FELTP is traditionally a two-year, full-time training program that helps MOHs build sustainable capacity for local detection and response to health threats, including sudden increases in malaria transmission. Some countries adopted the full program which includes the laboratory training piece which is a separate track within the program. Others implement the "field epidemiology" part only and are hence often referred to as FETPs without the "L". Over time, investment in FELTPs produce a cadre of public health workers that use science and data to identify, respond to, and manage acute health problems with appropriate strategies and policies. Some countries started to implement FE(L)TP in a tiered approach with basic, intermediate, and advanced levels to train a

large cadre of public health professionals more quickly. Graduates from the basic program may advance to the intermediate program and graduates from the intermediate may participate in the advanced program which is the traditional full two year training opportunity.

Approximately 25% of the FELTP training program time is spent in classroom instruction and 75% on field assignments, often including malaria control activities. The training is competency-based with close supervision, didactic and inductive teaching which includes courses in epidemiology, communications, economics, and management. Trainees also learn quantitative and behavioral-based strategies for mitigating public health problems. The trainees provide epidemiologic services to the Ministry of Health during their training, including surveillance system assessments and outbreak investigations, and gain experience in reporting their findings and recommendations to high-level decision makers, stakeholders, and the media. Graduates receive a certificate or, in some programs, a Master of Public Health degree.

FELTPs are helping to realize the long-term health systems capacity development component of President Obama's Global Health Security Agenda. As of FY 2016 planning, PMI is supporting FELTP trainees in twelve countries: Angola, DRC, Ethiopia, Ghana, Kenya, Burma, Mozambique, Nigeria, Rwanda, Tanzania, Uganda, and Zambia. The CDC FELTP Branch has also initiated a West Africa Regional FELTP, based in Burkina Faso, which includes trainees from Burkina Faso as well as neighboring countries such as Benin, Côte d'Ivoire, Guinea, Mali, Niger, Senegal, and Togo. Field Epidemiology and Laboratory Training Program residents/participants may be drawn from NMCP staff or from other applicants nominated by the Ministry of Health who have a medical or public health background. Field Epidemiology and Laboratory Training Program residents/participants receive financial support from a variety of funding sources with new funding now provided through the Global Health Security Agenda. PMI teams not only need to confirm PMI financial investment is needed for the malaria focused participants for programs where other sources of funding exist (e.g., Global Health Security Agenda), but also must coordinate closely with FELTP program leaders to ensure support for PMI malaria-specific training of FELTP participants.

Each program should expect to engage periodically in seminars organized twice-annually by PMI CDC Headquarters staff for purposes of updating PMI (CDC and USAID) on malaria-related FELTP projects and developing strategic approaches to strengthen this ongoing collaboration.

Although levels of financial support for malaria-focused FELTP residents and the costs of training will vary by country, PMI has established budget guidance parameters for PMI support for FELTP. PMI support for FELTP trainees is external to salary provided by the Ministry of Health. PMI support covers two years of training per trainee and includes tuition towards a certificate or degree (if applicable), a modest training stipend, field site supplies, as well as travel

expenses for didactic courses, field investigations, supervision, and scientific conferences. PMI focus countries proposing support for FELTP trainees should budget between $80,000 to a maximum of $150,000 per trainee per two-year assignment ($40,000 to $75,000 per resident annually) to support the FELTP program in their FY 2017 MOP budgets (please use country specific cost estimates when available). A maximum of two new trainees per year can be supported with PMI funds.

PMI country teams should ensure appropriate indicators are in place to document the impact of PMI support for the FELTP. Countries are expected to annually update a PMI-FELTP progress tracking spreadsheet which will be sent to the countries for completion and which includes the following indicators: total number of malaria FELTP trainees enrolled, total number of malaria FELTP trainees graduated, total number of malaria trainees who are employed by the NMCP or other malaria programs after graduation, list of malaria projects completed with some details about the activity or response effort if a malaria outbreak investigation, list of publications and presentations by malaria FELTP trainees, and any malaria training conducted for FETP trainees. Please refer to **Section B ("HSS Review Checklist")** for specific information to be included in the MOP.

Social and Behavior Change Communication

Introduction

PMI supports a range of SBCC[130] activities to increase the uptake of malaria interventions and contribute to reductions in malaria morbidity and mortality. Key areas of PMI support for SBCC include (1) developing or revising national malaria SBCC strategies, (2) capacity building and strengthening for SBCC, (3) implementing SBCC, (4) monitoring and evaluating SBCC, and (5) operational research for SBCC.

Achieving and maintaining the goals of PMI and NMCPs depends on the correct and consistent use of proven technical interventions (e.g., ITNs, IRS, RDTs and ACTs, SMC, and measures to prevent malaria in pregnancy). When tailored to the specific country context and needs, SBCC and other social mobilization activities play important roles in promoting uptake of these interventions and achieving the desired individual-level and public health impact.

PMI's SBCC guidance is designed to help country teams, NMCPs, and implementing partners design, implement, and evaluate high impact SBCC activities. Operational research to expand our shared understanding of SBCC's contributions to malaria control – and, where relevant, to the success of pre-elimination activities – remains an important consideration for PMI.

Key Areas of PMI Support for SBCC

A. Developing or revising national malaria SBCC strategies

PMI supports the development or revision of malaria SBCC strategies. It is important to understand that SBCC is most effective when messages are tailored to specific populations and behaviors are linked to malaria control objectives. PMI should work with NMCPs to ensure national malaria SBCC strategies align with the guidelines described in the *Roll Back Malaria Strategic Framework for Malaria Communication at the Country Level*. Additional recommendations are available in the RBM Framework. (Available at: http://www.rollbackmalaria.org/files/files/globaladvocacy/docs/BCCstrategicFramework.pdf.)

[130] PMI has replaced the term BCC with SBCC, a term already commonly used in the communications field. Referring to "social" and behavior change communications highlights the important role of systems and ecological perspectives beyond just the individual in considering behavior change; specifically, this refers to family and peer groups, social and cultural structures, and the broader environment.

Up-to-date national malaria SBCC strategies are important; however, country teams should consider the following before supporting the revision or development of a national malaria SBCC strategy:

- SBCC strategies should be clearly linked to the malaria control objectives and align with the timeframe laid out in the national malaria strategy.
- Existing SBCC strategies should be reviewed to ensure they reflect the most currently available data on malaria behaviors and epidemiology, including information collected from national household surveys, like the Demographic and Health (DHS) and Malaria Indicator Survey (MIS), as well as other special studies (e.g., health facility surveys and knowledge, attitude, and practice (KAP) surveys). Routinely collected data (e.g., HMIS) is another potential data source that could inform strategy revisions.
- Minimal time and resources should be spent on strategy revisions if there are no changes in strategic direction for SBCC activities based on changes in epidemiology, theory, global guidance, etc.

There is no single correct method to use when developing a national malaria SBCC strategy or PMI-supported SBCC implementation. However, collecting and understanding current data on knowledge, attitudes, and behaviors among the target population, and collaborating with NMCP and other partners, are essential steps prior to selecting and implementing activities.

B. Building and strengthening SBCC capacity

PMI-supported SBCC activities should aim to build capacity for SBCC among partner country counterparts. One approach is for PMI to support SBCC committees (the term "committees" refers to any national coordinating body including working groups and technical advisory groups). These committees can enhance coordination across ministries, donors, implementing partners, and the private sector. These committees could be malaria-specific (within the NMCP), but where technical and organizational capacity within the NMCP for SBCC is limited, which is commonplace across many PMI focus countries, it may make more sense to strengthen NMCP representation in cross-cutting SBCC committees. SBCC capacity building activities appropriate for PMI support are listed below.

At the **national level**, PMI funding can be used to support:

- Development, evaluation, or revision of national malaria SBCC strategies
- Analysis and interpretation of existing data to inform SBCC strategies and activities
- Coordination efforts between malaria SBCC activities with other non-health governmental partners, such as Ministries of Tourism, for example, and with the private sector

- Evaluation efforts to inform the development or expansion of PMI-funded SBCC activities (please see **SBCC Appendix 1** for a list of available resources)

At the **community level,** PMI funding can be used to support activities:

- To strengthen the technical and management capacity of local community-based organizations which are implementing SBCC activities
- To improve the skills of community-level and facility-based health workers to conduct interpersonal communication and to determine which interpersonal SBCC activities work best in a particular community
- To raise awareness and build SBCC skills among non-health care workers at the community level (e.g., school teachers, women's groups, community leaders)
- To measure the impact of SBCC activities as they are implemented

Many national-level malaria SBCC managers, district health management teams, and community health workers already have received training in SBCC from various partners, especially PMI- and Global Fund-supported partners. Additional national- or district-level training workshops, sensitization meetings, or refresher SBCC courses should take this into account and not duplicate training that already has occurred, unless necessary because of staff turnover or if refresher training is needed. As many countries invest in pre- and in-service medical education, PMI country teams may also investigate ways malaria-specific trainings may allow relevant health care workers (e.g., physicians, nurses, pharmacists) to earn continuing education credits.

C. Implementation of SBCC

PMI-supported SBCC implementation activities should complement and support the national malaria SBCC strategy objectives, which, in turn, should be linked to malaria control objectives in the National Malaria Control Strategy.[131] A clear linkage between specific SBCC implementation activities and the malaria control objectives they seek to address is best illustrated in a framework linking SBCC problems (e.g., low ITN use and low IPTp uptake) to the desired objectives. **SBCC Appendices 2a** and **2b** show examples of such frameworks; these templates can be adapted for different SBCC implementation activities. Social and behavior change communication implementation activities should be based on a behavior change theory. The most commonly used of these theories in public health are summarized in **SBCC Appendix 3**.

[131] A catalogue of current national malaria SBCC strategies can be found on the HealthCOMpass website: http://www.thehealthcompass.org/

All PMI-supported SBCC implementation activities, where appropriate, should align to support key malaria control objectives:

- Consistent and correct use of ITNs
- Acceptance of IRS
- Early and sustained ANC attendance throughout pregnancy
- Consistent delivery of IPTp during ANC visits
- Prompt care-seeking for fever
- Use of diagnostic testing to confirm malaria diagnoses
- Providing correct treatment to those who have a positive diagnostic test
- Patients' adherence to treatment as prescribed by health care providers
- Sustained adherence to SMC throughout a campaign period

Additional areas where SBCC interventions may improve outcomes include:

- Net care
- Quality assurance/quality improvement for diagnostics
- Promoting timeliness and quality in supply chain management
- Where relevant: identifying and mitigating outdoor exposure risk

Recommended core messages

To attain these objectives, below is a list of core messages that should be promoted in national malaria SBCC strategies and PMI-supported SBCC interventions. Most of these messages are designed to educate and inform the general population; however, several messages (e.g., use ACTs in conjunction with positive RDT results; promote IPTp use at every ANC visit) are targeted to healthcare workers. Each message should be linked to a desired change in behavior (see list below). If these messages look familiar, that's because they are. Simplicity, consistency, and repetition are three fundamental principles to keep in mind when developing a SBCC strategy or intervention.

Core Messages:

- Mosquitoes cause malaria
- Mosquitoes that bite at night are the main cause of malaria
- Malaria is serious and can be fatal
- Children under 5 and pregnant women are most vulnerable
- Malaria transmission can occur year-round (where epidemiologically relevant)
- You can prevent malaria in your home and community
- There are effective treatments for malaria

- IRS is an effective means of malaria prevention and control
- Insecticides used in IRS are safe
- ITNs are an effective means of malaria prevention for all ages
- ITNs must be used every night, especially by children under 5 and pregnant women
- It's important to take medicine to prevent malaria when pregnant
- The medicine used to prevent malaria in pregnancy is safe
- When children have a fever, it's important to seek care at a clinic or community health worker within 24 hours
- Patients with suspected malaria should be diagnostically tested to confirm whether they have malaria
- Treatment should only be provided to patients testing positive
- Patients testing negative should not be treated for malaria

Desired behavior change related to the core messages:

- Acquire an ITN
- Sleep under an ITN all night, every night
- Prepare buildings for spraying and allow sprayers inside structures
- Seek diagnosis and treatment from a qualified health worker within 24 hours of onset of fever of child
- Take the complete dose of antimalarial correctly
- Go to ANC within the first 4 months of pregnancy
- Attend ANC as scheduled
- Adhere to national guidelines for provision of IPTp (e.g., appropriate frequency of dosing and directly observed therapy)
- Adhere to national guidelines for malaria case management (e.g., only those testing positive by RDT/microscopy receive an ACT)

Recommended SBCC communications channels

Communication channels are the means by which the key SBCC messages are conveyed to the target audience. The selection of communications channels should be based on preferences and needs of the target audiences. Channels range from mass media, which includes broadcast media (e.g., radio and television), print media (e.g., pamphlets and comics), outdoor media (e.g., billboards), and information and communications technology (ICT) (e.g., mobile phones, SMS, and social media) to interpersonal communication, which includes individual and group communications (e.g., home visits, school demonstrations, community dramas).

While communications theory and scientific evidence should underpin SBCC strategies and implementation activities, communications materials, including verbal and written materials for guidance, training, and intervention activities, should be clearly written and easily understood by the target audience – whether this is forest workers in Cambodia, community health workers in Zambia, or physicians in Senegal.

Selecting the proper communication channels requires a careful evaluation of the type and size of the target population, the target behaviors, and the available budget. As with other aspects of SBCC, one-size-fits-all solutions are rarely effective. National SBCC strategies should focus on identifying appropriate communication channels and target populations.

Answers to the following questions can help when choosing the most appropriate recommended communication channels:

- What languages are spoken by members of the target population?
- What proportion of men and women can read?
- How many people in the target population own or have access to radios? TVs? Cell phones? Smart phones? Computers?
- Does the target population have access to the internet?
- What information do people receive via each device?
- How else do people learn and share information?

Where the answers to these questions are unknown, formative research should be conducted to determine appropriate channel selection. Data on different audiences' preferences for and access to various communications channels (especially those requiring electricity or technology such as radio/TV, internet, text messages, other social media), will help ensure that SBCC messages reach and are absorbed by the target audience. In addition to data collected through household surveys such as the DHS and MIS, KAP surveys can provide complementary data, while key stakeholder or focus group interviews can produce qualitative information.

Because different populations (or sub-populations) may have different SBCC needs, PMI recommends using a mix of communication channels for SBCC implementation activities.

- **Interpersonal communication**: Given high levels of knowledge and awareness about malaria in most PMI-supported, interpersonal communication is an important SBCC approach to achieve actual changes in behavior. Interpersonal communication facilitates and encourages appropriate actions, especially among marginalized populations, and helps people to discuss their beliefs and feelings about their ability to take appropriate action. Interpersonal communication activities can be a powerful tool in reinforcing

messages delivered by mass media. Various forms of person-to-person discussions should be considered. Examples include:

  - Home, school, or workplace visits by community health workers
  - Clinic-based counseling and other conversations between health care staff and patients
  - Community conversations using community leaders or groups equipped with simple messages
  - Radio or TV call-in programs through which individuals can ask experts questions in relative anonymity (note that this type of intervention can also have a mass media effect outside of the caller/expert exchange when listenership or viewership is wide)

- **Mass Media**: TV, radio (especially community radio), online platforms, and mobile technology can be a powerful tool in raising awareness and reinforcing messages delivered through interpersonal communication. Mass media activities expand the reach of information to wider audiences and can be a powerful inducer of change if included as part of a well-designed SBCC campaign. Country teams and implementing partners should work closely with local radio and television broadcasters and media professionals to ensure materials are not sensationalized and messages are reaching the target audience.

- **Cross-cutting**:
  - **Infotainment**: Infotainment, which can be classified as either interpersonal communication or mass media, depending on the method of delivery, can be an effective SBCC tool. Interpersonal infotainment tools, such as comic books or community theatre (e.g., street plays), can reach individuals or small groups, while mass media infotainment tools, such as radio or television dramas, game shows, or call-in programs, can reach larger audiences with effective messaging. Small-scale, community-based, in-person infotainment activities, such as songs, oral storytelling, or short plays may be more effective when they include an interactive exchange, such as Q&A sessions and audience participation or discussion immediately following a performance. Large-scale infotainment activities often do not provide an opportunity for the exchange of ideas or direct follow-up with audience members, and should be considered more carefully.
  - **Mobile Technology:** The proliferation of mobile telephones has opened a new, potentially powerful, tool for SBCC. Short message service (SMS) text messages have been used to encourage utilization of health services (e.g., remind women about ANC visits), health worker adherence to case management guidelines, and patient adherence to treatment regimens. Recent literature reviews have found

substantial use of SMS across multiple health programs, with a majority of studies showing some positive impact[132] or "a growing evidence base for … efficacy."[133] Countries should consult available literature and the PMI Headquarters SBCC Team to identify impact evaluation questions to include in any mobile technology-based intervention.

Table 1 shows the recommended level of PMI funding support by major communication channel – interpersonal communication and mass media. These percentages are only estimates to give an idea of a balanced mix of SBCC approaches. As other donors – primarily the Global Fund – have historically focused support on mass media, we recommend that PMI support should be more heavily weighted towards interpersonal communication channels. The appropriate mix, however, will be subject to country context, country malaria situation, actual costs of various activities, and priorities of other donor-funded SBCC activities.

[132] Kannisto, K. A., Koivunen, M. H., & Valimaki, M. A. (2014). Use of mobile phone text message reminders in health care services: a narrative literature review. *J Med Internet Res, 16*(10), e222. doi:10.2196/jmir.3442

[133] Hall, C. S., Fottrell, E., Wilkinson, S., & Byass, P. (2014). Assessing the impact of mHealth interventions in low- and middle-income countries--what has been shown to work? *Glob Health Action, 7*, 25606. doi:10.3402/gha.v7.25606

Table 1. Recommended Level of PMI Funding by Communication Channel						
	Communication Channels					
	Interpersonal Communication Recommended level of effort: approximately 70% of SBCC budget			**Mass Media Communication Recommended level of effort: approximately 30% of SBCC budget**		
Major Approaches	One-on-one Communication	Group Communication	Infotainment	Information Broadcasting	Print Media	Infotainment
Potential Channels	Health Workers Volunteers Peer to Peer NGO staff Peace Corps	Schools Group discussions Exhibitions Campaigns	Songs Oral Storytelling Short plays	Television Mobile phones Community radio	Pamphlets Posters Billboards	Radio Television

D. Monitoring and Evaluating SBCC

There is an increasing focus across PMI to develop more comprehensive and systematic data on the impact of SBCC interventions on malaria outcomes. With this comes a greater emphasis on accountability and reporting of SBCC interventions and ensuring monitoring plans tie process and output indicators to specific desired outcomes. All teams should review their M&E plans for SBCC activities and ensure a high level of rigor with regard to data collection and monitoring of SBCC activities. The M&E plans should reflect NMCP priorities as articulated in the NMCP's national SBCC strategy.

PMI recommends that the M&E section of work plans for implementing partners carrying out SBCC activities specify:

- Targeted behaviors, SBCC interventions to address those behaviors, intervention goal, key message(s), and intervention's target audience(s)
- Indicators for each intervention, including operational definitions (numerators and denominators), baselines, and targets (see below for description of indicators)
- Data sources to calculate the indicators, reporting frequency, responsible party(ies)

Monitoring Indicators

Process Indicators: Reflect tasks necessary to successfully implement an activity (e.g., pre-testing messages, printing materials, training sensitization teams).

Output Indicators: Reflect reach (e.g., number of people who hear the message) and delivery (e.g., number of people who receive the intervention) of the activity to the target audience. Reporting should specify the intervention's geographic coverage (e.g., number/proportion of districts vs. national coverage), as well as demographic information on individuals reached (sex and age), if available, by each activity. Note: Monitoring data typically come from partner records and reports.

Evaluation Indicators

Outcome Indicators: Reflect the degree to which the activity achieved the desired effect on the target audience that would ultimately lead to the behavioral outcome. These indicators should be reported as proportions with the denominator representing the target audience or a sample thereof and would measure:

- Behaviors
- Recall of messaging
- Knowledge and awareness
- Attitudes, including risk perception, self-efficacy, response-efficacy, and social norms

RBM SBCC Indicator Reference Guide

The RBM Communications Community of Practice (CCoP) has developed and disseminated the *Malaria Behavior Change Communication (BCC) Indicator Reference Guide* to support Ministries of Health, donor agencies, and implementing partners to evaluate the effectiveness of country-specific malaria SBCC interventions using a more rigorous and standardized approach. Each indicator in the guide includes an explanation of its purpose, definition (including numerator and denominator), measurement, interpretation, strengths, and limitations. **Please note that these are not considered required reporting indicators for PMI.** The purpose of the guidance is to encourage standardization of measurement and facilitate more robust evaluation of SBCC for malaria. Countries should select indicators that are most programmatically useful and relevant for their own programs and use the reference document to help guide their measurement.

The reference guide is available online in English, French, and Portuguese through the RBM website: http://www.rollbackmalaria.org/partnership/wg/wg_communication/docs/Malaria-SBCC-Indicators-Reference-Guide.pdf.

Evaluation data may be captured using existing data sources including national or sub-national household surveys, health worker reports, and health facility records. However, data from these sources may be difficult to interpret due to sampling issues, inconsistent reporting, or geographic areas of intervention. For example, national household surveys may not be able to provide the subnational estimates required to measure outcomes of a specific SBCC intervention, especially if the intervention is targeted to a limited geographic area. However, the data needed for measuring the recommended indicators will typically come from household surveys such as the DHS, MIS, and MICS. We acknowledge that adding questions to large household surveys requires planning, negotiation, and flexibility. The SBCC indicators should be selected as needed and their inclusion into these surveys should be discussed at the earliest planning stages. These indicators can also be collected through smaller sub-national surveys, particularly in areas where malaria communications were targeted and/or as part of baseline and end point implementing partner surveys which requires PMI staff to engage in the planning of these surveys.

It may not be possible to attribute changes in behavior, and to an even greater extent, changes in health impact to a specific SBCC intervention; however, descriptive behavioral outcome data, even in the absence of a statistically significant association, can suggest potential associations with SBCC interventions and be used to inform programmatic decision-making. The strength and confidence level of any measured association will depend upon data collection, sampling, and analysis methods. Multiple factors including resources and technical capacity, available data sources, and geographic coverage of the intervention will influence selection of an evaluation design.

RBM CCoP reporting guidelines

Reporting for malaria SBCC interventions are often missing key information which limits the ability to identify high-quality interventions and to reproduce those interventions. To address this gap, the RBM CCoP has developed a *Reporting Guide for Malaria Communication Evaluations* (http://www.healthcomspringboard.org/groups/malaria-sbcc/forum/topic/monitoring-and-evaluating-tools-for-malaria-bcc-now-available/). The objective of this document is to improve the transparency of reporting, increase efficiency of the writing and review process, and identify what SBCC approaches work in different contexts.

E. Operational research for SBCC

Operational research priorities will undoubtedly change in coming years, especially as more countries achieve malaria control objectives and move into the pre-elimination phase. However, for the majority of countries still battling to achieve control, country teams should focus limited resources on adapting and improving coverage and utilization of existing interventions. As countries confront SBCC-related OR questions, these questions should be brought to the attention of NMCPs, research teams (including the PMI Headquarters OR Committee), and the RBM CCoP for consideration of how to prioritize and address these questions.

As noted above, SBCC interventions should never stand alone: they must be designed to enhance communities' understanding, awareness and acceptance of PMI's priority interventions, and to improve coverage and use of – and epidemiological outcomes associated with – those interventions. Research projects should also not stand alone. PMI country teams should consider opportunities to embed SBCC OR (including technical assistance to build host country capacity to allow NMCP staff to conduct OR on their own in the future) into ongoing NMCP activities to minimize disruptions and diversions for technical and administrative staff.

To this end, research around malaria behaviors and SBCC can be considered using the following two categories:

1. **Improved understanding of factors that impede or encourage the recommended behavior**.
   Understanding factors that impede or encourage the recommended behaviors is essential to formulate and design effective messages and approaches. Pre-elimination behaviors may need to be considered separately, and behavioral research will be key as countries and regions move closer to pre-elimination.

2. **Improved understanding of effectiveness of various SBCC approaches/channels**.

An improved understanding of the effectiveness and costs of different approaches, or combinations of approaches, is important for maximizing reach and impact of communications given a fixed resource envelope. Country context is an important determinant.

As with other PMI-supported OR activities, OR proposals need to be developed according to PMI OR guidance. The RBM CCoP M&E Task Force is also working to identify OR priorities for SBCC.

Additional Considerations for SBCC

SBCC activities supported by PMI need to encompass more than just selecting radio spots for an ITN distribution campaign or sending SMS messages to pregnant women. Successful SBCC will demonstrate a clear understanding between intervention areas, audience, and key actions to be taken. The RBM CCoP has developed a framework to link malaria control interventions to key behavioral actions through the appropriate target audience. This framework is summarized in **Table 2**.

Table 2. RBM CCoP Framework

Intervention(s)	Audience	Key Actions
ITNs: Delivered free through mass campaigns, routine delivery through ANC/EPI visits, social marketing, voucher programs	Policy makers	• Ensure adequate supplies are available at front line facilities and in the community • Endorse the removal of taxes and major financial barriers • Support a coordinated and harmonized ITN strategy
	Families, decision makers, e.g., heads of households, mothers	• Acquire ITNs • Hang ITNs correctly; use them consistently
	Health service providers and community volunteers, distributors (vendors)	• Promote ITNs at every opportunity (ANC visits, well child visits, etc.) • Give information on how/when to use ITN, including demonstrating how to hang) • Distribute and explain vouchers, as needed, and provide information on where to get ITNs
	Community leaders, organizations	• Promote ITNs at every opportunity (community meetings, child health days, etc.) and special events • Demonstrate use, how to hang, etc.

Table 2. RBM CCoP Framework		
Intervention(s)	**Audience**	**Key Actions**
IRS: Delivered through annual/semi-annual campaigns prior to rainy season	Policy makers	• Explain the rationale and implications of IRS • Include IRS as a malaria prevention strategy for the national malaria control program
	Families	• Prepare buildings before spraying • Allow sprayers inside home • Don't wash walls after spraying
	Sprayers	• Carry out effective, quality operations • Wear protective equipment (ensure women are not pregnant, potentially exposing the fetus) • Facilitate spraying within their communities (planning, discussing with community, etc.)
IPTp: At least three or more doses delivered through routine ANC visits	Policy makers	• Understand the dangers of malaria during pregnancy • Enforce the national IPTp policy
	Pregnant women	• Attend ANC in first trimester and return regularly • Take SP doses at home on schedule if not at ANC
	Health care providers	• Provide correct SP dose to healthy pregnant women at correct times and explain its purpose and potential side-effects • Encourage early and frequent ANC attendance; give appointments for next visit Community leaders, organizations • Encourage early and frequent ANC visits, especially for IPTp
Treatment of Fever: Delivered through community/home-based channels, the private sector, at the health facility, and in	Policy makers	• Support the introduction of evidence-based practices for case management, including iCCM • Endorse classification of first line ACT for over-the-counter sale and distribution • Support the establishment of a quality control system for anti-malarials

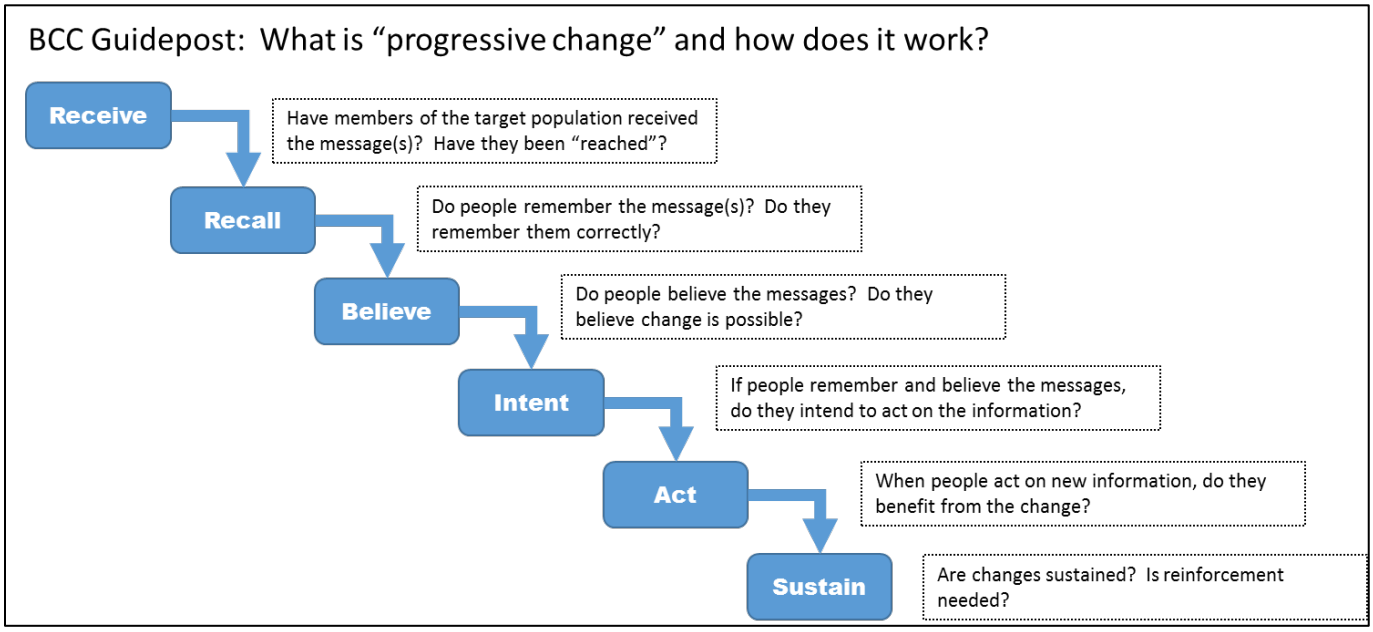
some cases, through traditional healers	Families	• Recognize signs and symptoms of malaria and the high risk that malaria poses for children under 5 and pregnant women • Seek treatment for children within 24 hours of fever on-set • Acquire and give the right ACT, in the right dose, for the right number of days • Recognize signs of severity/complications/failure to respond to treatment and seek help promptly
	Health care providers (including community-based and medicine dispensers, where appropriate)	• Ask about previous treatments (to identify treatment failures) and symptom history • Perform diagnostic test (if available) • Prescribe the right ACT in the right dose based on the diagnostic test results • Explain how to take medication and discuss side effects • Observe patient taking medicine, where possible • In areas of stable malaria transmission, treat all febrile children under 5 with the appropriate ACT. • Recognize signs of severe disease and treat or refer

In order to prioritize the appropriate actions and audiences for SBCC interventions, it is essential to use epidemiological data (e.g., disease burden in specific populations or geographic areas) to guide where and to which populations SBCC interventions are targeted. As such, SBCC teams should sustain (or build) strong relationships with M&E teams to ensure that SBCC campaigns reflect current evidence.

Communication strategies and activities should be designed to encourage specific target audiences to take specific actions. To ensure the messages have the desired impact, SBCC practitioners and stakeholders should be able to clearly explain why the proposed actions are important, how the suggested changes will benefit members of the target audience, and how behavior change in the target population may contribute to achieving malaria control objectives.

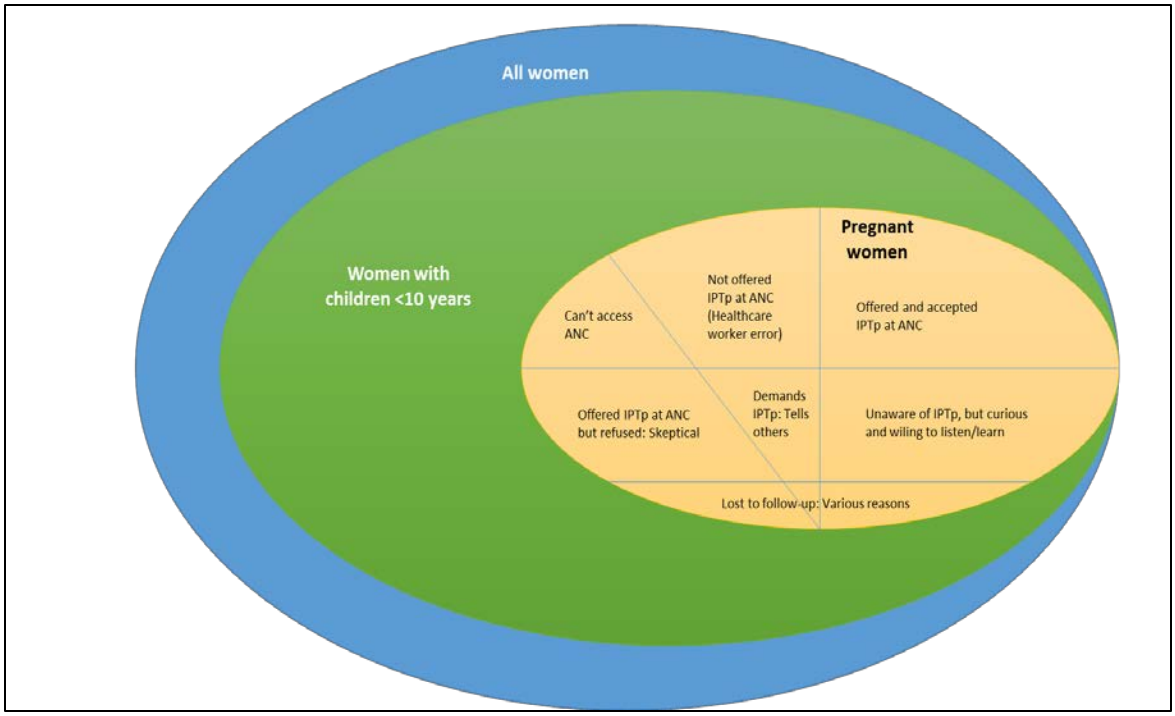
The theory of "progressive change" may help teams work through these questions. **Figure 1** illustrates the behavioral issues teams may confront as target populations receive information about malaria control interventions.

Figure 1: What is "progressive change" and how does it work?



Another important consideration for SBCC planning and implementation is a thorough understanding of the target audience. A recent PMI-funded desk review of national malaria SBCC for malaria in pregnancy in five countries concluded that audiences were not adequately segmented. In other words, SBCC interventions were too generic or broadly targeted and may have missed important differences within a broad population group. **Figure 2** is a visual example of how **audience segmentation** differs from basic population stratification (e.g., males, females, under five years, etc.). In this example, women can be broadly stratified into three main categories: All women (blue), women with children under the age of 10 years (green), and women who are currently pregnant (yellow).

Figure 2. BCC Guidepost: What we mean when we talk about "audience segmentation"



Segmentation allows each of these strata to be further sub-divided by variables related to individuals' knowledge, perceptions or beliefs. In this example, pregnant women can be segmented based on their attitudes and understanding of IPTp. Further, we see a range of potential reasons why women may receive or fail to receive IPTp during their pregnancy -- from women who can't access IPTp because of physical barriers to ANC; to women who fail to receive IPTp due to health care worker error or whose skepticism bars them from accepting the treatment; to women who have not heard of the treatment but are open to learning more; and women whose enthusiasm for the treatment makes them ambassadors to mobilize others. Understanding how sub-populations may be segmented by individual, familial, or small group beliefs, fears, or awareness can help improve the efficiency of SBCC interventions. To gather information about audiences, incentives, barriers, and communication preferences, first consult data from existing sources (e.g., MIS, KAP surveys, MOH documents). It may be important to conduct formative research or a sub-national assessment, such as a KAP survey, if existing data are not sufficient. Formative research could include rapid data collection for audiences that are not well understood; for example, surveys in rural health clinics or areas with mobile populations.

Note of caution about audience segmentation: Just as casting too wide a net may fail to address individual or small group fears or concerns, be aware that tunnel vision – focusing too intently on one sub-group – may blind you to helpful perspectives from peripheral populations. To carry the pregnant woman example a step further, the "helpful periphery" to keep in mind would

include family members (mothers, mothers-in-law, husbands) and health care providers – all people who can provide additional support to women in the target population or segments.

SBCC Appendix 1: Additional Communications Resources

PMI Communication and Social Mobilization Guidelines

- http://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/communication_social_mobilization_guidelines.pdf?sfvrsn=2

Malaria SBCC Indicator Reference Guide

- http://www.rollbackmalaria.org/partnership/wg/wg_communication/docs/Malaria-BCC-Indicators-Reference-Guide.pdf (English)
- http://www.rollbackmalaria.org/partnership/wg/wg_communication/docs/Malaria-BCC-Indicators-Reference-Guide-fr.pdf (French)
- http://www.rollbackmalaria.org/partnership/wg/wg_communication/docs/Malaria-BCC-Indicators-Reference-Guide-p.pdf (Portuguese)

RBM Strategic Framework for Malaria Communication at the Country Level

- http://rbm.who.int/globaladvocacy/pr2012-09-05.html

RBM CCoP Reporting Guide for Malaria Communication Evaluations

- http://www.healthcomspringboard.org/groups/malaria-sbcc/forum/topic/monitoring-and-evaluating-tools-for-malaria-bcc-now-available/

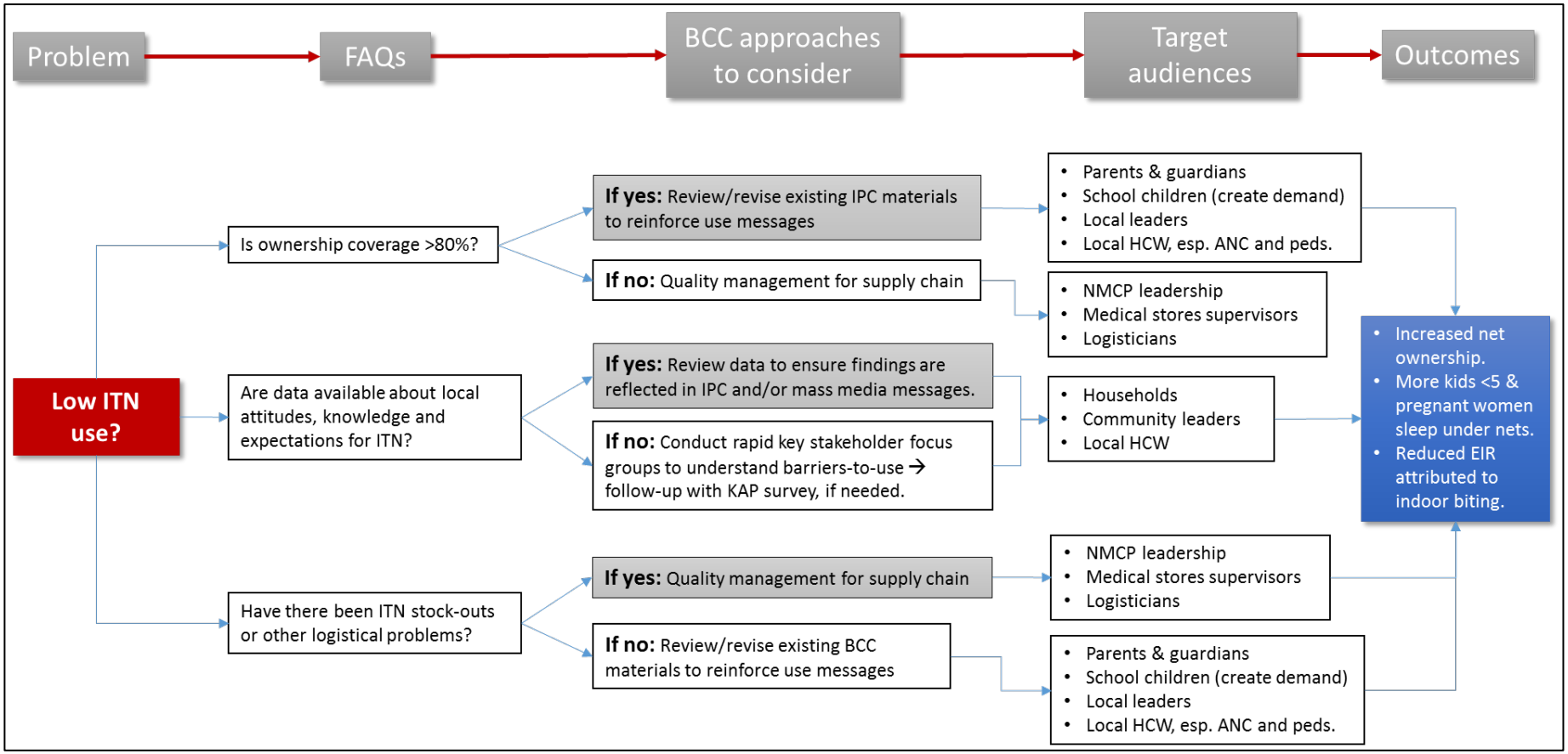
Other online SBCC resource repositories

Project & (Partner) Name	Project Focus	Web Address	Available materials
Soul Beat Africa (Communications Initiative)	MCH, malaria, HIV/AIDS	http://www.comminit.com/africa/search/apachesolr_search/?filters=tid:38 tid:38	• BCC methods manuals • BCC evaluations • Mass media campaigns • Search by country, issue, theme
Malaria Consortium	Malaria	http://www.malariaconsortium.org/pages/learning-papers.htm	• BCC project evaluations • BCC project development guides
K4Health	Malaria, other global health	https://www.k4health.org/toolkits/anemia-prevention/bcc-messages-and-materials	• Focus on anemia prevention and treatment • BCC strategy development tools
Health Communication Capacity Collaborative	Malaria, other global health	http://healthcommcapacity.org/collecting-and-curating-sbcc-resources-and-tools/	• Online courses • Materials library • Webinars

			• "Ideation"
Johns Hopkins Center for Communications Programs	Global Health (clearinghouse for HC3 and K4Health)	http://ccp.jhu.edu/resources/	• Toolkits • Professional networking
HealthCOMpass	SBCC capacity building	http://www.thehealthcompass.org/	• Capacity strengthening tools • Project examples

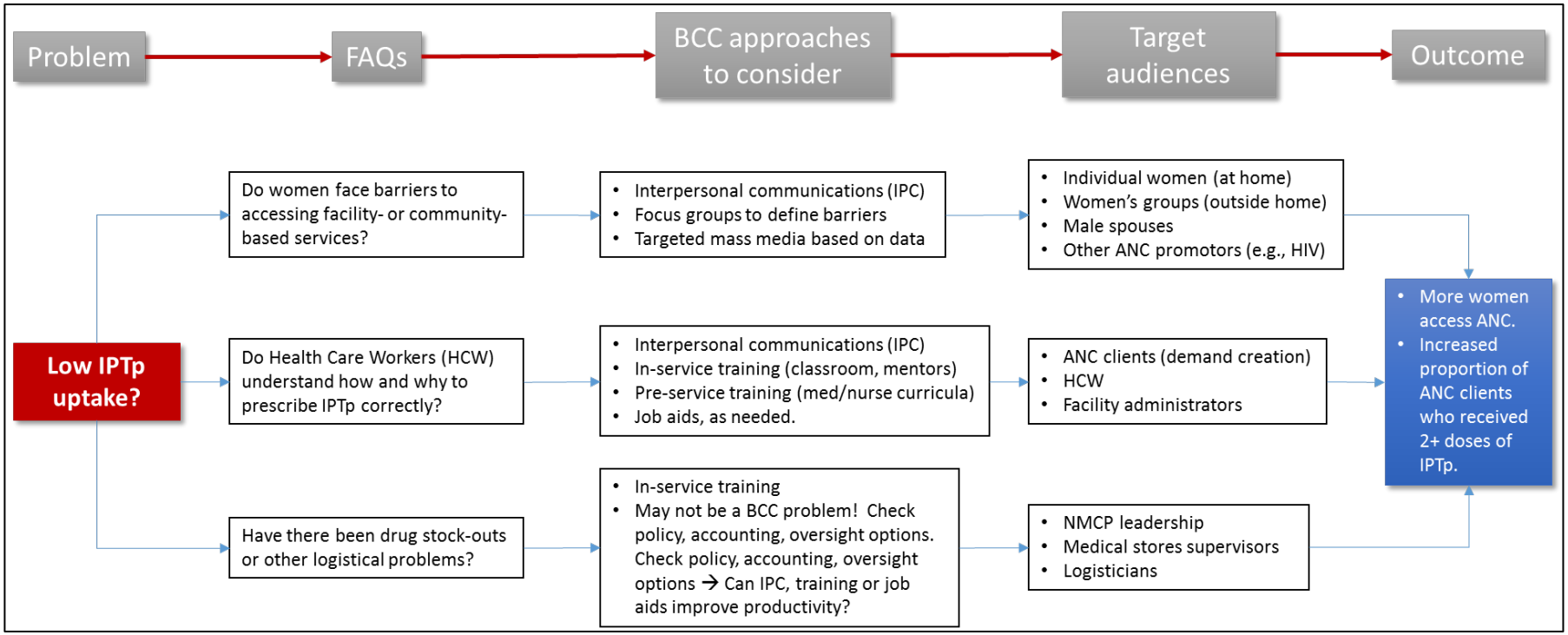
SBCC Appendix 2a: SBCC Decision-Making Algorithm Templates

Example: Low ITN use



SBCC Appendix 2b: SBCC Decision-Making Algorithm Templates

Example: Low IPTp uptake



SBCC Appendix 3: Common BCC Theories and How They Work[134]

Theory	Basic concepts	When to consider	Expected outcomes
Health Belief Model	Individuals' make health-related decisions based on: o **Belief** about their level of risk o **Perceived benefits** associated with changing behavior.	Promote net use, seasonal prophylaxis & prompt care for fever in low prevalence settings	• Individuals accept that malaria remains a serious disease, **even when rare**. • Prevention remains a priority even when perceived risk is low.
Transtheoretical Model / Stages of Change	Decision-making is a process. 1. **Precontemplation:** Need for change not recognized 2. **Contemplation:** Starting to think about change 3. **Preparation:** Planning for change 4. **Action:** New habits are adopted 5. **Maintenance:** Reinforcement	• To promote long-term (6-12 months) behavior change (e.g., net use) • Large, diverse pop. • Change requires multiple actions (getting, hanging, using a net)	• More people in **preparation** or **action** stages (measured by net ownership or use) • May be useful to **predict** pos. or neg. changes in coverage or uptake
Social Cognitive Theory	Personal experience guides decision-making…**but observing others' experience also important**	When addressing individual **self-efficacy**, or people's confidence that they **can overcome barriers to action**	Individuals cite "a friend told me" or "a colleague already did it" as reason for changing behavior.
Social Ecological Model	• Similar to social cognitive theory • **Multiple social and environmental cues** drive individuals' choices	Address multiple audiences with multiple interventions o **Policy, community, individual**	IPTp uptake increases with ANC attendance, e.g., "healthcare is free" policy reinforced; women demand IPTp; providers recall 2-3 dose guidance

[134] Theories and descriptive summaries adapted from National Institutes of Health: http://www.esourceresearch.org/eSourceBook/SocialandBehavioralTheories/1LearningObjectives/tabid/724/Default.aspx.

Extended Parallel Processing Model	• **Fear** inhibits decision-making • **Danger management:** Individuals adapt to real and perceived risks • **Fear management:** Individuals invest in managing fear, not risk	**Use with Caution** Risk of unintentionally reinforcing existing fears Focus instead on clearly explaining known risks and benefits	
Ideation	• Multiple factors influence individuals' and groups' behavior • Multiple skills and approaches needed to facilitate behavior change	• Most SBCC interventions may benefit from a multi-channel approach. • PMI recommends clearly describing each factor or intervention.	A coordinated, multi-pronged strategy is developed based on multiple sources of information about the target population.

Surveillance, Monitoring, and Evaluation

New/Key Messages in the FY 2017 Technical Guidance

- Household surveys will continue to be a key surveillance, monitoring, and evaluation (SM&E) activity
  - In medium to high prevalence areas, household surveys are recommended every 2-3 years
  - In low prevalence areas, household surveys are recommended every 3-5 years, with less emphasis placed on collection of biomarker data
- Health management information systems are a key investment area for PMI.
- The SM&E section of the MOP now has new required routine surveillance indicator table to track key indicators.
- For guidance on entomological monitoring (including insecticide resistance), ITN durability monitoring, and therapeutic efficacy monitoring, please refer to the **IRS**, **ITN** and **Case Management** chapters of this guidance, respectively. These activities and corresponding budgets should also be included in their respective sections, not the SM&E section of the MOP.

Introduction

The goal of PMI's updated strategy for 2015-2020 involves working with NMCPs and partners to accomplish the following objectives by 2020:

1. Reduce malaria mortality by one-third from 2015 levels in PMI focus countries, achieving a greater than 80% reduction from PMI's original baseline levels
2. Reduce malaria morbidity in PMI focus countries by 40% from 2015 levels
3. Assist at least five PMI focus countries to meet WHO's criteria for national or sub-national pre-elimination

These objectives will be accomplished by emphasizing five core areas of strategic focus: (1) achieving and sustaining scale of proven interventions; (2) adapting to changing epidemiology and incorporating new tools; (3) improving countries' capacity to collect and use information; (4) mitigating risk against the current malaria control gains; and (5) building capacity and health systems.

PMI Surveillance, Monitoring, and Evaluation Principles

Coordination and partnership

PMI is a member of the RBM Partnership and, as such, SM&E activities should, whenever possible, be carried out in coordination with other major partners and donor agencies, including the Global Fund, World Bank, WHO, UNICEF, DFID, etc. Surveillance, monitoring, and evaluation activities should also be in line with the principle of "The Three Ones" – one national malaria control coordinating body, one national malaria control strategy, and one national malaria control SM&E plan by supporting national SM&E strategies and encouraging NMCP leadership in SM&E. PMI should seek ways to support and strengthen MOH and NMCP capacity in SM&E by providing appropriate technical and material resources to build human and system capacity at the various operational levels throughout the national health system. Collaboration with other USG partners such as PEPFAR, USAID MCH programs etc., should be sought.

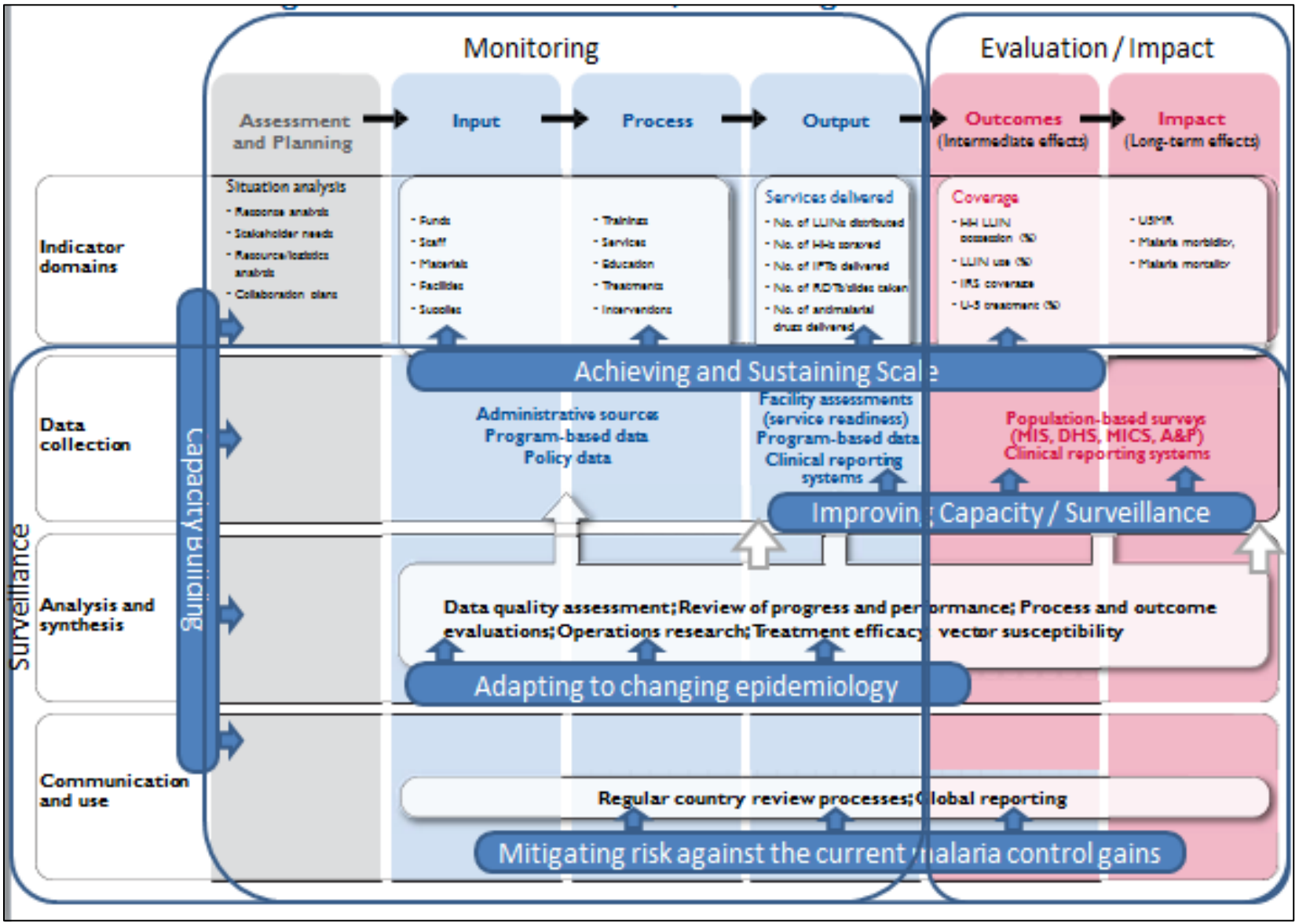
Cost-effective, sustainable solutions

The SM&E team is cognizant that funding for malaria and SM&E activities is finite and therefore strives to ensure that PMI-proposed SM&E activities are the "best buy" for countries and donors. Surveillance, monitoring, and evaluation activities should provide cost-effective long term solutions, and promote approaches and systems that are or can become sustainable with country resources. Although efficiencies in acquiring SM&E data and information for malaria may tempt to support stand-alone malaria SM&E activities, every effort should be made to ensure that PMI-supported activities are integrated into larger public health needs, leverage other investments (e.g., PEPFAR, MCH), and build on local approaches and capacity.

SM&E Framework

The PMI follows the SM&E framework shown in **Figure 1** in organizing its activities. The figure illustrates key indicator domains, potential data sources, and highlights the importance of data analysis, reporting of results, and use as a part of all SM&E activities from input to impact. The areas in the first four columns (grey and blue) are the monitoring domains and the areas in the last two columns (red: outcomes and impact) are the evaluation domains. PMI's three objectives are addressed under the Evaluation/Impact column while SM&E for PMI's five strategic focus areas are highlighted with specific boxes (dark blue).

Figure 1. Malaria Surveillance, Monitoring, and Evaluation Framework



Measuring PMI Objectives

Determining progress towards the three 2020 objectives requires estimating malaria morbidity and mortality in each PMI focus country. For countries nearing pre-elimination, subnational estimates are also required. The following sections correspond with PMI's objectives and focus areas and provide a general overview of what SM&E activities are expected to be included in the MOP and supported with PMI resources.

Objective 1- Reduce malaria mortality by one-third from 2015 levels in PMI-supported countries, achieving greater than 80% reduction from PMI's original 2000 baseline levels.

PMI has historically used DHS to track all-cause child mortality (ACCM) as an indicator of successful malaria control. In settings with high malaria prevalence, trends in malaria mortality and ACCM are highly correlated. PMI will continue to rely on DHS as a primary source of ACCM data, and ACCM will continue to be a key indicator to assess the impact of malaria intervention scale-up. But, as the fraction of all deaths attributed to malaria declines, trends in ACCM may be dominated by other diseases and may not reflect trends in malaria mortality.

Routine data collected by the ministries of health and the NMCPs through the national HMIS is the main data source for hospital-based deaths from malaria. Trends in mortality can also be tracked through longitudinal facility-based data collection systems. However since the number of deaths occurring outside health facilities is unknown, the *total* numbers of deaths should be interpreted with caution.

Objective 2 - Reduce malaria morbidity in PMI-supported countries by 40 percent from 2015 levels

PMI has relied on population-based surveys to measure malaria morbidity in the form of severe anemia (<8 g/dL) and parasitemia in children under five years of age. However, the cross-sectional nature of surveys makes it difficult to assess seasonal and temporal trends. Likewise, the large sample sizes necessary to obtain operable point estimates in medium to low-prevalence areas are making surveys prohibitively expensive for national malaria control programs and donors. Additionally, while parasitemia is an important indicator of malaria transmission, malaria parasitemia does not necessarily correlate with severity of clinical illness.

To date, weaknesses in routine health information systems have limited its use in following morbidity trends. The recent expansion of the District Health Information System 2 (DHIS-2) platform in many countries has aided routine health data reporting to become more complete, timely, and visible. Going forward routine health information will be critical to monitoring changing epidemiology, targeting resources, and measuring impact. Therefore, PMI encourages

more investment in disease surveillance strengthening through routine health information systems.

In most PMI focus countries, routine data collected by the ministries of health and the NMCPs through the national HMIS is the main data source for malaria cases and test positivity rates, hospital admissions, and hospital-based deaths from malaria. PMI recommends a surveillance strengthening strategy that addresses HMIS system strengthening needs.

Additional guidance on these routine health information systems and population-based surveys is in the "**Guidance on SM&E Approaches and Tools**" section below.

Objective 3 - Assist at least five PMI-supported countries to meet the WHO criteria for national or sub-national pre-elimination.

WHO defines the pre-elimination phase as a monthly slide or RDT positivity rate of less than 5% test positivity rate among all febrile patients throughout the year. In pre-elimination settings, parasite prevalence through household surveys for children under 5 years of age will be 0-3%. The sample size of these surveys generally is not sufficiently large to measure incremental changes at this very low prevalence, making it difficult to measure progress and impact. Thus, countries approaching pre-elimination must have a highly functioning routine health information system that includes community data. Further, it becomes increasingly important to collect individual case level data, to enable case investigations and follow-up activities. Preferred impact indicators in the pre-elimination setting would then include test positivity rate and incidence estimates based on the catchment population for health facility coverage areas.

A detailed discussion on SM&E in the pre-elimination setting can be found in the **Pre-Elimination** chapter.

Five Areas of Strategic Focus

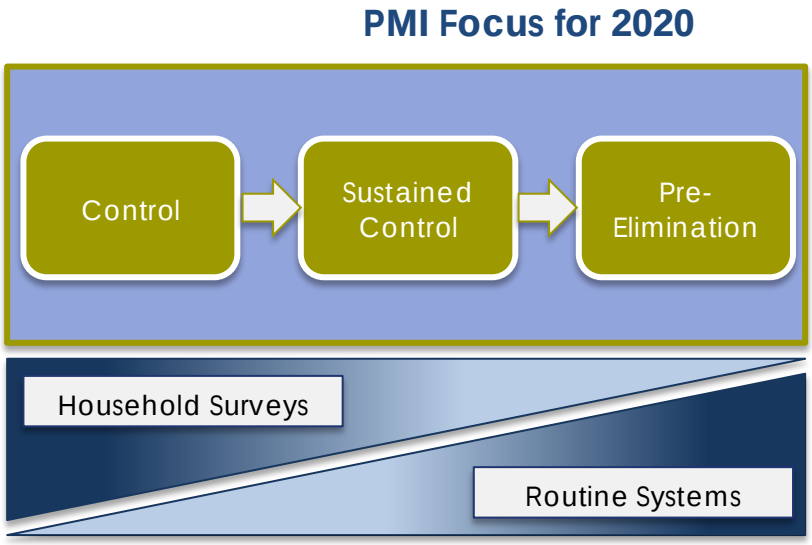
The updated PMI strategy has five areas of strategic focus that support the three updated PMI objectives. Focus areas need to be monitored to assess progress that will ultimately have impact on PMI's objectives. See the *SM&E Framework* (separate document) for more details on how these focus areas align with SM&E objectives.

SM&E for the Updated Strategy

PMI and the global malaria community have a long-term vision for the global eradication of malaria that is based on a progression through successive phases of malaria control and sustained control, and elimination (pre-elimination, elimination, and prevention of re-introduction) within countries.

PMI recognizes that countries are progressing toward achieving intervention targets at different paces and face new challenges in reducing malaria burden. As transmission changes, data needs, data collection methods, and the frequency with which data are collected and reported will change (see **Figure 2**). Countries' epidemiological profiles and health system capacity should be taken into consideration when developing and carrying out national SM&E strategies. Planning and funding data collection activities should be based on how the data will be used, by whom and with what frequency.

Figure 2: Changing SM&E in the Context of Progressive Phases from Malaria Control to Pre-Elimination



Guidance on SM&E Approaches and Tools

Malaria disease surveillance

Malaria disease surveillance plays an important role in the monitoring and evaluation of malaria control programs. In the context of PMI, disease surveillance is the continuous systematic collection, processing, analysis, presentation, interpretation, and dissemination of malaria data from service delivery points to those responsible for malaria control to use for timely decision making. Malaria surveillance data can be used to identify areas in need of interventions, and to measure the impact of interventions. When accurately recorded and reported, these data are important for monitoring changes in malaria over time. PMI recognizes that the country context – health system capacity, malaria epidemiology, implementing partner experience, among others – will determine how to best implement malaria surveillance.

Routine health information systems

Routine health information systems (RHIS) will be important for measuring the impact of PMI-supported interventions going forward. The RHIS is based on clinical data passively collected from health facilities, and in some cases includes data collected from the community. The type of RHIS used by national programs will vary from country to country. The most common system used in PMI-supported countries is the HMIS. The HMIS includes a broad set of health indicators (including several malaria indicators) representing all health services provided at the health facility. A few country programs are using the Integrated Disease Surveillance and Response system (IDSR). The IDSR collects and reports on a limited set of indicators for a small number of epidemic-prone diseases from health facilities. Both systems are affected by health-seeking behavior. The numbers of malaria cases reported through HMIS and IDSR may not be concordant due to differences in reporting time periods (monthly versus weekly), indicator definitions (country dependent), and the number of facilities covered. In general, the HMIS is the preferred system; however, the IDSR may be more appropriate in low endemic areas for timely detection of unexpected changes in malaria that may indicate an epidemic.

The concern for many PMI focus countries at this time is that data collected by health facilities and reported through the RHIS are not of sufficient quality (e.g., completeness, timeliness) to be useful for monitoring or planning malaria control activities. Many countries are now utilizing a DHIS-2 software platform that is facilitating the timeliness of reporting and visibility of the RHIS data.[135] Issues of completeness and accuracy remain, but this should not keep countries from using good, but less than perfect, information for tracking trends to inform programmatic decision making.

Countries should be supporting an integrated RHIS through MOP funding and technical assistance. In most cases, this will be the HMIS on a DHIS-2 platform. Strengthening the HMIS is a health system strengthening activity that will require ongoing support. In most countries, there are multiple stakeholders involved in these efforts. PMI should participate in necessary discussions with this broader set of stakeholders and promote the needs of malaria programs, identify opportunities for supporting activities that focus on malaria data, while assuring the stakeholders that our efforts also benefit the entire system. PMI should not be the sole funder of integrated reporting systems and PMI investments may be influenced by the ability to leverage other donors' support. Depending on country needs, capacity, and other donor activities, country teams may need to determine an appropriate balance of PMI support across routine systems in a country. In most cases, PMI resources should be prioritized to one system while other donor/country resources support other approaches.

[135] Note that there may be multiple reporting tools feeding into one reporting system. For example, the DHIS-2 is a common HMIS platform for many countries, and is capable of collecting, transmitting and reporting on a number of different diseases and frequencies. In some countries, the IDSR may also use the DHIS-2 platform.

Targeted approach for strengthening RHIS

Resource constraints and the large scale of RHIS strengthening needs will prompt most countries to consider a targeted approach to RHIS support. A targeted approach refers to the following aspects of PMI support for RHIS strengthening: prioritization of high burden areas, selection of high-impact strengthening activities, and a phased approach to implementation across districts and facilities. As targeted districts and facilities reach the end of their phased period, additional districts and facilities will be selected (see illustrative example below). The long-term goal of this targeted approach should be to strengthen RHIS and build capacity across all areas nationally in coordination with other partners. The time period of each phase should be determined based on country context and in collaboration with the MOH, NMCP, and all partners.

Illustrative Example:

In this scenario, targeted district X has 24 facilities

Phase 1: 8 facilities targeted for high level of effort (Group 1)
Phase 2: Group 1 facilities are continued with moderate level of effort and 8 new facilities are added with high level of effort (Group 2)
Phase 3: Group 1 facilities are continued with low level of effort, Group 2 facilities are continued with moderate level of effort, and 8 new facilities are added with high level of effort (Group 3)
Phase 4: Group 1 facilities are phased out, Group 2 facilities are continued with low level of effort, Group 3 facilities are continued with moderate level of effort, and now the district is covered. A new targeted district is now added, starting with a new group of facilities.

Malaria burden

In most instances, initial support should focus on districts with moderate/high malaria burden and overlap with other PMI-supported interventions where it will be important to monitor changes in burden, such as the addition or withdrawal of IRS.

Activities supported

PMI support for RHIS activities might include the following:

- An RHIS assessment if not already conducted
- Supporting the inclusion of key malaria data elements and indicators
- Strengthening data collection and reporting at the point of service
- Supporting data quality assessments
- Provision of computers at district level for data processing and analysis
- Training
- Strengthening supportive supervision and feedback
- Providing technical assistance in data analysis, interpretation, dissemination, and use

Data in a fully functional RHIS will move along a continuum: collection, processing, analysis, presentation, interpretation, use, and feedback. These activities also occur at different levels of the health care system. Thus, level of effort will vary depending on the status of implementation of the RHIS. A country that has just rolled out a DHIS-2 platform will need to focus primarily on data collection and processing. A country with 90% reporting would put additional effort into interpretation and use, while continuing to strengthen quality and timeliness at the data collection level. The intent would be to have a partner-coordinated phased plan that strengthens the national RHIS over time.

Implementation

Data of good quality from most facilities is more useful than perfect data from a few. The updated PMI strategy includes a focus area on improving capacity to collect and use information. This focus area positions surveillance as an intervention that requires scale up. With resources available, this scale-up must be a phased approach. Although targeting individual facilities can be an initial step in surveillance support, the preferred approach would be targeting entire districts in a phased, partner-coordinated roll out, with PMI focused on districts with moderate/high malaria burden and other PMI-supported activities (as mentioned above). The latter approach will also help build capacity at the district level for data use and decentralized decision making.

PMI supports a phased and progressive approach to RHIS strengthening that encompasses strengthening activities implemented across individual clinics, as well as at district and regional levels to improve data use. Implementation in individual health facilities should reflect an overall strategy to eventually cover an entire district or region, rather than several sites in isolation. PMI no longer supports sentinel sites, as they are defined by WHO, which are "established for the purpose of providing representative data, and deliberately involves only a limited network of carefully selected reporting sites."[136] Unlike sentinel sites, phased RHIS strengthening implies investing resources with a defined timeline for how long sites will be supported, and indicates how this support fits a longer term strategy to strengthen malaria surveillance in all malarious regions. The RHIS strengthening should focus on high burden areas but the long-term goal is to strengthen surveillance in all areas.

To avoid potential confusion with support for sentinel sites or clinical strengthening, PMI request only using the term RHIS strengthening (and not terms like "enhanced surveillance," "malaria reference centers"). This does not mean that those sites will no longer be supported but that the MOPs should be clear in describing the overall strategy for RHIS strengthening efforts aimed at facilities, and how this will be rolled out to encompass surveillance at district, regional, and

[136] http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/sentinel/en/

national levels with an overall long-term goal of nationwide reach of RHIS strengthening efforts.

To improve data quality at facilities, in some cases, the efforts will include improving diagnostics in addition to strengthening routine reporting. Improving diagnostics is critical to obtaining accurate malaria data, and integrating PMI activities across technical areas (e.g., case management and SM&E) almost always makes sense. In the country MOP, activities that support strengthening diagnostics should be included under the case management section while RHIS strengthening activities should be included under SM&E. If the same partner is implementing both activities, the level of effort must be estimated and budgeted accordingly.

Measuring results

As PMI increases investment in RHIS, there is a need for measurable results. In order to help track country progress in RHIS strengthening, the MOP template now includes the required routine surveillance indicator table below to track key indicators.

Indicators	Value	Comments
1. Total number of reported malaria cases Data source:		
Total diagnostically confirmed cases		
Total clinical/presumed/unconfirmed cases		
If available, report separately for outpatients and inpatients		
Outpatient number of reported malaria cases		
Diagnostically confirmed		
Clinical/presumed/unconfirmed		
Inpatient number of reported malaria cases		
Diagnostically confirmed		
Clinical/presumed/unconfirmed		

2. Total number of reported malaria deaths Data source:		
Diagnostically confirmed		
Clinical/presumed/unconfirmed		
3. Malaria test positivity rate (outpatients) Data source:		
Numerator: Number of outpatient confirmed malaria cases		
Denominator: Number of outpatients receiving a diagnostic test for malaria (RDT or microscopy)		
4. Completeness of monthly health facility reporting Data source:		
Numerator: Number of monthly reports received from health facilities		
Denominator: Number of health facility reports expected (i.e., number of facilities expected to report multiplied by the number of months considered)		

Note that in moderate/high-transmission settings it is not necessary or cost effective for a national surveillance system to track and monitor individual cases. Case registry, aggregation, and mapping is appropriate at a community health worker and health facility level; however at the district and national levels, aggregate data are more appropriate for following trends and malaria risk stratification for intervention planning in the moderate/high-transmission settings. (See the **Pre-Elimination** chapter for details on individual case level surveillance activities such as reactive surveillance.)

Parallel malaria-specific efforts

For surveillance purposes, PMI has supported both parallel malaria-specific surveillance systems and parallel malaria reporting systems. For clarity, here is a brief explanation of the difference between the two:

- **Parallel malaria-specific surveillance system**: This is a system operating outside of the RHIS used to collect specific malaria indicators that are implemented. These systems employ their own data collection tools, reporting tools, management, and supervision structures. Sentinel sites, as supported by PMI in the past, are an example of such systems. PMI support to these systems in the past was important because routine data on malaria cases and deaths were not widely available from other sources. As routine systems have improved over time with PMI and other partner support, PMI will not support such systems in existing PMI-supported. The exception to this guidance is when RHIS (e.g., HMIS) is not functional or the data are of such poor quality that they cannot be used to inform programmatic decision-making. In such cases, supporting a parallel malaria-specific surveillance system could be a temporary solution as part of a larger strategy to strengthen RHIS. The decision to support or develop a parallel system should be clearly justified and made in consultation with the PMI Headquarters SM&E Team.

- **Parallel malaria reporting structure**: This is an alternate reporting route for RHIS malaria data to ensure the data are received by the NMCP. In some countries, it has been difficult for the NMCP to access routine data from the HMIS or IDSR in a timely manner (or at all). In such circumstances, PMI may support the NMCP to develop a reporting "work-around" where districts or facilities report routinely collected malaria data directly to the NMCP in addition to the formal reporting mechanism for the RHIS. As above, PMI may provide this support as a temporary solution to NMCP data access issues, but again, only as part of a broader strategy to strengthen RHIS. The decision to support or develop a parallel reporting structure should be clearly justified and made in consultation with the PMI Headquarters SM&E Team.

In settings of low malaria burden, additional considerations for malaria surveillance strengthening may be warranted:

- **Epidemic prone areas**: In areas with low malaria burden, if the HMIS cannot be adapted or the IDSR is not functional, a parallel system that reports on malaria cases more frequently than monthly may be required to detect sudden upsurges that could indicate an epidemic. As timeliness of reporting is critical, epidemic detection systems should be based on at least weekly summary reporting from facilities. Another key component is setting appropriate thresholds so that every seasonal increase isn't investigated. Zanzibar's Malaria Early Epidemic Detection System is an example of a

malaria-specific surveillance system for epidemic detection. In most cases, it would be optimal for a country to build a malaria epidemic surveillance system into an existing reporting system such as the HMIS or IDSR, rather than establishing a stand-alone malaria epidemic detection and reporting system.

Countries should note that epidemic detection systems are meant for **LOW** burden areas. Moderate/high malaria burden areas maintain levels of immunity that make epidemics much less likely. That doesn't preclude an upsurge in malaria cases in these areas. However, rapid detection and response are typically not required, but rather adjustments to malaria control interventions. Countries should not use limited resources on investigating "outbreaks" in moderate/high burden settings.

- **Pre-elimination**: In situations where a country has transitioned into pre-elimination, either nationally or sub-nationally, a malaria-specific surveillance system may become necessary because individual case-level data is required to facilitate case investigations. Please see the **Pre-Elimination** chapter for more information.

Activities in support of malaria-specific surveillance may include surveillance system development, training, supervision, and communications. The decision to support malaria-specific surveillance systems in addition to routine information systems (HMIS/IDSR) should be informed by country context (e.g., need for epidemic detection, pre-elimination considerations, leveraging other donor support). Implementation must be thoughtfully and realistically conceived and closely monitored to adjust and revise the approach as needed. PMI experience has shown that establishing such systems is often challenging and resource-intensive. In settings where routine data are already of poor quality, a separate surveillance system will have to overcome the same issues: lack of capacity, poor infrastructure, and competing priorities for healthcare workers, among others.

Support for models to predict epidemics is not recommended with PMI country funding. There are currently global efforts to develop improved models.

Population-based surveys

National-level household surveys

For PMI SM&E needs, conducting a national-level household survey, within established survey timelines set by the Ministry of Health and other partners, is recommended. In moderate to high transmission areas a survey every 2-3 years might be appropriate; in low prevalence areas, an interval of 3-5 years would be more acceptable. The type of national-level household surveys supported by PMI will generally be a MIS, DHS or MICS that includes the standard malaria module. While PMI has typically funded an MIS in full or in partnership with the Global Fund, the contribution from PMI to a DHS or MICS has typically ranged from $350,000-$500,000. In

recent years, the frequency of such surveys has increased as donors seek evidence of the impact of their investments. There is also an increasing trend (not supported by PMI) towards removing malaria modules from DHS or MICS surveys and advocating for a separate MIS the same year or within 18 months of the DHS/MICS. If a DHS or MICS is planned for a given year, PMI should support it and ensure that the appropriate malaria questions have been included, rather than supporting a separate MIS during the same year. If appropriate, the inclusion of biomarkers in these surveys may be negotiated with the survey planning teams. PMI does not support national-level household surveys that collect malaria indicators more frequently than every two years regardless of donor source.

Some NMCPs and partners are requesting that national-level household surveys be expanded to obtain estimates with sufficient statistical power for sub-regions or population sub-groups (e.g., school-age children or people over 15 years of age). Per RBM Monitoring and Evaluation Reference Group (MERG) guidelines, PMI has supported surveys with sample sizes large enough to estimate coverage of interventions by malaria transmission zones as defined by the Mapping Malaria Risk in Africa climate suitability index (usually 3-5 zones per country). To obtain reasonable estimates for sub-regions or for sub-populations outside of RBM-MERG-recommended ones, sample sizes and survey complexity and cost will increase. These concerns, in addition to on-going efforts to ensure that the quality of survey data are maintained, PMI and RBM-MERG currently do not support such survey expansions. If the NMCP and/or PMI country team believes it needs such estimates and is requesting PMI support, the PMI in-country team is asked to consult with the PMI Headquarters SM&E Team. In some situations, other cross-sectional survey methodology may be more appropriate.

The MIS includes measurements of parasitemia and anemia while the DHS includes anemia as part of the nutrition module but does not routinely include parasitemia. The UNICEF MICS does not routinely include any biomarkers, but technical assistance can be provided to include biomarkers to the MICS.

Parasitemia measurements in population-based surveys

PMI supports parasitemia testing in children 6-59 months of age in countries with a national prevalence estimate of >3%. In general, PMI does not support parasitemia testing outside of this age group to the following considerations:

- PMI does not recommend parasitemia testing below six months of age. The number of children under six months of age that test positive for malaria parasites would be very small and would result in an under-estimate of malaria parasite prevalence.
- Adding other age groups (i.e., school-age children, pregnant women) to be tested will make the survey process more labor intensive and runs the risk of compromising the quality of the survey.

- Gaining access to school-aged children (5-14 years old) can be logistically difficult and more costly. Often these children are at school when the surveyors come by the house, requiring repeat visits. The children that are at home may be the sick children, therefore resulting in selection bias.
- Testing pregnant women for malaria parasites during household surveys raises ethical concerns. Survey protocols require appropriate treatment with ACTs for anyone testing positive for malaria during the survey. If women of reproductive age (15-49 years) are included in surveys, it presents the possibility of pregnant women in their first trimester (who do not know they are pregnant or are not disclosing they are pregnant) being treated with ACTs, which are not approved by WHO for treatment during the first trimester of pregnancy.

If a planned MIS or DHS contains parasitemia testing in age groups outside 6-59 month olds, PMI will support the survey (provided it has been approved by the PMI Headquarters SM&E Team), but will not fund the testing in the additional age groups.

As countries enter the pre-elimination phase of malaria control, the focus will shift to heightened surveillance systems that provide continuous information, rather than periodic nationwide household parasitemia surveys. Therefore, PMI recommends that in countries where national parasite prevalence in children under 5 years of age is below 3% in two successive national surveys, collection of parasite burden by microscopy or RDTs and hemoglobin through national surveys should be discontinued. Exceptions can be made in countries where parasitemia has substantially declined in some regions of the country, but remains greater than 3% in other regions.

Combined national-level surveys

While collaboration with other groups conducting large-scale health surveys (such as a national census or an AIDS Indicator Survey) can be mutually beneficial, past experience has shown that there can be serious challenges when surveys are combined. The logistics for planning surveys is complex and combining surveys increases the complexities and introduces additional coordination issues across partners and technical areas, resulting in increased sample sizes, delayed surveys, and impacting overall data quality. If combined surveys are planned, it is recommended that PMI in-country teams consult with the PMI Headquarters SM&E Team to help negotiate with other stakeholders to ensure that PMI needs will be met, including an agreement such as an memorandum of understanding that outlines PMI's participation in the review of preliminary malaria data, as well as receipt of the full report and final dataset within an

agreed upon time limit.[137] The standard malaria modules in the DHS, MICS, and MIS surveys are interchangeable. If concerns exist about the quality of any of these surveys, country PMI teams are encouraged to speak with the PMI Headquarters SM&E Team in the early stages of survey planning.

Special cross-sectional surveys (e.g., post- LLIN campaign surveys)

Special cross-sectional surveys can be designed to answer programmatic questions that pre-planned national-level household surveys cannot. Issues related to timing or a need for detailed data that cannot feasibly be added to a DHS or MIS may necessitate a separate survey. These surveys may focus on particular sub-populations or geographic areas of programmatic interest. They may, for example, be used to assess the result of a particular intervention strategy (e.g., LLIN ownership after a sub-national LLIN distribution campaign), or malaria burden in a sub-group of individuals (anemia and parasitemia in school-age children), or utilize malaria measures other than parasitemia or RDT (e.g., serology or PCR). PMI only recommends these surveys when a clear and necessary programmatic question needs to be answered and no other suitable data source for addressing the question exists. If the timing of a larger planned survey, such as DHS or MIS, coincides with the desired timing of a special survey, every effort should be made to utilize the planned DHS or MIS. Special surveys should be timed for optimal data collection based on the programmatic question they are intended to answer and should not be repeated annually.

If special surveys are proposed in country MOPs, country teams should provide concise descriptions of the activity that outlines the programmatic question, scope, scale, and timing of the survey, in addition to how the information would be used to improve program implementation. A clear determination should be made whether the survey proposed is operations research; and in such cases coordination with the PMI Headquarters Operational Research Committee should be done.

Health facility-based surveys

Health facility surveys (HFS) capture cross-sectional data from health facilities on several aspects of the health system including availability of commodities, appropriateness of case management, data reporting, record reviews, diagnostic capacity, health worker training, and other indicators critical to malaria programs. They can be used in establishing a baseline level of health system function before interventions or changes in policies (that could result in changes in malaria programs) are implemented. Changes in relevant indicators after the intervention activity has taken place (or policy changes implemented) can be measured through follow-up HFSs. Health facility surveys are useful in situations where routine information systems and household

[137] The DHS Program includes an MOU for all surveys (DHS and MIS) that agrees to provide public access to the dataset after the national dissemination of the final report. In surveys that are implemented by other partners and partially or fully funded by PMI, an MOU should be developed and negotiated for access to the dataset.

surveys may not be able to provide the necessary information to meet the needs of the NMCP or PMI. The type of information required, the level of detail, and other factors will determine the appropriate HFS methodology to be used. Health facility surveys should not be used as replacements for the HMIS, and therefore, should not be repeated more than every 2-3 years, depending on the information required.

There are several types of health facility survey protocols, which vary in the aspects of the health system on which they focus, the overall cost and complexity, as well as how the results should be interpreted. For PMI purposes, HFSs that produce estimates quickly – within three months – should be favored as commodity data rapidly becomes non-actionable. Several of the HFSs collect data associated with other diseases of childhood. Whenever possible, integration of data collection of other child health conditions should be pursued.

Finally, costs will vary widely, from $150,000 to over $1 million depending on the sample size and method. In general, because health facility surveys can be very comprehensive and include many other health delivery systems, PMI should not cover the full cost of a facility survey. PMI can support up to 30% of all HFS costs.

Service provision assessment

Service provision assessment (SPA) surveys examine the supply side of health care and the strengths and weaknesses of a country's public and private services. A SPA is one of the most complex of the facility surveys and collects data from a large sample of health facilities on the readiness and availability of specific health services and commodities as well as quality of services. The SPA focuses on nine key services: (1) child health; (2) maternity and newborn care; (3) family planning; (4) sexually transmitted infections; (5) HIV/AIDS; (6) malaria; (7) tuberculosis; (8) basic surgery; and (9) non-communicable diseases. The SPA includes assessment of health provider practices in each of the key services through direct observation, health worker interviews and exit client interviews. Instruments typically used in a SPA are:

- Health worker interview
- Exit interviews
- Observation protocols
- Inventory

The tool can be found at: http://dhsprogram.com/What-We-Do/Survey-Types/SPA.cfm

Service availability and readiness assessment (SARA)

The SARA is designed to assess and monitor the service availability and readiness of the health sector and to generate evidence to support the planning and managing of a health system. The SARA is designed as a systematic survey to generate a set of tracer indicators of service

availability and readiness. The SARA has been developed by WHO in conjunction with global partners to fill critical data gaps in measuring and tracking progress in health systems strengthening. While the SARA is not malaria-specific, it is possible to include a patient exit interview module to assess malaria case management practices; an optional data quality assessment module is also an option. Instruments typically used in a SARA are:

- Staffing
- Inpatient and observation beds
- Infrastructure
- Available services
- Diagnostics
- Medicines and commodities
- Interviewer's observations

The tool can be found at: http://www.who.int/healthinfo/systems/sara_introduction/en/

Integrated management of childhood illness health facility surveys

The IMCI HFS collects health facility data exclusively on childhood diseases including pneumonia, diarrheal disease, and febrile illnesses (malaria, including trigger points for management and referral for severe malaria). This survey produces findings within 12 weeks from start of implementation and can be adapted to different sample sizes. Instruments typically used in the IMCI HFS are:

- Health worker observation checklist
- Exit interview – caretaker of child
- Re-examination
- Equipment and supply checklist
- Health workers interview (optional)

The tool can be found at:
http://www.who.int/maternal_child_adolescent/documents/9241545860/en/

End-use verification (EUV) tool

Although not a HFS in every extent, the EUV does collect facility-based data. PMI must ensure that USG-procured malaria commodities are reaching health facilities and are available to end users. The EUV Tool, or another tool that monitors the availability of malaria commodities at the facility level, should be used in a sample of health facilities in all PMI focus countries two to four times a year. Stockouts of key commodities should be followed up and quantification, procurement, and logistic issues resolved as soon as possible. In countries (Guinea, Liberia, and Malawi) with a small number of facilities (<750), the EUV can produce, depending on how the

sample is taken, nationally representative annual estimates. When not representative, the estimates produced by the EUV Tool in a given quarter/semester are meant to give a general picture of malaria commodity availability at district or sub-district levels and encourage timely action to correct problems.

Evaluation

Evaluation is a critical component of any national malaria control program and should be integrated into national SM&E strategic plans. PMI supports both program and impact level evaluations at the country level, however there are a number of considerations to take into account when programming funds for evaluation activities.

PMI generally does not support evaluations aimed at establishing/researching a specific intervention's impact on morbidity or mortality. PMI is based on a principle of implementing **already-proven interventions** and thus does not support individual country programs to test/research any one intervention or package of interventions to assess its impact of malaria morbidity or mortality. Also, given PMI's success in increasing coverage of multiple interventions across countries, conditions do not lend themselves easily to evaluate the impact of single interventions.

As interventions are being scaled-up, PMI encourages evaluations in countries where these interventions are not resulting in the expected outcome. These evaluations can help to identify ways to improve the effectiveness, coverage, or service delivery of individual interventions.

Program evaluation

There may be a number of times in a program's lifecycle when an evaluation is necessary to inform further programming decisions. Some examples of when a program evaluation might be useful include evaluating a pilot to inform decisions about scale-up of interventions, evaluating the effectiveness of one programmatic approach against another, or evaluating project achievements at the end of an activity before a programmatic redesign process.

Malaria program reviews per WHO methodology is generally supported by PMI. Malaria program reviews should be carefully planned and coordinated with all partners, last less than one year, not be repeated more frequently than every four years, and produce actionable data and information. No more than $100,000 of PMI resources should be budgeted in total for a malaria program review.

Impact evaluation

Evaluations of impact are generally good practice; however PMI will not be funding these evaluations in every country. Impact evaluations are used to determine whether supported activities have had the desired effect on morbidity and mortality under operational conditions.

Generally, evaluations of impact should be carried out only when interventions have reached sufficient coverage to expect impact. Globally-accepted methodologies preferably sanctioned by the WHO or the RBM MERG should be used to ensure consistency and comparability across time and countries. Evaluations of impact should be transparent and participatory. As many stakeholders, both within malaria control and without, should be encouraged to participate in the design, analyses and production of reports.

The PMI Headquarters SM&E Team will reach out to countries that should consider an evaluation of impact to help plan it and support it.

Activities No Longer Supported By PMI

Demographic surveillance system sites

PMI does not provide direct support demographic surveillance sites to monitor births, deaths, and health in geographically-defined populations continuously over time. It is possible, however, that PMI might provide some limited support for data analysis of existing data in the context of impact evaluation activities.

Verbal Autopsies

Following several pilots of the use of the verbal autopsy procedure, PMI has taken the decision to no longer use verbal autopsies to assess impact on malaria-specific mortality. The specificity and sensitivity of verbal autopsies for several fever-associated diseases, such as malaria, is low and verbal autopsies cannot be used to determine malaria-specific mortality within acceptable bounds.

SM&E Appendix 1: System Requirements at Various Health System Levels During Control and Pre-Elimination Phases

	Control (SPR >5% amongst all febrile patients)	Pre-elimination (SPR <5% amongst all febrile patients)
Community Health Worker	Test and treat malaria appropriately Document and report all cases Supervision and feedback	Test and treat malaria appropriately Document and report all cases
Health Facility	Test and treat malaria appropriately Malaria cases, diagnostic testing results, and case management documented in registers Cases are graphed monthly to quarterly to identify trends Aggregated data transmitted monthly to district and higher ideally electronically Supervision and feedback	Registers of individual malaria cases, diagnostic testing results, and case management documented Cases are graphed daily to weekly to identify trends that may require focal response Data transmitted weekly to district and higher ideally electronically
District / Province	Aggregate data of uncomplicated cases, severe disease, and deaths summarized monthly to allow an understanding of the burden by district and health facility catchment levels Analysis of data Data used to set priorities for interventions	Aggregate case and death data summarized weekly or monthly to allow an understanding of the needs by health facility catchment or village level to help set priorities for interventions Register of severe cases and deaths maintained and case investigations performed to identify program breakdowns and needs
National	Monthly to quarterly tabulation of cases and deaths to assess control efforts and prioritize activities Analysis of data Data used to set priorities for interventions	Weekly tabulation of cases and deaths to assess control efforts and prioritize activities

Operational Research

New/Key Messages in the FY 2017 Technical Guidance

- Annual deadlines for OR studies proposed in MOPs and reprogramming requests: September 23, 2016 and February 10, 2017.
- All manuscripts and abstracts resulting from PMI-funded OR must be reviewed by both agencies prior to submission (see separate guidance on clearance) and shared with PMI Headquarters OR Management Team after acceptance (this is not new policy, but will now be implemented fully).
- MOPs should include brief description of national OR strategy, implementation or policy changes resulting from OR findings (progress in any OR studies conducted since PMI was launched), and progress in OR during the last 12-18 months.
- MOPS should clearly state research question(s) and study rationale for any proposed FY 2017 OR studies.
- A diagram of the OR approval process from concept note development to project implementation is included below.

Introduction

Operational Research (OR) plays an important role in improving the successful implementation of PMI malaria control strategies and in achieving the PMI goal. Since 2006, PMI has supported numerous OR studies addressing a range of programmatically-relevant topics and continues to do so in support of the new *PMI Strategy 2015-2020.* Appropriate questions addressed by OR studies include how to improve scale-up of interventions, how to further increase effectiveness of existing interventions, how to implement combinations of these interventions in sequence or in parallel, and how the interventions should be tailored to different epidemiological settings. Additional important questions include how to implement interventions in the most cost-effective manner, how to preserve the effectiveness of proven interventions threatened by resistance or other risks, and how best to incorporate promising new interventions and innovations that have the potential to further reduce malaria morbidity and mortality, including in areas where some of the proven interventions currently available are either not sufficiently effective or where implementation is not feasible.

PMI OR Objectives

To achieve its goal, PMI will support program- and policy-relevant OR that will:

- Improve effectiveness of existing interventions and increase scale-up, including assessing combined interventions (e.g., ITNs and IRS)
- Evaluate ways to mitigate insecticide and drug resistance
- Identify and assess improved and cost-effective approaches to monitoring changes in malaria burden
- Identify and assess approaches to improve the capacity of health systems to better deliver malaria interventions
- Assess new interventions that offer the potential for use by PMI-supported programs in the near future
- Assist in optimizing program efficiency by addressing bottlenecks in malaria prevention and control

Funding Sources and Channels/Mechanisms for PMI Operational Research

Funding for PMI OR activities may come from two places within the PMI budget:

- **PMI country/MOP budgets**: PMI OR studies funded with country MOP funding are generally conceived and designed by PMI country teams in consultation with NMCPs and local partners and are frequently implemented by local research groups. These tend to be shorter-term studies (duration of 12-15 months) and typically have had budgets below $150,000, although these are not restricted to this time frame or funding limit. The amount of country funding proposed for country-specific OR activities varies by country and by year.
- **PMI core funds allocated for OR priorities**: PMI OR studies funded centrally with PMI core funding generally address broader issues applicable across the initiative and tend to be larger with higher budgets than country-generated OR activities. These may involve two or more PMI focus countries and/or require several years to complete. The amount of core funding made available for priority OR activities varies from year to year depending on several factors including the overall total PMI budget, other PMI core budget priorities, and the incremental funding needs for multi-year studies funded in previous years.

Whether the source of OR studies is core- or country- (MOP) funding, a variety of mechanisms are available to carry out PMI funded research and which mechanism is selected depends on a variety of factors including the research question. Options include, but are not limited to: USAID

country bilateral and central implementing partner mechanisms including USAID direct funding of local research institutions, funding through the CDC IAA with direct implementation by CDC staff and/or implementation together with local partners, or a combination of the above. It is expected that PMI will continue to make use of multiple funding channels/mechanisms in the future. Prior approval is required if proposed research studies involve PMI funding to CDC to then move to a local research partner or institution as the CDC IAA includes policy restrictions for USAID appropriated funding to pass to CDC and on to a third party. Direct funding of MOH/NMCP/host country governmental institutions can be considered through a USAID G2G mechanism. Funding MOH/NMCP/host country government institutions through CDC with USAID appropriated funding is prohibited (see **Section A**, "**G2G**" section).

PMI co-funding of activities with other institutions and organizations also occurs and is highly encouraged. Examples include the multi-center study on SP efficacy in pregnancy co-funded with CDC, European and Developing Countries Clinical Trials Partnership, and others. This type of cooperative research effort is encouraged during the review process, especially for studies whose results are applicable to a new global policy recommendation or one under revision where a larger body of evidence will be desired.

PMI OR Priorities

PMI staff have developed a priority listing of OR topics organized by programmatic area. Consistent with recommendations from the external evaluation of PMI, this listing was reviewed by external partners, including donors, USG agencies, and malaria researchers. Because PMI core and country-level OR funding is limited, it is important to set priorities for funding and to avoid unnecessary duplication with studies supported by other malaria research initiatives. There may be unique situations where PMI may choose to prioritize support for a research study that complements ongoing research by others, particularly where the research question is of priority importance to PMI. The list of PMI OR priorities is reviewed approximately biennially as new research findings and issues in malaria control emerge and to ensure the list remains flexible and responsive to changes in malaria epidemiology and health systems. The current priority list (finalized in December 2013) is being revised and will be shared with the field for input in early 2016.

While basic research questions and exploratory research studies should continue to be part of the larger USG malaria research portfolio, PMI will not provide financial support for these types of studies, which are primarily funded by other USG agencies such as CDC (non-PMI), National Institutes of Health and Department of Defense. Rather, PMI will advocate for investments by other agencies and donors supporting basic and applied malaria research to consider funding activities that complement PMI's programmatic and OR activities.

Individual countries may have different priorities than those found on the priority OR listing. Country-specific OR activities are eligible for MOP funding, even if they are not included on the list, provided they are consistent with the guidelines for selection of OR activities for PMI funding.

Guidelines for Selection of OR Activities for PMI Funding

The following guiding principles were developed to assist the OR Committee when considering which OR activities (country or core funded) should be prioritized for funding. These guidelines apply to all PMI-funded OR activities. In general, OR research funded with PMI country-specific MOP funding responds to country-specific priorities and needs while core-funded OR typically addresses broader issues that are relevant across PMI's programs. Core-funded OR may be conducted across multiple countries and may address fundamental questions to achieve optimal impact from proven interventions.

Guiding principles:

1. The OR study should be aligned with one of the PMI OR objectives. In addition, in the case of MOP-funded OR activities, the OR activity must focus on a country-specific priority that is consistent with the country's immediate needs and national OR strategy.

2. Priority should be given to studies that improve the implementation of existing PMI-supported interventions and are likely to produce information that will have the greatest impact in reducing malaria burden and, in some areas, eliminating transmission.

3. When considering whether to prioritize a study for funding, the OR Committee will take into account the number of studies that PMI is already funding on the same subject, whether another donor is funding similar research, and the number of ongoing PMI-supported OR activities in a given country and the capability of the PMI team to oversee those studies given their other responsibilities.

4. In the case of core-funded OR, priority will be given to OR proposals that take advantage of PMI's capacity to conduct research across multiple PMI-supported countries. Lower priority for core-funding will be given to OR proposals that can be conducted through smaller country-specific studies.

It is recognized that some high priority OR activities may take several years to complete. Therefore, PMI does not impose restrictions on study length nor likely time from study start to intervention implementation for PMI OR studies. However, when considering which of several high priority studies to fund, the time from study start to likely time of intervention

implementation will be considered, recognizing that research itself can accelerate the timeframe to policy adoption and intervention implementation.

All PMI-supported OR studies, regardless of the implementing partner or funding source, will be reviewed, approved and monitored by an interagency OR Committee to ensure efforts are coordinated and support PMI's goal. It is expected that CDC will be a key implementer of PMI-supported OR, as specified in the Lantos-Hyde Act, when CDC has a comparative advantage over other institutions and organizations for conducting that research.

OR Study Development, Review, and Approval Process (MOP-Funded)

Review of concept notes and protocols will now be synchronized with the MOP cycle. Concept notes for activities funded with reprogrammed funds will be reviewed in October (**due September 23, 2016**). Concept notes for OR activities proposed in draft MOPs will be reviewed in February (**due February 10, 2017**). Ad hoc review of concept notes and protocols will be possible if a study timeline requires off-cycle review.

OR concept development and inclusion in the MOP

When developing potential OR topics, country teams should ensure that they will address a pressing country need, are feasible to answer considering the budget and length of time required, align with the country operational research strategy or priorities, and fall within the PMI-OR priority list or guidelines for selection of OR activities. When proposing OR in the MOP or reprogramming request, teams should include a brief background or justification, along with references to similar or completed studies in the same or different country setting. In addition, clear research question(s) should be presented in the MOP narrative. During the MOP review process, the proposed research concept will be reviewed to determine if: (1) the proposed research question is a priority and thereby given a green-light to proceed to full concept note development and submission; or (2) the proposed research question is not a priority and the country team is *not* advised to further develop and submit a concept note.

Concept note review

Once proposed OR is approved in a MOP or reprogramming request, the study team must submit a concept note for review by the interagency OR Committee using the template provided in **OR Appendix 1**. The concept note will first be screened by the PMI Headquarters OR Management Team for completeness within one week of submission incomplete concept notes will be returned without review. Complete concept notes will then be sent to the OR Committee for review and a response returned to the study point of contact (POC) within four weeks of the submission due date. Concept note review by the OR Committee can have the following three outcomes:

- **Approve:** The OR Committee determines that the proposed study will provide valuable information and is technically sound and recommends it for funding. Protocol development may proceed and must incorporate any outstanding questions or issues identified by the OR Committee. The full study protocol must be submitted for review by the OR Committee for final approval.

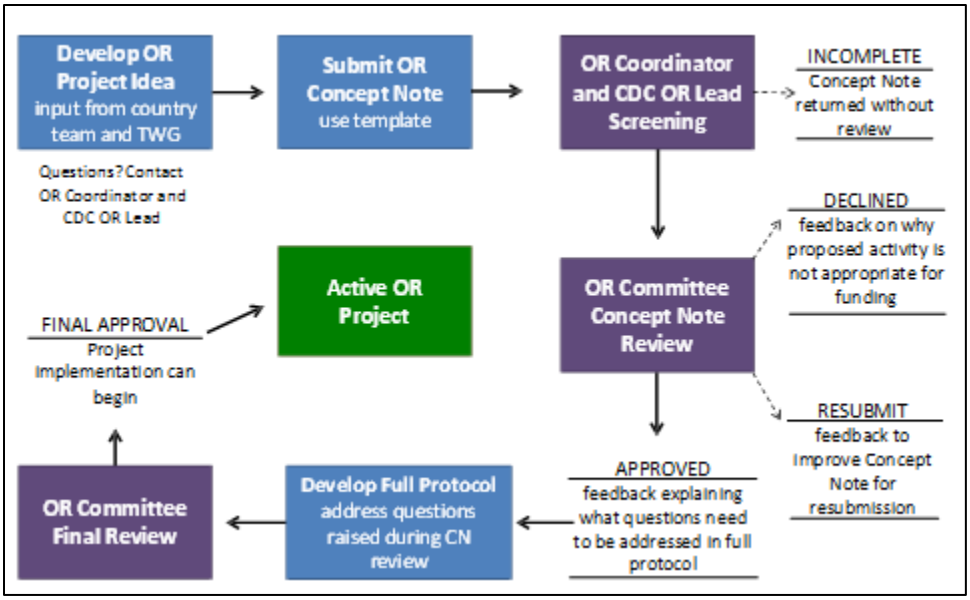
- **Resubmit:** The OR Committee determines that the concept has significant problems with the study design as proposed. The committee recommends that the concept note be revised and resubmitted, providing extensive feedback to help guide revisions. The OR Committee will work with the study POC to establish a resubmission and review timeline.

- **Decline:** The OR Committee determines that the proposed study is not appropriate for funding. Clear feedback will be provided explaining why this conclusion was reached. If the declined approval seems unjustified, an appeal of the decision can be made which can include a review of the OR Committee decision by PMI leadership. All appeals should be directed to the PMI OR Coordinator.

Protocol review

Protocols must be submitted to the PMI OR Committee for review prior to submission to relevant Institutional Review Board approval(s). Protocols will be reviewed to ensure the study is technically sound and is consistent with what was proposed in the concept note, including study budget and timelines. Outstanding questions or issues identified by the OR Committee during concept note review must be addressed in the protocol. Any significant changes to the study that have occurred between concept note approval and protocol submission must be explained. Protocol review results will be returned to the study POC within six weeks of the protocol submission due date. **Figure 1** depicts the OR review and approval process from inception to implementation:

Figure 1. MOP Funded OR Project from Idea to Implementation



Reporting Requirements for Ongoing OR Activities

PMI-funded OR activities are required to submit **semi-annual progress reports** regardless of funding mechanism. Progress reports must provide information regarding study activities for the preceding six months. A report covering activities January-June will be due in July; a report covering activities July-December will be due in January. A template to guide preparation of the progress report can be found in **OR Appendix 2**. Information submitted on progress reports will be used to monitor study implementation, coordinate among studies, and for internal or external updates including the IAG and PMI annual report. A final report and/or data presentation is required at study completion. **Conference abstracts and manuscript drafts resulting from the study must also be submitted for clearance through PMI HQ prior to submission (see Section A for additional guidance on clearance) AND as final versions to the OR Management Team upon acceptance.** Please note that submission of abstracts and manuscripts to the OR coordinator is not for review but for notification purposes only.

Authorship Publications Resulting from OR Activities

PMI encourages early discussion of authorship with all parties involved in the design, implementation, data analysis, interpretation, drafting, and revision of manuscripts resulting from PMI-funded OR activities. A widely accepted International Committee of Medical Journal Editors guidance on defining roles of authors and contributors is available online: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.

Prior to preparing manuscripts and abstracts for submission to scientific peer-reviewed journals and conferences, authors should consider reviewing and adopting the reporting guidelines developed for different study designs such as:

- CONSORT for randomized trials (www.consort-statement.org)
- Clinical Trials (https://clinicaltrials.gov/)
- STROBE for observational studies (http://strobe-statement.org/)
- STROME-ID extension of STROBE for Reporting of Molecular Epidemiology for Infectious Diseases (http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(13)70324-4/abstract)
- PRISMA for systematic reviews and meta-analyses (http://prisma-statement.org/)
- PRISMA-P for systematic reviews and meta-analyses protocols (http://www.prisma-statement.org/Extensions/Protocols.aspx)
- STARD for studies of diagnostic accuracy (www.stard-statement.org/).
- SRQR Standards for reporting qualitative research: a synthesis of recommendations (http://www.ncbi.nlm.nih.gov/pubmed/24979285)
- CHEERS Consolidated Health Economic Evaluation Reporting Standard Statement (http://www.ispor.org/Health-Economic-Evaluation-Publication-CHEERS-Guidelines.asp)
- Reporting guidelines for implementation and operational research (http://www.who.int/bulletin/volumes/94/1/15-167585/en/)

Guidelines for Listing PMI and Agency Affiliations for OR Activities

Please refer to the **Section A** ("**Branding, Marking, and Communications**" section)

OR Appendix 1: PMI OR Study Concept Note- Submission Template

Study title:
Point of contact (specify both PMI POC and project PI, if different):
Country (-ies):
Program area(s) (e.g., ITNs, Case Management, MIP, IRS, etc.):
Type of study:
Total Study Budget:
Annual study budget by FY (if funded from multiple FY):
Source of study funds (e.g., Core, MOP including reprogrammed MOP funds):
Study start and end dates (anticipated):
Mechanism and partners (clearly indicate prime partner and local partners if applicable, including NMCP):

Concept note should be 2-4 pages in length, not including header material and budget justification. Be as clear and explicit as possible in each of the sections. Information that must be included is described below. If the requested information is not included in the concept note it will be returned for completion before OR Committee review.

Project Background:

- What is the main research objective(s)? Clearly state what the study will examine and its anticipated outcomes.
- How will the anticipated study outcomes impact NMCP programs, national policy or operational issues and/or PMI strategic efforts at large?
- How does the proposed research study address country-specific operational research priorities or the current PMI Operational Research Priorities? If it does not address a current PMI research priority, please explain why the research is important for the NMCP/country where the research will be performed. The current list of PMI Operational Research Priorities is available in the PMI Guidance Appendix and found at www.PMI.gov.
- Please describe briefly any other studies (current, planned or recently completed) addressing similar questions in the same or different locations. A list of PMI-funded Operational Research studies is available at www.pmi.gov. If other similar studies are being done, what added value will come from the proposed study?

Research Methods:

- Clearly and concisely describe the study methods, including the parameters below where applicable:
    - Study area
    - Study Population
    - Human subjects clearance process/ethical clearance (specify institution(s))
    - Study design
    - Sample size (must be sufficient to achieve study objectives)
    - Subject and control recruitment
    - Interview data collection
    - Biological sample collection and tests
    - Statistical analysis
    - Timeline

- Describe how data and results of the research will be disseminated to relevant in-country partners (e.g. NMCPs) to ensure that outcomes are known on a timely basis.

Budget Justification: Explain the study costs including overhead charges using the table provided below.

PMI Operational Research Project Budget Justification

Item	**Cost (USD)**
Personnel	
Supplies	
Equipment	
Training	
Travel	
Result dissemination/outreach	
Overhead	
Other costs	
Total	

OR Appendix 2: PMI OR Research Study Update Template

Title:
Country (if multiple please list):
Research Institution:
PI name and email address:
PMI POC name and email address:

Study start date (mm/yyyy):
Study end date (actual or expected – mm/yyyy):
PMI budget amount:
Funding source(s) (Core and/or MOP):
Fiscal year(s) of funds:
Funding mechanism:
Program area (e.g., Case Management, LLINs, IRS, MIP, SBCC, Pre-Elimination/ Transmission Reduction, HSS, and/or SM&E):
Summary (2-4 sentences summarizing the study objectives):
Status (CN approved, Protocol approved, Ongoing, Completed, or Published):
If study has not started, explain why:

Progress in the past six months (July 2015-December 2016) and results to date (2-4 paragraphs, include preliminary data and figures where possible):

Conclusions:

Major Outcomes:

Program or other impact:

Publication status and citation(s) if relevant:

Commodity Procurement and Supply Chain Management

New/Key Messages for the FY 2017 Technical Guidance

- Please refer to Appendix 1 for average lead times and costs of malaria commodities. Country teams are asked to review this list carefully, as, for example, current lead times are one year for LLINs, one year for AQ+SP for SMC campaigns, and 11 months for SP.
- PMI does not procure LLINs approved through the WHOPES equivalency program (i.e., "me-too" nets).
- PMI no longer supports the procurement of HRP2/pLHD 3-line tests.
- PMI is required to immediately report to the Inspector General any type of loss or theft of commodities.

Commodity Procurement

Introduction

Under the new PMI strategy, one of the five key areas to achieve our objectives is the continued scale up of proven interventions, all of which are predicated on the availability, in one way or another, of high quality commodities.

Prior to MOP visits, country teams should work with their NMCPs and partners to update national-level gap analyses – typically using information from stakeholder-coordinated forecasting and supply planning efforts and/or Global Fund concept notes – for all key malaria commodities in order to have a thorough understanding of the priority commodity needs looking forward. In the estimated commodities costing sheet, found in **Commodity Procurement and Supply Chain Appendix 1**, the cost of commodities includes the costs of goods plus estimates on freight, insurance to port, clearance costs, and required quality assurance testing. Country teams should also take into account the difference in planning requirements for warehousing and distribution needs of the various commodities when preparing order requests and build in the additional funding to the appropriate partner if needed. Countries should be aware of product lead times, which include production, quality assurance testing, shipping and customs clearance; the procurement of many malaria commodities require a lead time of eight months to more than a year. (Refer to **Commodity Procurement and Supply Chain Management Appendix 1** for product and country specific lead times).

Types of Commodities

Commodities procured by PMI include: LLINs, ACTs, SP (for IPTp and where appropriate, seasonal malaria chemoprevention), drugs for severe malaria, laboratory equipment, microscopes and supplies for microscopy, RDTs, insecticides for IRS, spray equipment, and related personal protective gear. For IRS-specific commodities, please refer to the **IRS** chapter, as this chapter will not address IRS commodities.

Long-lasting insecticide treated nets

PMI procures nets with specific approval through the WHOPES. Published by the advisory group to WHOPES, findings from product evaluations help inform procurement decisions of the global community, including PMI. Currently, there are 15 WHOPES-approved LLINs. However, for technical and programmatic reasons, PMI does not procure LLINs approved through the WHOPES equivalency program (i.e., "me-too" nets), as "me-too" nets have only passed phase I (laboratory-based) testing and the "me-too" determination is only based on chemical equivalency to the innovator net. Please refer to details regarding the decision to deviate from WHOPES found on pmi.gov http://pmi.gov/docs/default-source/default-document-library/tools-curricula/itn_procurement_specifications.pdf?sfvrsn=4.

All net procurements must be issued by the procurement agent in a formal request for quote to all PMI eligible manufacturers. PMI must ensure full and open competition in compliance with USG regulations. The expectation from Congress and the Administration is to ensure value for money, which could be construed as procuring more nets for the same dollar value. However, in the past, a limited number of PMI focus countries have procured conical nets, which are costlier than rectangular nets. Therefore, the PMI Headquarters Commodity Procurement and Supply Chain, in collaboration with the ITN Team, culled data from six years of net procurement and commissioned VectorWorks to analyze net preference versus use, and is in the process of recommending standard specifications for net procurement (e.g., size, denier, shape) to PMI leadership. The definition, as well as the process for seeking exceptions to the standard specifications, will then be disseminated to all PMI staff.

There are ongoing durability studies which may impact procurement policy in the future (see the **ITN** chapter for information on LLIN durability).

Long-lasting ITN campaigns often require very early planning, ordering, delivery, and significantly greater net quantities, all of which must be considered in order for the timely arrival of nets and for manufacturers to be able to meet production demand. In contrast, continuous LLIN distribution often requires planning for more regularly spaced orders, adequate permanent warehousing options, and more consistent net quantities. **Regardless of the distribution**

mechanism(s), LLIN lead times are approximately one year, and must be accounted for during planning processes.

Artemisinin-based combination therapies, other antimalarial drugs, and essential medicines

PMI's policy for antimalarial drug procurement remains to prioritize PMI support for procurement of a country's first-line drug and leaving procurement of second line drugs to the MOH and other partners. For countries with antimalarial treatment policies inconsistent with WHO guidance (e.g., the few countries that have more than one first-line drug), a prioritization of one of the first-line drugs for PMI procurement is required. Exceptions to this policy require PMI leadership approval. Although PMI procures a range of antimalarial drugs, consistent with WHO malaria treatment and prevention guidelines (as well as aligned with IMCI guidelines under PMI's iCCM rubric), PMI does not procure ACTs without *either* an approval through a stringent regulatory authority (SRA)[138] (such as the U.S. FDA) or the WHO-Prequalification Program (PQP).[139] SRAs employ a robust drug dossier review to consider the safety, efficacy, and quality of pharmaceuticals intended for human use.[140] Given the history of malaria epidemiology in developed countries, research and development for new products by large pharmaceutical companies was lagging significantly before 2000. Historically, this meant there were few products indicated in the treatment of malaria with approval by an SRA. Although several SRA-approved ACTs have come to market in the last 10 to 15 years, when no SRA-approved ACT is available, PMI depends on approval by the WHO PQP. While the WHO is not a regulatory body, their PQP for artemisinin-based products applies a robust dossier and manufacturing site review process, resulting in approved products of known quality, safety and efficacy.[141]

Currently, there are only three ACT products approved by a stringent regulatory authority, two of which have been procured with PMI funding: Novartis' Coartem® (artemether-lumefantrine), Sigma-Tau's Eurartesim® (dihydroartemisinin-piperaquine), and Shin Poong's Pyramax® (pryonaridine/artesunate).[142] There are also several fixed dose combination ACT formulations that have received approval through the WHO PQP. The PQP approval process operates on a

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[138] Currently, the drug regulatory authorities of the European Union, Japan, USA, Canada and Switzerland have implemented International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) guidelines and are considered stringent regulatory authorities; there are also various industry organizations from the aforementioned countries who hold SRA status, and some member states with observer status. For more information, visit http://www.ich.org/about/faqs.html

[139] http://apps.who.int/prequal/query/ProductRegistry.aspx

[140] The ICH is an internationally recognized body comprised of representatives from regulatory agencies and pharmaceutical companies globally to help develop standards around drug registration with an objective to harmonize interpretation and application of technical guidelines.

[141] Historically, the WHO PQP approved only ACTs antimalarials (co-blistered products and now co-formulated). It is currently, however, reviewing dossiers for non-ACTs used in SMC.

[142] PMI has yet to receive a request from any PMI country to procure Pyramax.

rolling basis, which means new products are approved periodically. Several fixed-dose combination formulations of both artemether-lumefantrine and artesunate-amodiaquine have been approved by WHO PQP and therefore added to the WHO prequalification list[143] over the recent years. PMI can procure these products and subjects them to the same testing requirements of other non-SRA approved pharmaceuticals procured with PMI funds.

Of note, in 2015, Novartis received approval from the WHO PQP for a new adult presentation of Coartem, an 80 mg artemether/480 mg lumefantrine co-formulated oral tablet. The new adult-only presentation is intended to improve compliance relative to the previous 20 mg/120 mg presentation, which necessitated an individual to take four tablets twice a day for the three-day regimen (i.e., a 24-tablet burden). The new 80 mg/480 mg formulation requires the individual to take only one tablet twice a day for the three-day regimen. Unlike the other Coartem formulations, the adult formulation may not be substituted for the lower weight band presentations. This new formulation is registered in several countries, including some PMI focus countries in sub-Saharan Africa. There are generic formulations of the 80/480 presentation, but none are approved through the WHO PQP and therefore PMI cannot procure them. Novartis is in the process of developing job aids on the 80mg/480mg for countries. Please contact the PMI Headquarters Commodity Procurement and Supply Chain Team if you plan on procuring this drug.

PMI policy to procure either SRA-approved or WHO-prequalified ACTs is one element of ensuring quality of pharmaceutical products procured with PMI funds. Despite this, ensuring good quality non-ACTs and other essential medicines, continues to be challenging. For example, PMI sources quinine from pre-approved wholesalers.[144] The wholesaler agencies are routinely evaluated against internationally accepted quality assurance standards by a USAID-led team, comprised of USAID in-house pharmacists, QA implementing partners, and consultants with significant experience in both current good manufacturing practices and U.S. FDA practices. Wholesalers are required to employ strict QA/QC measures with their vendors. Re-evaluation with site visits and desk audits is routinely carried out. Product sampling is conducted at qualified laboratories; ISO-17025 compliance and/or a WHO prequalification are acceptable facilities.

Average lead times for ACTs are currently about 6-8 months from time of receipt of a completed commodity procurement information request (CPIR) (and average lead times for other anti-malarials and essential medicines are about 10-14 months). Although lead delivery times for ACTs fluctuated substantially in 2011 and 2012 when volatility in the artemisinin market resulted in lead times that tripled and quadrupled, the market has since stabilized. Regardless, given artemisinin is a plant-based, there is still the potential for volatility.

[143] http://apps.who.int/prequal/query/ProductRegistry.aspx
[144] Please see most recent ADS 312 for more information on currently approved wholesalers.

Sulfadoxine-pyrimethamine

PMI supports the procurement of SP, although in-country needs for SP used for IPTp are strongly encouraged to be covered by Ministries of Health – particularly given this is a low-cost commodity relative to ACTs. To date, there has been no WHO PQP or SRA approved options for SP; as such, PMI has sourced SP from pre-approved wholesalers[145] (while there is one prequalified SP-AQ co-blistered presentation, WHO has only qualified it for use in SMC; see "AQ+SP for seasonal malaria chemoprevention" section below). However, there is currently one dossier up for review by the WHO PQP for monotherapy SP intended for use in pregnant women as part of IPTp.

SP lead times are lengthy, around 11 months from date of receipt of completed CPIR to delivery in country. Confounding already long lead times are issues around lack of registered product in the presentations required by PMI focus countriesand acquiring the appropriate importation waivers. As country teams quantify national level SP needs during operational planning visits for IPTp and SMC, consideration must be given regarding lengthy lead times.

AQ+SP for seasonal malaria chemoprevention

In 2012, WHO issued a formal policy recommendation for SMC which entails the administration of four rounds of amodiaquine and sulfadoxine-pyramethamine (AQ+SP co-blister or loose AQ and SP) to children ages 3 months to 59 months in the Sahel region. While this will not apply to most PMI-supported, PMI can procure AQ+SP for use in SMC campaigns in those countries where SMC is applicable. Currently, there is one WHO prequalified vendor for the co-blister AQ+SP (i.e., packaged in a blister pack together for ease of use) and loose AQ, both from the same manufacturer, with limited global production capacity. Historically, this has led to challenges in implementing SMC in PMI-supported. As of December 2015, there is a dossier for a dispersible co-formulated presentation of AQ+SP under review by the WHO PQP, although a lack of prequalification would not preclude PMI from procuring the product, given PMI would test the product regardless of WHO pre-qualification status.

Given SMC campaigns are time sensitive (i.e., administration of SMC medicines takes place only during the rainy season and peak malaria transmission), commodity procurements must take place well in advance, taking into account lengthy lead times of these medicines and the need to preposition commodities where they are geographically needed. The PMI Headquarters Commodity Procurement and Supply Chain Team is ready to collaborate directly with the subset of PMI country teams where SMC is indicated as well as to facilitate coordination with other donors to enable PMI focus countries access to sufficient quantities of the globally-limited

[145] Please see most recent ADS 312 for more information on currently approved wholesalers.

supply of qualified product.[146] **If SMC is relevant to your country team and PMI is requested to procure commodities, orders must be firmly placed at least one year in advance of planned campaign dates to ensure availability of the needed drugs in advance of the campaign.**

Rapid diagnostic tests

To help countries select RDTs appropriate for use given country-specific epidemiology, WHO, FIND, and CDC have conducted five complete rounds of standardized product testing of commercially-available RDT kits, submitted voluntarily by manufacturers. Through this testing, 147 products have been evaluated for accuracy in detecting standardized whole blood samples of *P. falciparum* and *P. vivax* (for tests designed to detect multiple species). Products also underwent assessment for heat and humidity stability. These assessments identified a number of RDTs that performed well at parasite densities of 200 parasites/microliter; some tests, however, did not perform as well. A summary of results from rounds 1–5 of WHO product testing of malaria RDTs can be found here: http://www.finddiagnostics.org/export/sites/default/resource-centre/reports_brochures/docs/malaria_rdt_Round5_results-summary_eng.pdf

Building on the results of five rounds of product testing completed to date, WHO, in collaboration with PMI and other development partners, has developed an information note on recommended selection criteria for procurement of malaria rapid diagnostic tests. Of those products submitted and tested to date, the note lists all RDTs that meet quality standards and are, therefore, recommended by WHO for procurement. At the time of publication of this document, the most recent WHO procurement selection note can be found here (revised in March 2015): http://www.finddiagnostics.org/export/sites/default/resource-centre/reports_brochures/docs/rdt-selection-criteria-sept2014.pdf

PMI allows country programs to request procurement of a specific RDT (thereby necessitating a sole-source procurement). While the choice to use a specific malaria RDT is made at the discretion of the NMCP, three criteria must be met in order for PMI to procure an RDT for any given country:

1. The RDT is appropriate to the country's detection settings and epidemiology. (PMI recommends that countries in sub-Saharan Africa procure RDTs that test for *P. Falciparum* only unless a country can produce evidence that there is high prevalence of non-falciparum mono-infections, with the exception of Ethiopia and Madagascar where *P. vivax* is common; see the **Case Management** chapter for a more detailed explanation)

[146] There are at least two dossiers in preparation for submission to the WHO Prequalification Program for pediatric formulations of SMC SP/AQ; however, dossier submission, review and approval is a lengthy process and these products are not expected to be brought to market until 2017.

2. There is demonstrated historical familiarity with the RDT and/or previous health care worker trainings
3. The product has met a minimum set of performance criteria specified by the WHO-FIND RDT Product Testing Program

Historically, PMI does not frequently fund switches from one RDT to another on a national level, given the programmatic challenges of transiting healthcare workers from one type to another. However, given the dynamic malaria epidemiology and the commitment by PMI to support pre-elimination activities in several countries when appropriate, the need for more than one RDT (or to transition from one to another) is possible.

There are currently issues with the buffer solution in the point of care tests. PMI is working with WHO, the Global Fund, and respective manufacturers to resolve the issues and will not be procuring them until the buffer evaporation issues have been resolved. Please refer to the **Case Management** chapter ("**Diagnostics**" section) for more information on the point-of-care kits. PMI will only procure multi-species RDTs in countries where other non-*falciparum Plasmodium* species are abundant (see the **Case Management** chapter for more details). PMI no longer supports the procurement of HRP2/pLDH 3-line tests. Interpretation of these tests is more difficult and likely to lead to significant confusion of health workers, resulting in incorrect diagnosis and treatment decisions. In addition, PMI will not be procuring the HRP2/pLDH 2-line tests unless an exception has been granted by the PMI Headquarters Commodity Procurement and Supply Chain Management and Case Management Teams.

In those PMI focus countries where malaria elimination control activities are appropriate, PMI country teams may field requests to procure point-of-care RDTs for the detection of a glucose-6-phosphate dehydrogenase deficiency.[147] Currently, there are several products available, although PMI has yet to procure this RDT. Preliminary findings indicate, however, relatively high costs around the development and implementation of a QA/QC testing protocol. If relevant in your country programs, please contact the PMI Headquarters Commodity Procurement and Supply Chain Management and Case Management Teams as soon as possible in advance of planned roll-out of the G6PD RDT.

Lab supplies

Lab supplies (microscopes, reagents, slides additional parts etc.) are rather specific and can require significant time to procure, please plan orders accordingly. For information on procuring entomological supplies, see to **Entomological Monitoring and Insecticide Resistance** chapter.

[147] WHO's current recommendation around the use of single low-dose primaquine for the radical cure of falciparum malaria in low transmission settings does not require G6PD screening; see information note here: http://www.who.int/malaria/publications/atoz/policy-brief-single-dose-primaquine-pf/en/

Quality Assurance/Quality Control

Quality, safety, and efficacy issues continue to be a major concern and top priority in the procurement of all malaria pharmaceuticals. Therefore, all pharmaceuticals (including RDTs) approved by non-SRAs, including those approved through the WHO PQP, must be tested prior or concurrent to shipment (depending on how they were approved and also on the procurement history with PMI) in accordance with PMI standard operating procedures. For all pharmaceuticals, there is a quality testing strategy, with WHO-prequalified and wholesaler-sourced products do require compendial testing. For the latter group, the timing of testing – either pre-shipment or concurrent – is dependent upon time from PMI procurement of a newly qualified product or batch quantity testing.[148]

All test reports (of ACT and RDT quality) are kept on file electronically with PMI's quality assurance partner and with the PMI Headquarters Commodity Procurement and Supply Chain Management Team. These may be obtained upon request by PMI country teams and regional advisors. To share these results beyond PMI, please ensure the data are treated as sensitive.

Products will not be released for delivery until results are received by the QA/QC team and deemed as passing (i.e., in compliance with industry and internationally accepted QA/QC standards).

Emergency Commodity and Financial Accounts

Country teams, with the assistance of supply chain/pharmaceutical management implementing partners, are requested to monitor the availability of all key malaria commodities (i.e., ACTs, SP, RDTs, LLINs, and related drugs and supplies for severe malaria) procured and distributed in country, regardless of donor, and take action when disruptions in supply are likely. Fluctuations in donor funding, commodities availability and resulting stockouts have been a recurrent problem for country programs and may continue with potential decreases in donor contributions. As in previous years, several PMI focus countries have experienced difficulties with funding leading to disruptions in the supply of key commodities. In these situations, country teams should be aware that PMI holds an emergency commodity funding account that can be utilized by countries to help avert stockouts of ACTs, RDTs, and severe malaria drugs, and maintain

[148] Until 2013, all products approved through the WHO-PQP went through concurrent testing (i.e., product was released for distribution prior to the receipt of passing test results). However, several times throughout 2013, we experienced product failure during testing (NB: no poor quality product was distributed as testing happened prior to product distribution). As a result, concurrent testing of a WHO-approved product occurs only after 12 months from time PMI begins procurement of the WHO prequalifed product *or* a minimum of 10 (ten) batches of product pass quality testing.

flexibility in commodity funding.[149] Additionally, PMI has developed an ACT stockpile, which holds a relatively small cache of buffer stock, including all four original weight bands for Coartem® (artemether/lumefantrine). Countries may access this buffer stock to help mitigate pending ACT stockouts, albeit quantities are relatively limited so large-scale emergency procurements are not possible. In addition, PMI leadership is committed to assisting country teams with high-level donor or Ministry negotiations in cases of major bottlenecks or program disruptions.

Commodity Theft, Diversion, and Expiry

PMI implements stringent methods to try and ensure that all malaria commodities procured arrive to the intended country and user. However, malaria commodities, especially ACTs, are considered of high street value and most have relatively shorter shelf lives compared to other pharmaceuticals. Although PMI is ever vigilant to combat and avoid all forms of theft, diversion, and expiry of our malaria commodities, these issues can still occur. If your country is aware of, suspects, or hears of any form of loss of malaria commodities whether through theft, diversion, or destruction (e.g., fire), it is crucial to immediately report the incident to the USAID Office of the Inspector General and to USAID/Headquarters (including the PMI USAID Agency Lead) and the PMI Headquarters Commodity Procurement and Supply Chain Team (listed below) with any information such as photos, lot numbers, location where the loss took place, etc. PMI is required to report to the Inspector General any type of loss or theft. In addition, it is crucial to understand any potential issues for our programs in country. Such issues require immediate attention as they can become the interest of Congress and the media, indicate there may be a broader systemic issue in the country, represent a loss of U.S. tax dollars, and mean fewer people are protected from and treated for malaria.

In regards to expiry, PMI, our procurement agent, manufacturers, and wholesalers aim to deliver medicines into country with the maximum shelf life possible. At times, delays with manufacturers and/or freight forwarders, combined with poor infrastructure in country and a lack of prepared distribution plans, collectively can lead to commodities arriving with shorter than preferred shelf-life. Because most countries also have a minimum required shelf-life for pharmaceuticals and related medical commodities, they may reject product on this basis. All methods to avoid expiry of any malaria pharmaceuticals should be tried before allowing expiry. PMI should be informed well in advance if there is potential for expiration, as USAID/Washington may be able to find ways to support emergency re-distribution to areas that could use the needed commodities. If expiry does occur, PMI should be immediately informed and a report will need to be documented for the record regarding the expiry as expiry of USG donated commodities falls under waste/fraud/abuse statutes.

[149] Given the typical quantities of LLINs, long lead times, method of transportation and sheer physical bulk (necessitating shipment by sea only), the emergency commodity funds are not used for the procurement of LLINs.

Central Commodity Mechanisms

While PMI has two central procurement options available to Missions for procurement of non-IRS commodities, the central procurement and supply chain management agent (listed first below) is the required mechanism for pharmaceuticals and other non-IRS commodities unless prior approval is sought and granted by the U.S. Global Malaria Coordinator (exceptions have been granted to allow UNICEF to procure LLINs when/where it makes programmatic sense).

1. PMI's Central Procurement and Supply Chain Management mechanism (Currently DELIVER Malaria Task Order 7) will transition to a new task order under the Global Health Supply Chain – Procurement and Supply Chain Management IDIQ). The requirement (unless granted an exception) to work with PMI's central procurement agent is due to PMI's stringent quality assurance and quality control standards for all pharmaceuticals and related commodities procured as well as some pre-negotiated contracts to obtain the best pricing, based on volume and pooling of orders. The central procurement agent also has flexibility in accommodating last minute order changes and the ability to handle in-country logistics, clearance procedures and if necessary, distribution needs. Their familiarity with USAID regulations and requirements is an added advantage; other procurement agents' lack of familiarity can translate into significant delays in the arrival of commodities. The mechanism's scope also covers in-country supply chain, pharmaceutical management, and logistics for ACTs, RDTs, LLINs, SP, etc.
2. UNICEF Umbrella Grant—As stated above, and only with prior approval from the U.S. Global Malaria Coordinator, PMI teams may choose to use the UNICEF Umbrella Grant to procure specific malaria commodities (e.g., LLINs for a joint campaign where UNICEF is already procuring a portion of LLINs for the campaign) where UNICEF has a country presence and is already engaged in malaria commodity procurement,

Regardless of the mechanism used, no PMI funds may be used to procure products of questionable quality; this typically precludes local procurements of commodities.

Government-to-Government Funding for Commodities

In March 2012, USAID/Washington released the *Global Health Implementation and Procurement Reform (IPR) Commodities Procurement Guidance* to better explain the Agency's role under the USAID Forward Initiative as it relates to the procurement of health commodities. In response to a growing interest by some countries to move toward a greater level of self-sufficiency in maintaining national health commodity supply chains, USAID/Washington may be supportive of the procurement of health commodities by host country governments through local systems. The Implementation and Reform guidance sets forth specific criteria for malaria commodities to be considered for local procurement. These include successfully completing a

Public Financial Management Risk Assessment to identify fiduciary risks, as well as an additional programmatic risk assessment, the development of an associated risk mitigation strategy, and the inclusion of specific QA/QC measures at the level PMI employs for the procurement of its own commodities. These criteria must be met and require discussion between PMI headquarters and host-country USAID missions in order to move this new process forward while meeting all USG, PMI, Mission and country regulations, requirements and needs. To date, no PMI resources have supported local procurement by partner governments.

Supply Chain Management

Introduction

According to the Council of Supply Chain Management Professionals, "supply chain management encompasses the planning and management of all activities involved in sourcing and procurement, conversion, and all logistics management activities. Importantly, it also includes coordination and collaboration with channel partners, which can be suppliers, intermediaries, third-party service providers, and customers." The success of health programs is dependent on their ability to reliably and consistently supply access to essential medicines and commodities through a well-functioning supply chain management system. Working closely with ministries of health and NMCPs, PMI supports strengthening supply chain management systems to ensure an uninterrupted supply of safe, quality-assured commodities. Supply chain management of malaria commodities poses unique challenges due to special characteristics, including limited products, short shelf life of products, complex dosing requirements, and varied demand due to the seasonality of malaria.[150] These characteristics and other considerations need to be taken into account when allocating PMI resources for activities to strengthen supply chain management systems.

PMI supports the provision of technical assistance to strengthen in-country supply chain management systems and strongly recommends leveraging supply chain strengthening support by other health elements and donors. It is essential to avoid fragmentation of supply chain system strengthening support to realize sustained supply chain systems strengthening results. Malaria-only supply chain technical assistance investments must be avoided unless malaria resources are the only element/donor resources available. Even then, a systems approach to address the key bottlenecks preventing malaria and other commodities from routinely reaching end users needs to be taken. Where other resources are available (e.g., PEPFAR, MCH, etc.) and where other health elements are relying on government systems, PMI investments must be coordinated with

[150] Guidelines for Managing the Malaria Supply Chain. http://deliver.jsi.com/dlvr_content/resources/allpubs/guidelines/GuidManaMalariaSC.pdf

other USG health supply chain investments. Key activities under this support are described below.

Logistics Management Information Systems

A logistics management information system (LMIS) is the foundation of a supply chain management system. An LMIS is the system of records and reports that is used to collect, organize, and present logistics data gathered across all levels of the system. An LMIS enables logisticians to collect the data needed to make informed decisions around procurement that affect product availability for health service delivery. LMIS data can be used to track trends in overall consumption, enabling more accurate forecasting and allowing adjustments to be made to country procurement plans and to in-country distribution plans. LMIS data can also be used to identify trends in dispensing practices or to detect anomalies in consumption practices. When used together with HMIS data, LMIS data can provide insight around expected correlations between services data and logistics data. In fact, PMI has country examples where correlating HMIS and LMIS data has led to detection of ACT theft at facility levels, which only underscores the importance of using these two data sources together when possible.

PMI provides technical assistance to NMCPs and other stakeholders to ensure the capture and consistent use of LMIS data. PMI country teams are encouraged to participate in discussions concerning the consistent use and improvement of an LMIS. Given that LMIS systems are integrated, PMI should coordinate support with other health elements and donors. Electronic LMIS (eLMIS) systems have been established in some PMI-supported. Open LMIS software is available to countries interested in an eLMIS. PMI country teams should participate in discussions on whether to transition to an eLMIS to ensure all key issues are taken into consideration.[151] For example, internet access, IT support, computer access, etc. should be taken into account when transitioning to an eLMIS system. Routine comparisons of LMIS and HMIS data should be conducted to bring together health services data and logistics data. Comparison of these two data sources over time can reveal important information such as trends in consumption, data management adherence, and other information that is that is useful to both program and supply chain managers.

Product Selection

In addition to epidemiologic considerations for product selection, a number of other key factors must be taken into consideration when selecting products to procure. These include whether a product is part of the country's National Essential Medicines List or is registered by the National Drug Regulatory Authority. Other issues to consider relate to logistics. What are the storage

[151] eLMIS Selection Guide :Electronically Managing Supply Chain Information. http://deliver.jsi.com/dlvr_content/resources/allpubs/guidelines/eLMIS_SeleGuid.pdf

requirements of a product at the central, health facility and community level? Is there enough capacity within the country to distribute the products? Do they require cold chain during storage and distribution? What is the shelf-life of the product? PMI country teams should work with NMCPs and stakeholders to ensure both epidemiology and logistics are considered in selecting products for the program and/or building the logistics and technical capacity to accept and use the product.

Quantification and Forecasting

Quantification is the process of estimating the quantities and costs of the products required for a specific health program (or service), and determining when the products should be delivered to ensure an uninterrupted supply for the program. Countries may use a variety of tools, including the RBM forecasting tool, which is often used for Global Fund concept notes. Three types of data can be used for forecasting: consumption data, services data, and demographic data. PMI focus countries use all three types of data for quantification and forecasting. Demographic data tends to provide an upper estimate whereas consumption and services data are influenced by data quality in the LMIS and HMIS, respectively, and can misrepresent need due to stockouts and misuse, although of the two, consumption data is preferred. Quantification is not a one-time event; it requires continuous monitoring and regular updating depending on the needs of the program. **It is important that PMI country teams participate in ongoing quantification and forecasting exercises.**

PMI provides technical assistance to build the capacity of the NMCP and other country stakeholders to lead and take ownership of the quantification and forecasting process. In most PMI focus countries this remains an area for ongoing priority attention. In general, countries should conduct annual commodity forecasts, ideally with quarterly updates. These forecasting exercises are also part of the Global Fund concept note preparation. Historically, the forecasting for the concept notes has been supported by RBM partnership members in country and from RBM West African Regional Network and South African Regional Network. PMI country teams should participate in the process of quantifying and forecasting for malaria commodities, including Global Fund forecasting activities, as NMCPs are often intimately involved along with national supply chain units and PMI input from regional advisors is appropriate. Most countries either have an established Supply Chain Technical Working Group or a Logistics Management Unit (LMU)[152] that is charged with this responsibility, in addition to general coordination of malaria supply chain management. Once quantification and forecasts have been developed, periodic reviews of supply plans should be conducted to ensure timely adjustments are made based on actual deliveries and consumption patterns and planned procurements.

[152] Logistics Management Units: What, Why, and How of the Central Coordination of Supply Chain Management. http://deliver.jsi.com/dlvr_content/resources/allpubs/guidelines/LogiManaUnits_Guide.pdf

PMI teams should use the country's annual forecasts as a starting point when preparing the MOP gap analysis tables. However, due to the number of questions generated by gap analyses for RDTs and ACTs during last year's MOP review, an interagency team worked to develop a new gap analysis tool (included as an accompanying excel file to the PMI Guidance) to help countries in preparing RDT and ACT gap analyses for MOPs. The tables in the tool do not need to be included in the MOP, and the tool is not meant to replace in-depth forecasts performed in country. Rather, the tool should be used by MOP teams to review the assumptions and generate a rough estimate of the RDT and ACT needs as a point of comparison to the needs generated by more in-depth forecast.

Warehousing, Storage and Distribution

The purpose of a storage and distribution system is to ensure physical integrity and safety of products and their packaging as they move from the central storage facility to service delivery points. A sound system will preserve quality of products and will protect products from excessive heat, direct sunlight, moisture, water, pests, pilferage, and expiry. A sound system will have sufficient warehousing space that meets Good Manufacturing Practices (GMP) standards, for all products at all levels of the system. Policies will be in place to prevent expiries such as first-to-expire, first-out or procedures for what to do with short-dated stock. Procedures and policies should also be in place for waste, management, disposal and product recall.

PMI supports the use of local in-country warehousing and distribution systems, usually through a government-owned or parastatal central medical store. As part of agreements between the USG and country governments, USG-funded commodities are exempt from all taxes. With prior approval, PMI resources can be used to pay for service fees related to warehousing and distribution of malaria commodities if there are clear agreements that describe the use of these funds. Payment of these fees requires pre-approval by the U.S. Global Malaria Coordinator. Where transparency and accountability is in place, PMI uses central medical store warehouses and distribution systems. At the same time, PMI will provide technical assistance to ensure supply chain management systems maintain or improve their performance and standards.

Where accountability and transparency are not in place or where storage and distribution systems do not meet GMP standards, PMI will support the use of parallel warehousing and distribution mechanisms that are outside of government owned or government managed systems. Use of parallel systems should be coordinated with other health elements, where appropriate. Approval from the U.S. Global Malaria Coordinator is required for PMI-supported countries to shift from reliance on government systems to supporting private and/or parallel warehousing and distribution systems particularly given PMI's priority for strengthening government capacity and systems and the often significant increased costs of supporting particularly parallel systems. While using private mechanisms, PMI provides technical assistance to strengthen the capacity of

public mechanisms, with the long term goal of transferring PMI funded commodities into strengthened public systems.

Quality Monitoring

As described above, quality, safety, and efficacy issues continue to be a major concern and top priority in the procurement of all malaria pharmaceuticals. Quality is important not only prior to shipment, but throughout the logistics cycle. PMI country teams should work with the NMCP to ensure that QA standards are adhered to throughout the logistics cycle and any concerns are addressed. While significant resources have gone toward ensuring only good quality products enter malaria public supply chains, support for drug monitoring of products once in circulation is also critical. Historically, PMI support toward this has focused on surveillance for both antimalarial availability and quality, in both the private and public sectors.

Monitoring and Supervision

To ensure optimum performance, supply chain systems should be monitored and evaluated on a regular basis. PMI country teams should work closely with program managers and supply chain managers to review data across all levels of the system to improve system performance. The Supply Chain Technical Working Group or LMU is a good venue to facilitate monitoring and evaluation of supply chain system performance. In addition to typical monitoring and supervisory tools recommended for all supply chains (e.g., LMIS reports, supervisory checklists, etc.), PMI uses malaria-specific tools to routinely monitor the supply chain system.

- **The Procurement Planning and Monitoring Report for malaria (PPMRm)** provides data on central-level stock availability for critical malaria commodities (ACTs, SP, and RDTs). The report describes stock status of anti-malarial products on a country-by-country basis and is produced quarterly by PMI's central procurement and supply chain management mechanism. Data are used by PMI to highlight and address needs and potential supply challenges, including stockout situations through the provision of critical emergency shipments. All PMI-supported are required to provide data for the PPMRm, and PMI country teams should routinely review their countries' PPMRMs to flag low stocks.
- **End-Use Verification Survey** (described in the **SM&E** chapter): PMI must support efforts to verify that USG-procured and donated malaria commodities are reaching health facilities and are available to end users. The EUV Tool, or another tool that monitors the availability of malaria commodities, should be used in a sample of health facilities in all PMI focus countriestwo to four times a year. Stockouts of key malaria commodities should be followed up and quantification, procurement, and logistic issues resolved as soon as possible.

Capacity Building

The performance of supply chain systems is reliant on adequately trained and motivated personnel. Without properly trained supply chain management personnel, system breakdowns can occur resulting in poor performance of the system or product stockouts. To ensure supply chain systems staff are properly trained, PMI provides technical assistance to build the capacity of supply chain management personnel. Activities can include providing technical assistance to update in-service training content for pharmacy personnel and health workers. PMI also provides technical assistance to build capacity of health facility and community health workers in supply chain management. PMI country teams are encouraged to work with the NMCP and other stakeholders to identify and address human resources constraints that can negatively affect malaria supply chain systems.

Commodity Procurement and Supply Chain Management Appendix 1: Commodities Costing Assumptions

Parenteral severe malaria drugs-quantification

Regarding the procurement of intravenous, intramuscular, or rectal preparations of antimalarials indicated in the treatment of severe malaria, individual treatment dosages are weight-based, which can create challenges in quantifying total number of units needed. Country teams will have access to population data, stratified by age (and an understanding of estimated weight bands), which must be used when calculating severe malaria commodities needs. For parenteral artesunate, the general rule of thumb for number of vials needed per treatment is:

- <25 kg: 1 vial
- 26 - 50 kg: 2 vials
- 51 - 75 kg: 3 vials
- 76 - 100: 4 vials

Average weights for healthy toddlers, children, young adults and adults (where 1 kg = 2.2 pounds) can be found at both the WHO website and the CDC website (http://www.cdc.gov/growthcharts/who_charts.htm#). With the case of parenteral artesunate, as an example, one would need four vials of parenteral 60 mg artesunate for an average man weighing 170 pounds, or about 77 kilos.

For rectal artesunate dosing, WHO treatment guidelines, second edition, recommend a 10 mg/kg pre-referral dosage. For example, a child weighing 10 kg would require (10 kg) x (10 mg/kg) = 100 mg total final dose. Available preparations are 50 mg and 200 mg capsule suppositories (note: given the risk of expulsion of suppositories after dosing, using fewer suppositories is recommended). Again, country teams will have to make estimates based on available population data. Calculations for pre-referral needs, however, are likely further confounded due to a lack of complete information on extent of roll out and patient population accessing pre-referral services.

For other injectables, such as quinine and artemether, both will also rely on patient weights. When country teams are putting together CPIR requests in advance of procuring parenteral severe malaria commodities, the PMI Headquarters Commodity Procurement and Supply Chain Team (which includes a clinical pharmacist) can be available for consultation to help prepare accurate requests (based on available data)

Pre-Elimination

****New Chapter** Key Messages for FY 2017 Technical Guidance**

- The *PMI Strategy 2015-2020* aims to assist at least five PMI-supported countries to meet the WHO criteria for national or sub-national pre-elimination by 2020. Pre-elimination phase as described by WHO includes areas where universal coverage of preventive and case management interventions has resulted in reduced malaria transmission to a level where less than 5% of all febrile patients tested are confirmed to carry malaria parasites and health information systems are in place to track that progress.
- Several PMI focus countries are moving towards pre-elimination, either nationally or sub-nationally. However, substantial technical, operational, and financial challenges accompany any commitment to achieve pre-elimination.
- In countries where malaria burden varies significantly in different areas and thus sub-national elimination is being pursued, priority should be given to supporting interventions to further reduce mortality and morbidity in high burden areas first and foremost with PMI resources.
- As countries approach elimination, the role of entomological monitoring changes as focal interventions tailored to particular environmental characteristics become more important and site selection for entomologic monitoring becomes more dynamic and driven by epidemiological data.
- WHO currently recommends that all countries in Africa, regardless of reductions in malaria transmission that have occurred, should maintain IPTp as a preventive strategy for pregnant women.
- All parasitologically confirmed malaria cases and infections should be treated with effective antimalarials and the addition of single, low-dose primaquine for Plasmodium falciparum could be considered in the pre-elimination context.
- Timely, complete, and accurate reporting of passively detected and confirmed malaria cases diagnosed in both the public and private sectors is required in pre-elimination settings and will serve as the foundation for tracking progress and identifying foci and cases for additional response measures in elimination settings.

Introduction

In the past several years, as worldwide morbidity and mortality due to malaria have continued to decline, the global malaria community has increasingly embraced the feasibility of malaria elimination and the longer-term vision of eradication. Over the past century, over 100 countries, including the United States, have eliminated malaria from within its borders. Most recently, several countries, mainly in the WHO's European, Eastern Mediterranean, and Pan American regions, have interrupted local transmission. Although elimination is being achieved globally, in the context of sub-Saharan Africa the focus continues to be on control and further reduction of

malaria mortality. Within the context of this scale-up, a sub-set of PMI focus countries have made tremendous progress and are poised to focus on building the systems required to move towards pre-elimination and subsequently elimination.

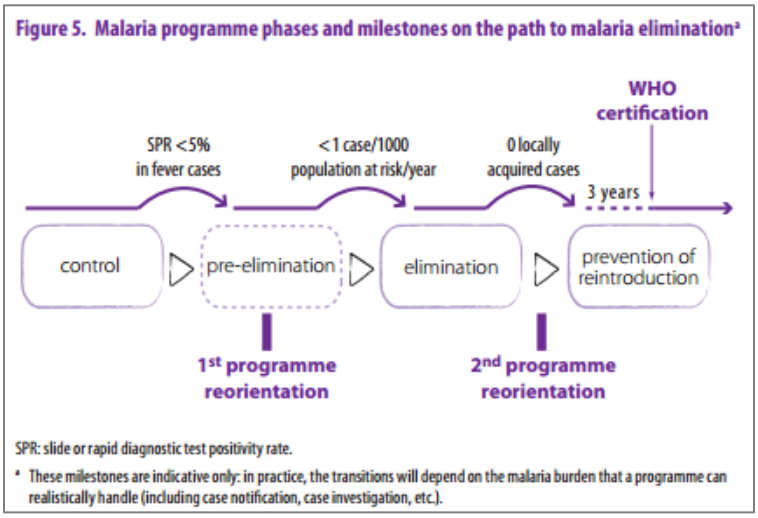
In 2015, three noteworthy global policy documents were released—the World Health Organization's *Global Technical Strategy for Malaria 2016-2030*, the RBM Partnership's *Action and Investment to Defeat Malaria 2016-2030*, and the multi-partner *From Aspiration to Action: What Will It Take to End Malaria?*—that advocate for malaria elimination and eradication and outline key operational, technical, and financial strategies to achieve the longer-term vision of malaria eradication. PMI shares the global, long-term vision of a world without malaria. The *PMI Strategy 2015-2020,* also released in 2015, sets as one of its three objectives to assist at least five PMI-supported countries to meet the WHO criteria for national or sub-national pre-elimination by 2020.

Malaria elimination builds on the foundation laid by intensive malaria control, with universal coverage of efficacious interventions for vector control among populations at risk and case management nationally. As the malaria program evolves, the targeting of operations increase, and the area of intervention narrows from the wider population to transmission foci, to individual malaria cases.

The WHO *Global Technical Strategy for Malaria 2016-2030* emphasizes that the progression towards malaria-free status is a continuous process. It recognizes that countries, subnational areas, and communities are situated at different points on the path towards malaria elimination, and their rate of progress will differ and depend on the level of investment, biological determinants (related to the affected populations, the parasites and the vectors), environmental factors, the strength of health systems as well as social, demographic, political, and economic realities. The new strategy lays out a pathway to malaria elimination that notes the increasing heterogeneity of malaria transmission as intervention coverage increases and the burden of malaria decreases and the performance of national health systems as a key determinant of the rate of progress along the path.

The first priority for all countries where transmission rates of malaria are high or moderate is malaria control to ensure maximal reduction of morbidity and mortality through sustained provision of universal access to quality-assured and appropriate vector control measures (i.e., LLINs and/or IRS) and diagnostics and antimalarial medicines, together with the implementation of all WHO-recommended preventive therapies that are appropriate for that epidemiological setting. Although WHO's *Malaria Elimination: a field manual for low and moderate endemic countries* (2007) is currently being revised, it had previously defined the major phases and epidemiological milestones and the necessary reorientation of the program on the path to malaria elimination (**Figure 1**).

Figure 1. Malaria Programme Phases and Milestones on the Path to Malaria Elimination



Source: WHO *Malaria Elimination: A field manual for low and moderate endemic countries*, 2007

Historically, WHO laid out four program phases from control to pre-elimination to elimination to prevention of re-introduction. An indicative epidemiological milestone of pre-elimination phase is the monthly slide or RDT positivity rate among febrile patients tested of less than 5% throughout the year, hence malaria case-loads are becoming small and manageable to conduct case investigation and response activities. Although most PMI-supported are far from achieving this indicative epidemiologic milestone of pre-elimination of less than 5% test positivity rate, there are several countries that have made tremendous progress in malaria control as evidenced by low overall malaria prevalence rates. Several of these countries have now set national or sub-national goals of malaria elimination (see **Table 1**).

Table 1. Progress in Reaching Pre-Elimination or Elimination in PMI-supported	
Population-based children under five years of age malaria parasite prevalence rate* – approaching pre-elimination	
<5%	Burma, Cambodia, Ethiopia, Rwanda, Senegal, Thailand, Zambia, Zimbabwe
5-10%	Kenya, Madagascar, Mainland Tanzania
Test Positivity Rate – Pre-Elimination	
<5%	Thailand, Vietnam, Zanzibar
5-10%	Lao PDR
Annual Parasite Incidence – Elimination	
<1/1000 population	Thailand

Source: WHO *World Malaria Report* 2014 and FY 2016 MOPs; *Based on either microscopy or RDT

Once programs have reduced transmission to very low levels, they should assess the technical, operational and financial feasibility of elimination and the programmatic capacity, including the ability of surveillance systems to track and manage every case of malaria infection necessary to eliminate malaria. The following factors will be important to consider:

Technical Feasibility:

- Evidence-based data on the achievement of successful malaria control
- Proven efficacious technologies and tools to eliminate malaria in a given eco-epidemiological setting

Operational Feasibility:

- A health system capable of accurate and timely diagnosis and treatment of all malaria cases
- Ability to ensure ongoing high-level coverage of vector control interventions
- A surveillance, monitoring, and evaluation system able to identify, investigate, and control malaria hotspots, rapidly respond to malaria cases, and reliably measure elimination targets
- Enabling environment with strong political commitment and collaboration amongst relevant ministries

Financial Feasibility:

- Strong political commitment evidenced by a dedicated, sustained budget to achieve and maintain malaria elimination

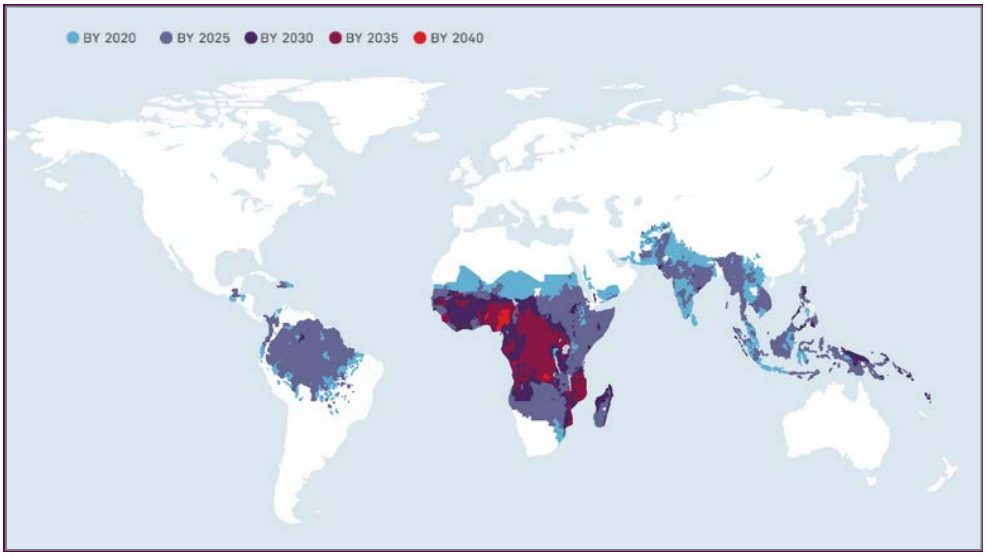
Shrinking the Malaria Map

The worldwide malaria map continues to shrink with global economic development and increasing political and financial support for control and elimination. The specific measures to be applied in order to achieve malaria elimination and national goals and targets will always be governed by local conditions. Within its allocated funding envelope, PMI will support evidence-based national strategies and approaches. This will largely continue to focus on scaling up and sustaining control interventions. However, in applicable countries, additional support to further prioritize strengthening surveillance systems and operational research to determine cost-effective and feasible elimination approaches are being implemented. **In countries where malaria burden varies significantly in different areas and thus sub-national elimination is being pursued, priority should be given to supporting interventions to further reduce mortality and morbidity in high burden areas first and foremost with PMI resources.** These control

efforts focused on high transmission areas will be crucial in limiting the exportation of source cases to pre-elimination or elimination areas within the country.

Figure 2, which was derived from an epidemiological model by the Malaria Atlas Project, illustrates one potential pathway to malaria eradication by 2040. In order to aspire for a malaria-free world, all PMI focus countries, including those likely to achieve elimination last, need to rapidly scale-up control interventions and invest in strengthening its health systems – such as strengthening surveillance, supply chain management and case management services – to prepare the needed foundation to pursue elimination.

Figure 2. The Shrinking Malaria Map



Source: *From Aspiration to Action*, 2015

Entomological Monitoring and Vector Control

Entomological monitoring

In high transmission areas, longitudinal entomological monitoring via fixed sites is necessary and cost-effective given the likelihood of finding mosquito vectors at a particular site is high and thus where one samples is less important than sampling consistently and rigorously. In contrast, marked heterogeneity in malaria transmission within regions and even villages becomes apparent as transmission decreases. Furthermore, vector numbers may decline markedly, making mosquito collections more time-consuming and costly. Heterogeneity and sparse vectors present challenges for entomological monitoring. Long term trends may be more difficult to discern and sample sizes needed to assess insecticide susceptibility may be more difficult to obtain. To respond to these challenges, sampling sites for entomological monitoring should be guided by epidemiological data, by focusing on areas where transmission is likely to be occurring.

Availability of such epidemiological data, assuming routine malaria surveillance is of good quality, is critical to focusing entomological monitoring in low transmission areas.

Site selection for entomological monitoring

In pre-elimination settings, decisions as to where entomological monitoring should be carried out should be based upon malaria burden data, whether passively collected case data or prevalence survey data. Entomological monitoring should concentrate on foci of ongoing higher-level transmission. As a first step, collation and synthesis of existing published and unpublished entomology data will be needed to avoid unnecessary duplication of effort. As foci of higher transmission may be stable, it may be possible to conduct monitoring in the same foci for several years. Once transmission in a given focus area is interrupted, continued entomologic monitoring is likely to be of little value. Nonetheless, limited longitudinal fixed site monitoring is of value to maintain vector monitoring capacity and to train field staff. The PMI Headquarters Vector Monitoring and Control Team will help advise for specific pre-elimination settings.

Ad hoc entomological surveys in response to ongoing transmission foci may also be indicated. Such situations may deserve entomologic assessment, as they may have been the result of a failure or reduced effectiveness of vector control interventions.

Role of entomological monitoring in support of vector control

The role of entomological monitoring changes as transmission levels decline, as focal vector control interventions tailored to particular environmental characteristics may be applied. Interventions that may not be appropriate in a control context, where broad scale coverage is needed, may be needed in pre-elimination settings to tackle residual transmission; these may include interventions targeting larvae or outdoor biting mosquitoes. **PMI's support for implementing such interventions would depend on evidence that such interventions are effective in the specific geographic/ecological/epidemiologic context and may require that such strategies first be evaluated through OR.** Over the long-term, the common interventions broadly scaled up in control areas – LLINs and IRS – could be targeted to areas where transmission is occurring. Although no clear criteria for stopping LLIN distribution exist, vector control intervention coverage should be maintained at least until transmission has been interrupted. In the case of Ethiopia, for example, districts with an annual parasite incidence between 0 and <1 case/ 1,000 population will not receive LLINs in their upcoming mass distribution campaigns. If vector control measures are withdrawn, countries must ensure that surveillance systems are in place to monitor the situation closely.[153]

[153] WHO Information note on the risks associated with the scale back of vector control in areas where transmission has been reduced, November 2015. http://www.who.int/malaria/publications/atoz/scale-back-vector-control/en/

As for areas of high transmission, entomologic monitoring in areas of low transmission needs to include vector incrimination and insecticide resistance monitoring to inform programs on the effectiveness of vector control interventions and insecticides used. Monitoring of the durability and effectiveness of LLINs also will remain important. For further information on the needed components of entomological monitoring, vector incrimination, and insecticide resistance monitoring, refer to the **Vector Monitoring and Control** chapter.

Two additional roles of entomological monitoring will become important as transmission declines — addressing residual transmission as well as foci investigation. Because residual transmission may be occurring away from houses or outdoors, operations research to determine the acceptability and effectiveness of interventions to address residual transmission (e.g., insecticide treated clothing or hammocks, repellents, or other vector control approaches) may be needed.

As malaria transmission declines, recalcitrant foci of transmission or hotspots may emerge. Entomological investigation of such foci should first determine coverage of standard interventions – whether LLINs or IRS – followed by prompt corrective action should coverage be low. If coverage is high and transmission is ongoing, then epidemiological and entomological investigations should be conducted to determine the source of residual transmission and if it is related to certain work related settings (e.g., forest, mining, or agriculture). In some cases, it may also be necessary to assess the resistance profile of the predominant vector, should this be feasible. In addition, in recalcitrant foci of transmission or hotspots in elimination programs, assessment of the vulnerability of larval populations within and near such foci may be of utility. The rubric of ‘fixed, few, and findable’ may be less relevant in a severely circumscribed focus when the object is malaria elimination, as the interventions may not need to be sustained in the long term once malaria is eliminated.

Malaria in Pregnancy

The impact of malaria infection on the health of the pregnant woman and her developing fetus depends to a large extent on the level of malaria transmission in the region in which she lives. In low-transmission areas or epidemic areas, women may be less exposed, particularly when transmission is related to specific occupational risks. Consequently pregnant women will have little or no acquired immunity, and are more likely to present with clinical malaria (although asymptomatic infection can still occur). They are also at an increased risk of anemia and severe malaria. Even in low transmission settings, MIP is associated with spontaneous abortion, stillbirth, prematurity, and low birth weight. For these reasons, all PMI focus countries regardless of transmission levels should continue to address prevention and control of malaria in pregnant women.

Prevention

ITN

Countries proceeding towards pre-elimination should continue to provide ITNs to pregnant women both through campaign distributions and through routine antenatal care depending on the country's distribution strategy. In countries which do not currently implement IPTp, ITNs are the only preventive measure that can be applied throughout the pregnancy.

IPTp

In many countries, transmission has been substantially reduced due to effective prevention and control measures. Some PMI focus countries (e.g., Kenya, Madagascar, and Zimbabwe) have opted to implement sub-national or focal IPTp policies targeting only moderate/high burden areas. As malaria burden decreases in countries, questions have arisen around the continued effectiveness of IPTp in low transmission settings. **WHO currently recommends that countries in Africa that have reduced malaria transmission should maintain IPTp as a preventive strategy for pregnant women and PMI supports this recommendation.** Currently there is insufficient data to determine a transmission threshold below which IPTp is no longer cost effective or efficacious. IPTp with SP remains safe, effective, and relatively inexpensive to implement. In addition, recent data has shown the deleterious effects of even low-level infections on pregnant women and their babies. Therefore, PMI will continue to support the implementation of IPTp-SP in all countries where it is currently part of the national strategy regardless of decreasing levels of malaria transmission to pre-elimination levels.

Outside of Africa, there is not sufficient evidence to support IPTp-SP as a prevention strategy and countries are encouraged to focus on ITN provision to pregnant women and prompt health care seeking for fever.

Case management of pregnant women

As with all suspected cases of malaria, parasitological confirmation by RDT or microscopy is recommended. The treatment protocols for uncomplicated and severe malaria in pregnancy for low transmission or pre-elimination settings are the same as recommended for high transmission or endemic areas.

Other interventions: ISTp and MDA

Recent studies have shown that ISTp is not as effective as IPTp-SP in reducing the malaria burden in pregnancy for African settings where *P. falciparum* is prevalent. ISTp was associated with more maternal clinical malaria episodes, and was more costly when compared to IPTp-SP. In certain settings (e.g., Asia), where *P. vivax* is common and IPTp-SP has not been deployed, the alternatives are less clear and further evidence is needed. Although methods of detection of parasitemia (peripheral or placental malaria smear, RDT or histopathology) underestimate the

burden of malaria in pregnancy even in low transmission settings, available evidence indicates that if screening is done, it will be most effective early in pregnancy.

In the context of MDA, care must be taken to avoid inappropriate treatment of pregnant women. Recent MDA pilots excluded infants and pregnant women from receiving the intervention. It is also important to note that primaquine is contraindicated in pregnancy and lactating women. PMI focus countries considering some of the newer approaches to control of malaria in pregnancy should consult with the relevant PMI Headquarters teams (Pre-Elimination, Case Management, and MIP) in the planning phases of such activities.

Case Management

Diagnosis

As in any other setting, the diagnosis of a clinical case of malaria both at facility and community levels should be based on the result of a diagnostic test, either microscopy or RDT. When performed and interpreted correctly, both microscopy and RDTs can detect parasites in concentrations at or below 200 parasites per microliter, which is sufficiently sensitive for identifying parasitemia in patients with clinical symptoms. More sensitive RDTs may soon be on the market and may be more appropriate for pre-elimination/elimination settings, as the parasite density required to cause symptoms in very low transmission settings is generally lower than in higher transmission settings.

In pre-elimination settings, high priority must be placed on confirming every suspected malaria case, not only to ensure that all malaria cases are rapidly and correctly treated, but to enable accurate and timely case reporting, investigation and follow up. Therefore, clinical diagnosis should be strongly discouraged, except in those cases where a delay in initiating treatment could increase the risk of severe disease or death. Even in those situations where treatment must be provided without a diagnostic test and where possible, effort should be made prior to commencing treatment to collect samples for testing at a later time. Testing could also be carried out as soon as is feasible after initiation of treatment to confirm the diagnosis although any delays in obtaining samples (e.g., more than 24 hours) would reduce reliability of a negative microscopic blood film examination. In contrast, RDTs will generally remain positive for days to weeks after clearance of parasites from the blood, particularly RDTs based on detection of the HRP-2 antigen.

As in higher transmission settings, microscopy is the preferred diagnostic test for patients with severe febrile illness, so that parasite density can be monitored, and also in cases of suspected treatment failure. In field settings, RDTs and microscopy are generally of equivalent accuracy in the hands of competent health workers.

One of the challenges in pre-elimination settings is that the skills of laboratory technicians in malaria microscopy and RDTs can deteriorate as positive tests become increasing rare and the parasite densities detected in samples from patients with clinical malaria are much lower than in higher transmission settings. Extra efforts must be made to maintain the skill of malaria microscopists, through periodic refresher training, frequent supervision, and establishment of a proficiency testing program. PMI should prioritize support to ensure these skills are retained in these settings.

A proficiency testing program uses panels of well-prepared, well-characterized blood slides that are periodically sent to microscopists as unknowns. The microscopists are asked to read these slides and report results to the program administrator The reported results are compared with the known results and errors in reading addressed through follow-up supervision or retraining, as appropriate. A validated national slide bank can be used to prepare such proficiency testing panels, as well as standardized training sets. All PMI focus countries, and particularly those moving towards pre-elimination, should have such a slide bank. PMI is supporting development of slide banks in a number of countries. Standardized protocols for development of these slides banks have been developed and are being finalized. The draft protocol can be obtained from the PMI Headquarters Case Management Team.

The highest priority must be placed on ensuring an uninterrupted supply of essential diagnostic and treatment commodities in pre-elimination settings, as any delay in diagnosis or treatment of a malaria case increases the risk of progression to severe illness and also onward transmission of that infection. In addition to routine supply chain strengthening, there may be a need for an urgent resupply strategy using strategically located buffer stocks and clear notification systems. PMI focus countries should consider prioritizing support to help ensure these uninterrupted supplies.

The need for rapid diagnosis, treatment, and response to malaria cases also necessitates quick and easy access to care for affected populations. In pre-elimination settings, village or community health workers often become the foundation for both malaria case management and the subsequent investigations. Additional approaches, including mobile or migrant health workers, border clinics, health services provided in high risk settings (such as plantations or mining camps) also have been used to facilitate access to care.

Treatment

Drug treatment of uncomplicated and severe malaria cases does not differ in pre-elimination settings from areas of higher transmission. When moving towards pre-elimination, additional efforts are recommended to ensure treatment adherence and clearance of infection. Use of DOT, often in a modified form where each morning dose is observed by a CHW, and repeat testing with microscopy to document clearance of parasitemia after completion of treatment, are being

used in some settings (particularly in the Greater Mekong Subregion, where treatment failures to ACTs have been identified).

Single, low-dose primaquine for P. falciparum

In 2015, WHO updated its guidelines for the administration of a single gametocytocidal dose of primaquine to be given in addition to an ACT for falciparum malaria **in low transmission areas.**[154]

WHO Recommendation (2015)

In low transmission areas, give a single dose of 0.25 mg/kg primaquine with ACT to patients with P. falciparum malaria (except pregnant women, infants aged < 6 months and breastfeeding women of infants aged < 6 months) to reduce transmission. Testing for G6PD deficiency is not required.

The WHO recommendation is updated slightly from the previous 2012 recommendation, which excluded infants < 1 year of age. Further recommendations include administration of single dose 0.25mg/kg primaquine on the first day of ACT treatment and with food to improve tolerability, and advice to individuals to monitor for signs of acute hemolytic anemia including dark urine and to seek medical attention should signs arise.

Previous mass administrations of a longer course of primaquine (14 days) without testing for G6PD deficiencies have been administered successfully. Based on these historical data, WHO guidance states that "Clinically significant haemolysis is not expected to occur in either G6PD-normal or -deficient individuals given a single 15-mg adult dose (0.25 mg base/kg) of primaquine" and "there is no need for systematic testing for G6PD deficiency before administering a single dose of 0.25 mg primaquine base per kg body weight.[1]" Specific information on symptoms and management of side effects can be found in the WHO updated policy brief.[91]

Even though WHO has issued guidance that G6PD testing is not required for the administration of the single 0.25 mg base/kg dose of primaquine, countries have been reluctant to adopt this policy. There are currently ongoing studies to assess the safety of this single low dose in G6PD deficient patients both in Cambodia with PMI funding and in various African settings including Mali, Kenya, Swaziland, Zanzibar, Zimbabwe, and Senegal. The Cambodia study is currently enrolling patients and the Swaziland study noted no G6PD deficient patients in their cohort. Preliminary results of administering single dose primaquine during MDA in the Mekong and

[154] Policy brief on single-dose primaquine as a gametocytocide in Plasmodium falciparum malaria, January 2015: http://www.who.int/malaria/publications/atoz/who_htm_gmp_2015.1.pdf

dosing of G6PD deficient adult males without malaria in Mali have not noted any clinically significant hemolysis. To support future safety monitoring efforts, investigators at UCSF are collaborating with WWARN to establish a common pharmacovigilance tool.

Studies show that primaquine kills gametocytes, which reduces the infectivity of *P. falciparum* malaria. Population-level reductions in transmission are only possible when a high proportion of patients are treated AND there is not a large asymptomatic human reservoir. Furthermore, modeling has shown that the addition of primaquine to first-line treatment of symptomatic falciparum patients in higher transmission settings would have no impact on transmission. Therefore, PMI recommends the addition of single, low-dose primaquine only in areas of low transmission (Although WHO does not define low prevalence, it is reasonable to use a health facility test positivity rate of ≤5% or a community-based parasite prevalence of <1% as being low prevalence) and/or in a setting with artemisinin resistance.

Treatment of asymptomatic infection

Asymptomatic infections are rarely identified in a clinical setting, but rather through active case finding activities that are carried out in pre-elimination/elimination areas. This would include case finding around an index case (reactive case detection) or community surveys (active case detection).

In pre-elimination/elimination settings, any detected infection, whether symptomatic or asymptomatic, is considered a malaria case and treated as such. Treatment for asymptomatic infections would be the same as that for uncomplicated clinical cases, including the addition of low-dose primaquine, as guided by the national malaria treatment policy.

Surveillance, Monitoring, and Evaluation

Household surveys

PMI relies on household surveys to monitor coverage of interventions on a national or sub-national scale (for countries with large malaria-free areas), including ITN and IPTp coverage. As discussed in various sections of this guidance, high-level coverage of these interventions will need to be sustained for elimination efforts to be successful. Therefore, PMI will continue to support periodic household surveys, every 3-5 years, as appropriate, to ensure that coverage of these critical interventions does not wane. In countries with high heterogeneity of transmission, sampling frame will need to be adjusted to ensure that surveys sample areas with malaria transmission risk. Although population surveys may still be needed in a pre-elimination setting to monitor coverage of interventions, they become less useful for measuring morbidity. PMI has historically used national household surveys (e.g., MIS) to collect data on anemia and parasitemia, and DHS to track all-cause child mortality as impact indicators. For those countries moving towards pre-elimination, the national household surveys will become less sensitive given

the same sample size to changes in parasitemia and malaria-related anemia as the prevalence of those conditions declines. PMI recommends that in countries where parasite prevalence in children under five years of age is at or below at or below 3% in two successive national surveys, collection of parasite burden by microscopy or RDTs and hemoglobin through national surveys should be discontinued. Exceptions can be made in countries where parasitemia has substantially declined in some regions of the country, but remains significantly greater than 3% in other regions. Although not routinely recommended at present, the role of other more sensitive methods for parasite detection (e.g., PCR or serology) is being evaluated in PMI focus countries as operations research. **Countries transitioning to pre-elimination should increasingly use longitudinal health facility-based surveillance data, if of sufficient quality, to monitor seasonal and annual trends in malaria burden, as described in the surveillance section below.**

Similarly, national DHS is used in high burden countries as a means to measure all-cause child mortality as an impact indicator for malaria control. In high burden settings, malaria contributes a large percentage of the mortality burden in children under five years of age, so a reduction in ACCM is seen as an appropriate measure of malaria control efforts. However, as countries move towards pre-elimination, the proportion of child mortality attributable to malaria declines and ACCM is no longer an accurate indicator to measure malaria elimination progress. Countries will still need to collect ACCM as a basic demographic indicator and to measure progress in maternal and child health beyond malaria; however, PMI should bear less of the financial and logistic burden of organizing the DHS surveys in pre-elimination settings.

As a country or region approaches pre-elimination, stratification of malaria risk will be more important to target interventions. In most high transmission settings, most national malaria risk maps are derived from a combination of parasite prevalence data from household surveys, and data from various sources on rainfall, temperature, and vector ecology. Countries approaching pre-elimination with improved surveillance systems rely on their malaria case incidence data to generate and update malaria risk maps. Countries able to investigate their cases can further refine their risk maps distinguishing local from imported cases. Ecologic factors as well as robust surveillance data should be used by NMCPs to make strategic decisions regarding the deployment of various interventions, and to monitor progress towards elimination. With the use of routinely collected surveillance data, malaria risk maps can be continuously updated, but PMI recommends that a more comprehensive map that will guide intervention decisions be updated approximately every 3-5 years.

Disease surveillance

As transmission decreases, data needs, data collection methods, and the frequency with which data are collected and reported will change. Countries' epidemiological profiles and health system capacity should be taken into consideration when developing and implementing national SM&E strategies, including those targeting elimination. Strengthening surveillance systems is a long, on-going process and is addressed in detail in the **SM&E** chapter. Countries in pre-elimination are expected have a well-functioning routine surveillance system that is collecting timely, aggregate data which is a pre-requisite for any country aiming to achieve this phase. For countries in pre-elimination phase, the focus of disease surveillance activities should be on strengthening malaria case detection and timely reporting along with building capacity for individual case reporting and investigation and response that will be needed during the elimination phase.

Once a robust surveillance system able to collect aggregate data is in place, WHO recommends the additional capacity/requirements for the surveillance system at various health system levels during pre-elimination or elimination phases (see **Table 2**).

Table 2. Additional Capacity/Requirements for Surveillance System During Pre-Elimination or Elimination Phases

	Pre-elimination (SPR <5% amongst all febrile patients)	**Elimination (API <1/1000 population)**
Community Health Worker	• Test and treat malaria appropriately • Document and report all cases	• Test and treat malaria appropriately • Document and report all cases
Health Facility	• Registers of individual malaria cases, diagnostic testing results, and case management documented • Cases are graphed daily to weekly to identify trends that may require focal response • Aggregate data transmitted weekly to district and higher ideally electronically	• Case based surveillance with capacity to investigate each case • Cases graphed daily to quickly identify outbreaks • Daily notification of individual cases to district and higher ideally electronically or by phone
District / Province	• Aggregate case and death data summarized weekly to allow an understanding of the needs by health facility catchment or village level to help set priorities for interventions • Register of severe cases and deaths maintained and case investigations performed to identify program breakdowns and needs	• Document case investigation and registry foci of transmission • Cross reference maps showing control efforts, and malaria foci to help direct interventions • Reports program and surveillance data to national level in preparation for certification of malaria elimination
National	• Weekly tabulation of cases and deaths to assess control efforts and prioritize activities	• Tracks case reports and febrile illness blood examination rates • Monitors response efforts

Surveillance system requirements for pre-elimination

1. **Implementation of a national routine systematic collection and analysis of confirmed malaria case-based facility data to reliably measure malaria incidence in all regions of the country**: Countries (or regions) approaching pre-elimination will require a surveillance system capable of reporting malaria incidence in increasingly smaller areas and timeframes. Such a surveillance system can quickly identify focal areas of continued or new malaria transmission and rapidly respond to prevent outbreaks and/or epidemics. A comprehensive surveillance system will need to incorporate data from all sectors beyond the public sector to include private sector, non-governmental organizations, military, etc.

2. **Surveillance in regionally diverse settings**: In countries where national parasite prevalence in children under five years of age is low but regional transmission intensity varies widely, greater disaggregation of data will be necessary to appropriately target control interventions and plan a pre-elimination strategy.

3. **Ability to identify, investigate, and control malaria transmission foci**: In the pre-elimination setting, surveillance systems must be capable of timely (no less frequently than weekly) reporting of malaria cases by location of transmission. These should be analyzed for possible hotspots, or foci of transmission to allow for targeted malaria control efforts.

4. **Building disease surveillance capacity**: Building disease surveillance capacity should be supported in all PMI focus countries regardless of where they sit on the control-to-elimination continuum. While priorities and available resource will vary by country, in pre-elimination countries the capacity of local health authorities to rapidly identify and report all cases becomes critical and thus PMI should work with NMCPs and partners to prioritize support where needed.

Surveillance system requirements for elimination

1. **Ability to identify, investigate, and react to individual cases of malaria**: Rapid notification of individual malaria cases to appropriate national and sub-national control program authorities will trigger case investigation and response measures. Additional individual level case data including residence, occupation, and travel history that are not typically captured by the routine surveillance systems need to be collected during case investigation. Case specific detail will be necessary to verify source of transmission (i.e. local vs. imported). The investigation of the index case and subsequent response measures (reactive case detection as mentioned earlier) could include testing and treatment of family members and close neighbors. Geolocation will be beneficial to identify areas of ongoing transmission and allow cross-referencing of control activities in the area to target additional efforts.

2. **Building capacity to analyze, interpret, and use disease surveillance data**: In elimination settings, capacity of local health authorities to rapidly identify, investigate, and respond becomes critical. Support in such settings will require training and supervision of health workers and surveillance officers on detecting, investigating, reporting and responding to each malaria case.

Disease surveillance tools

National disease surveillance systems

Depending on country needs, capacity, and other donor activities, PMI will need to determine an appropriate balance of support across the various surveillance systems. Prioritization based on consultation with the national control program and other donors will be necessary to ensure that critical surveillance capacity necessary for pre-elimination activities exists. The following points should help in making these decisions.

Country teams should consider support to these systems based on the following conditions/contexts:

- **Integrated, health facility-based routine information systems (HMIS, IDSR—for a more general description of these systems see SM&E chapter)**: Briefly, HMIS typically reports on a monthly basis of aggregate health-facility level data which does not have the resolution or timeliness to be relied on exclusively for pre-elimination efforts (e.g., transmission foci detection) regardless of quality. There may be exceptions where other surveillance tools, collecting case based data, can be integrated into HMIS via an electronic platform such as DHIS-2 giving this national system the timeliness and detail needed in the pre-elimination setting. In general, it is expected that countries nearing pre-elimination already have a well-functioning routine aggregate data system and would be changing focus to collect more timely case-based data.

  Other data systems, such as the IDSR system, are designed to provide timely aggregated case alerts (weekly or even daily if necessary) though may lack the higher resolution data needed for individual case investigation and response. IDSR systems could be used in outbreak detection and monitoring interventions in a timelier manner.

- **Stand-alone or dual-reporting malaria surveillance systems**: Existing surveillance systems if robust and timely might be sufficient to meet the needs of a pre-elimination program. However, surveillance system's ability to track individual cases and conduct reactive surveillance is a key requirement for elimination. PMI can support a supplementary systems which may be stand-alone (parallel) or dual reporting (where surveillance data is reported both through the HMIS and directly to the NMCP) in

situations where the existing systems, although perhaps adequate for countries in control phase, do not provide timely data necessary for those moving towards pre-elimination or elimination. Any considerations of support for supplementary systems need to be discussed with the PMI Headquarters SM&E Team and PMI leadership.

It is important to understand that HMIS and IDSR are often managed by different departments within the MOH and may have different goals and reporting frequency. Consequently, it is possible that a national malaria control program may have limited access to malaria data already collected by HMIS or IDSR. Thus, some countries may also require a malaria specific, supplementary surveillance system that that builds on the HMIS/IDSR platform and reports directly to national or sub-national malaria control authorities. In pre-elimination settings, weekly IDSR reporting is likely an adequate platform. However, most countries in the elimination phase, will likely require additional systems that can accommodate individual case data collection, reporting to the national and regional levels within days of diagnosis, and detailed investigations on every case.

Hardware/software

There are no specific requirements regarding hardware and software for an effective pre-elimination surveillance system. It is possible that even a paper-based system could be adequate. However, rapidly sharing data is essential when approaching pre-elimination and the use of computers and mobile phones/tablets will facilitate rapid reporting. The selection of appropriate technology needs to be in line with the data collection needs identified, the overall surveillance strategy, and the national telecommunication infrastructure and policies. It is ultimately the decision of the partner government. Examples of surveillance tools and equipment that assist in rapid case notification, investigation and response include:

- SMS-based reporting: minimal case information can be entered and sent via SMS from CHW or local providers to surveillance staff to alert them to newly confirmed cases. This approach does not require a smart phone or data network to function as information is transmitted via cell phone network. This may be appropriate in locations where only the cell phone network is available.
- App-based reporting: some electronic surveillance platforms support an integrated tablet-based or smart-phone based reporting and response system. These can be used to collect patient specific information and direct surveillance officer investigations of newly diagnosed cases and case clusters. Officers can record exact response activities in real time and either transmit to the central surveillance system or upload when connectivity is available. These technologies can also facilitate geo-location of the cases through built-in GPS functions, but requires functional data network.

Surveillance approaches

The following are approaches to surveillance that can be supported through PMI funding where appropriate:

- **Passive surveillance**: Passive surveillance systems are those that rely on health facility or health care workers reporting case data to a surveillance system. Cases in these systems are those individuals who present for care within the health system. In pre-elimination, the system needs to include all cases in a geographic area (including public and private sector data). Passive surveillance does not generally capture cases and deaths that occur outside of a health care setting, but can include individual case reporting. However, a passive system can be extremely informative in both control and pre-elimination settings and should be part of PMIs support as countries move along the control to elimination continuum. This reporting has the important advantage of high granularity in that clinics may be located throughout the country, allowing mapping of heterogeneity of reported cases. Note, however, that interviews with patients will be needed to confirm whether the case was locally-acquired or possibly imported from another area. Passive systems generally require less resource and system capacity than active surveillance as at a minimum they require a health care worker or facility filling out a paper reporting form and sending it to malaria control personnel. In general, passive surveillance should be fully functioning and providing actionable data for a NMCP before pursuing active surveillance strategies.

- **Malaria mortality surveillance**: As stated in the **SM&E** chapter, monitoring changes in malaria-specific mortality is a challenge for malaria control programs. As programs approach pre-elimination, accounting for deaths and confirming malaria infection will improve as all malaria cases are diagnostically confirmed and health information systems are strengthened. Malaria mortality data from routine surveillance will become increasingly accurate and reliable and malaria's contribution to ACCM estimates collected from surveys will decrease. Furthermore, malaria deaths should become increasingly rare in pre-elimination and elimination settings.

- **Active surveillance**: Active surveillance includes efforts to seek out additional cases of a specific disease and can take several forms. It can include community health workers or health workers visiting villages and going door to door looking for people with signs and symptoms of malaria or testing all residents regardless of symptoms. Active surveillance is very resource and time intensive and is generally not considered until countries have a strong passive surveillance system and reach pre-elimination when cases are few and health system capacity and resources allow. Active surveillance can be used in the pre-elimination setting in several ways:

- Identification of areas of high transmission or high risk populations – case or infection finding among high risk groups where higher prevalence or outbreaks might be expected based on historical epidemiologic, vector, meteorological, and/or migration data.
- Border screening efforts to screen those coming into the country, or a low prevalence area within a country, for malaria

The effectiveness of active case detection in reducing disease burden remains unclear and such strategies should be carefully considered before they are implemented. Given the limited sensitivity of currently available RDTs and microscopy, especially in low prevalence settings, teams need to balance the costs and potential benefits of this type of approach. Alternative approaches such as MDA are being evaluated as a transmission reducing and interrupting strategy. See **Other Preventive Approaches** chapter ("**MST**" and "**MDA**" sections) for more detail. In addition, it is strongly advised that if active case detection activities are being considered, this should be done in consultation with the PMI Pre-Elimination Working Group and strong consideration should be given to conducting such activities as OR, assuming other evidence of effectiveness is unavailable, so that its effectiveness can be assessed.

- **Reactive case detection**: Pre-elimination countries with robust health systems and capacity to investigate cases may employ various surveillance methods that combine passive and active surveillance. Case notification, investigation and response efforts such as China's "1-3-7"[155] approach fit in the category of reactive case detection. Cases are first identified by passive surveillance and reported within one day. A case investigation is completed within three days of notification, which includes both geolocating the case's residence and collecting information that helps to determine whether the case was likely to be locally-transmitted or imported. Action is taken within seven days which often includes reactive case finding in a predefined radius around the identified case where the patient lives or works and treatment either of additional confirmed cases or mass treatment of all contacts.

  Most countries targeting malaria elimination conduct reactive case detection activities. However, countries vary greatly in what triggers response measures, what diagnostic tests if any are used to identify additional cases and infections, the targeted radii, and the additional vector control and community education activities conducted in response. Countries use a wide range of response radii from the index household to up to 3km, often dictated by operational feasibility. Increasing evidence suggests that if local

[155] Cao J, Sturrock HJW, Cotter C, Zhou S, Zhou H, Liu Y, et al. (2014) Communicating and Monitoring Surveillance and Response Activities for Malaria Elimination: China's "1-3-7" Strategy. PLoS Med 11(5): e1001642. doi:10.1371/journal.pmed.1001642

transmission is occurring, the likelihood of finding additional cases is highest in the index household and decreases rapidly as you move beyond 200m. Determining the optimal radius for the area for case finding activities should also be balanced by what is operationally feasible in the particular setting and by factors, such as housing density and topography.