

U.S. 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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U.S. PRESIDENT'S MALARIA INITIATIVE



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Acronyms and Abbreviations

ACCM	all-cause child mortality
ACT	artemisinin-based combination therapies
ANC	antenatal care
AQ	amodiaquine
CDC	Centers for Disease Control and Prevention
CHW	community health worker
CN	concept note
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
FANC	focused antenatal care
FETP	Field Epidemiology Training Program
FIND	Foundation for Innovative New Diagnostics
FY	fiscal year
G2G	government-to-government
G6PD	glucose-6-phosphate dehydrogenase
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
MDA	mass drug administration
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
NDA	new drug application
NgenIRS	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
PCV	Peace Corps Volunteer
PCW	positive control well
PEA	programmatic environmental assessment
PEPFAR	President's Emergency Plan for AIDS Relief
PMI	President's Malaria Initiative
PMS	post-marketing surveillance
POC	point of contact
PPMRm	procurement planning and monitoring report for malaria
PQ	Pre-Qualification Program
ProACT	Proactive community treatment
QA	quality assurance
QC	quality control
RBM	RBM Partnership to End 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 FDA	United States Food and Drug Administration

USG	United States Government
WHO	World Health Organization
WHOPES	World Health Organization Pesticide Evaluation Scheme
3GIRS	third generation of IRS

Vector Monitoring and Control

New/Key Messages

- The MOP template includes 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.
- **New:** Updates on the transition from WHOPES to WHO Pre-Qualification for evaluation of vector control products.
- **New:** Guidance on the use of vector control tools with new insecticide classes, and monitoring resistance to them, is included in the **Entomological Monitoring and Insecticide Resistance, ITN, and IRS** chapters.

Two of PMI's main interventions – insecticide-treated mosquito nets (ITNs) and indoor residual spraying (IRS) – are aimed at controlling mosquito populations. These two interventions rely on a limited number of insecticides, in six classes, many of which have already been compromised by resistance. 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 highest quality and 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 in combination with varying levels of access to case management, including diagnostics and ACTs. The World Health Organization (WHO) issued revised guidelines for combining IRS with ITNs in 2014, which can be found at <http://www.who.int/malaria/publications/atoz/who-guidance-combining-irs-llins/en/>. The guidelines affirm 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 high pyrethroid resistance plus high transmission:** ITNs have been shown to provide protection even in areas with moderate pyrethroid resistance.¹ In the presence of high pyrethroid resistance (as defined by low mortality frequency or strong resistance intensity across multiple sites), 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 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 in areas where pyrethroid-treated ITNs have been distributed.

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).

New Vector Control Tools

A Gates-funded project called Innovation to Impact (<http://innovationtoimpact.org>) is working to streamline the WHO vector control product evaluation process, ensure products are periodically re-evaluated for quality once approved, and that normative guidance is provided for new product categories. As of January 1, 2017, the WHO Pre-Qualification Program (WHO PQ) team has been leading evaluation of vector control products, with WHOPES maintaining its other roles in supporting integrated vector management and insecticide resistance monitoring. Up-to-date information is available on the WHO PQ website.²

In the past year, two new tools with new classes of insecticide have received WHO PQ recommendation: Sumishield for IRS, and Interceptor G2 ITNs. Additionally, WHO has issued

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>

² <http://www.who.int/pq-vector-control/en/>

guidance on when to deploy PBO-synergist ITNs. Please see the IRS and ITN chapters for further guidance on where and how to deploy these tools.

Entomological Monitoring in Non-IRS Countries

In countries with IRS programs, entomological monitoring is fairly standardized and straightforward. In non-IRS countries, however, methodology and indicators may be tailored to better answer programmatic questions. Examples may include:

- Determining which vectors are most important for malaria transmission in different geographic areas, to ensure insecticide resistance is being monitored in the correct species.
- Monitoring spatio-temporal changes in vector behavior and biology to guide deployment of vector control tools. This is increasingly important as insecticide resistance in major malaria vectors may drive behavioral shifts towards more exophilic (rests outdoors), exophagic (feeds outdoors), and/or crepuscular (dawn/dusk) biting tendencies.
- Monitoring entomological indicators before and after ITN campaigns to determine impact on vector populations.
- Providing data to include in Global Fund grants to fund IRS.
- Ensuring baseline data are available to monitor any changes in vector control implementation (e.g., starting or ending IRS, introduction of a new insecticide, introduction of a new net).
- Monitoring resistance intensity to the pyrethroids used in ITNs, in conjunction with monitoring susceptibility to PBO and non-pyrethroid active ingredients, to determine whether an area might benefit from deployment of next-generation ITNs.
- Monitoring the impact of pilot deployment of PBO or next-generation nets.
- Cone bioassays for monitoring residual efficacy of LLINs.

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>.

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 PMI 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 **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 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

- To ensure that the correct species of mosquitoes are assayed for insecticide susceptibility, PMI recommends 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 via PCR is a useful and necessary adjunct to morphological identification.
- **Entomological monitoring in pre-elimination settings:** 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.
- A number of **new products** have recently received WHO PQ recommendation, or WHO has issued policy guidance on their use: Interceptor G2 ITN (pyrethroid + chlорfenапyr), SumiShield insecticide spray (clothianidin), and PBO synergist ITNs. As part of routine entomological monitoring, PMI recommends that countries should evaluate the effect of PBO synergists on pyrethroid-resistant mosquito populations, as well as test susceptibility to chlорfenапyr. Additionally, those countries that conduct IRS should also test vector susceptibility to clothianidin.

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.³ 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.

³ [Nature](#). 2015 Oct 8;526(7572):207-11

The first step in responding to the threat of insecticide resistance is increased monitoring (in frequency and/or number of sites) 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 that 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,⁴ only six classes (pyrethroids, carbamates, neonicotinoids, organophosphates, organochlorines, and pyrroles) 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 Scheme (WHOPES) website (see <http://www.who.int/whopes/en/>).

Understanding insecticide modes of action is essential for devising and implementing an insecticide resistance management strategy, which often includes switching or rotating

⁴ <http://ipmworld.umn.edu/chapters/ware.htm>

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.⁵ 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 have the potential to work against all six 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. funestus* population in Kwa-zulu Natal, South Africa to become highly resistant to pyrethroids, forcing the NMCP to temporarily return to using DDT.⁶

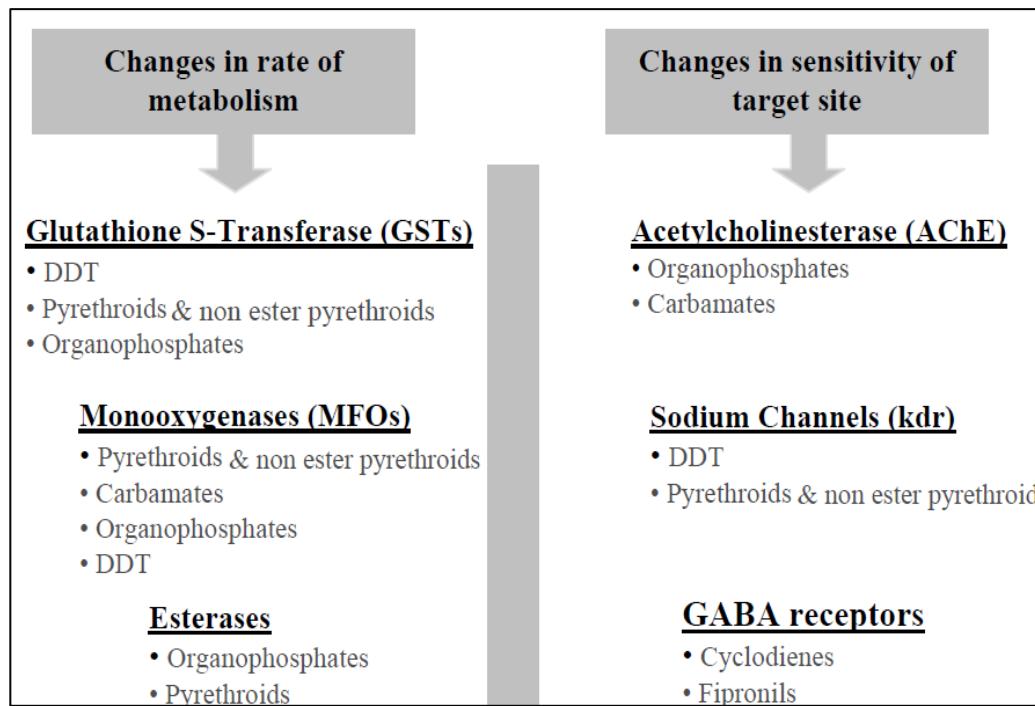
The second major type of physiological resistance, “target site insensitivity,” is related to the unaltered insecticide molecule being prevented from binding to its target (e.g., preventing sodium channel binding by DDT and the pyrethroids, and acetyl cholinesterase binding by the organophosphates and 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

⁵ Insecticide Resistance Action Committee, 2015, Mode of Action Classification Scheme.

⁶ <http://malariajournal.com/content/6/1/30>

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, 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.⁷

Cross-resistance

⁷ Wood et al (2010) Cuticle thickening associated with pyrethroid resistance in the major malaria vector *Anopheles funestus*. Parasites & Vectors 3:67.

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.⁸

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*.⁹ 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.

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,¹⁰ Cameroon,¹¹ and West Africa¹²), or oil pollutants contaminating the water table,¹³ may contribute to selection pressure resulting in resistance. Conversely, in some situations there is evidence that IRS drove the selection of

⁸ Brook Bulletin of Entomological Research 2001

⁹ Duangkaew Arch Insect Biochem Physiol 2011

¹⁰ Lines Parasitology Today 1988

¹¹ Chouaibou Tropical Medicine and International Health 2008, Antonio-Nkondjio Malaria Journal 2011

¹² Diabate Am J Trop Med Hyg 2002, Tia Bull Soc Pathol Exot 2006, Yadouleton Malaria Journal 2009

¹³ Djouaka Malaria Journal 2007

insecticide resistance (e.g., in Sri Lanka and Sudan).¹⁴ 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.¹⁵

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. **To better predict the operational impact of resistance, PMI highly recommends implementation of resistance intensity bioassays (using the CDC bottle assay method where the discriminating dose plus other, increasing doses are tested), alongside standard resistance frequency bioassays using a single discriminating dose (by WHO tube assays, or alternatively, if insecticide-impregnated papers are unavailable, CDC bottle assays).**

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

¹⁴ Lines Parasitology Today 1988

¹⁵ Czeher Malaria Journal 2008, Mathias et al. Malaria Journal 2011, and Stump Am J Trop Med Hyg 2004

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*.¹⁶ 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.¹⁷ 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 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 CDC and USAID Entomology backstops. For more information, see the section below called '***Monitoring Sites***.' 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 2019 malaria operational plans (MOPs) because, if needed, these supplies can be procured via an implementing partner.

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.

- 1. Species composition, abundance, and seasonality of malaria vectors in intervention areas**

¹⁶ Maharaj *SAMJ* 2005

¹⁷ N'Guessan *Emerging Infectious Diseases* 2007 and Asidi *Emerging Infectious Diseases* 2012

Purpose: To determine which vectors exist, their abundance, relative proportions, and distribution in intervention areas over time. This should always be the first step in an entomological monitoring program, because all entomological indicators measure a particular mosquito vector population—and if a non-vector species is being monitored, these data are not useful to malaria programs. 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 traps, exit traps, and pyrethrum spray collections, which 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>.

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 whereas 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. PMI has also begun sending a subset of samples for molecular identification to outside laboratories as a quality check on morphological identification performed in the field.

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](http://whqlibdoc.who.int/offset/WHO_OFFSET_13_(part1).pdf) and [http://whqlibdoc.who.int/offset/WHO_OFFSET_13_\(part2\).pdf](http://whqlibdoc.who.int/offset/WHO_OFFSET_13_(part2).pdf)).

Time frame: To accurately capture seasonality, collections should be performed once per month, encompassing 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. Insecticide susceptibility

Purpose: To determine vectors' susceptibility to a single diagnostic dose of insecticides currently in use or to be used in the future.

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 and WHO tube bioassay are roughly equivalent¹⁸ and either may be used for insecticide resistance testing. Concerns about standardization and quality assurance when technicians are coating their own bottles can be alleviated if pre-dosed bottles are used. Therefore, CDC is distributing free-of-charge premeasured samples of all WHO-recommended insecticides to 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.

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.¹⁹ 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.²⁰ Protocols for the WHO and

¹⁸ <http://malariajournal.com/content/8/1/208>

¹⁹ Note, however, that if sufficient specimens are available, determining the susceptibility of wild-caught, adult mosquitoes may provide additional supplementary information

²⁰ 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

CDC bottle assay are available online (see http://apps.who.int/iris/bitstream/10665/80139/1/9789241505154_eng.pdf & http://www.cdc.gov/malaria/resources/pdf/fsp/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 and updated in 2016, 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 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. Similar criteria for defining resistance status are applied to results of knocked-down mosquitoes from CDC bioassays.

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.

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 if susceptibility falls below 98%, or 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.

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 $27\pm2^{\circ}\text{C}$ and never at temperatures exceeding 30°C .

3. Insecticide resistance intensity

Purpose: To determine the intensity of identified resistance across a range of concentrations of insecticides currently in use or to be used in the future.

Method: The CDC bottle assay is used to determine the intensity of insecticide resistance. This assay allows for the creation of dose-response curves (using a range of insecticide concentrations) to determine the intensity/magnitude of resistance in a given area and to detect incipient resistance (described below). Additionally, the CDC bottle assay can be used with synergists to determine the resistance mechanism (see below).

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 doses²¹ 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 – when insecticide-based interventions fail to kill mosquitoes at a rate high enough to impact malaria transmission – 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 only be measured using the CDC bottle assay. WHO has developed papers at 5X and 10X of the diagnostic dose. However, these have not been validated. 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.²²

- *Differential pyrethroid resistance*

²¹ Concentration of an insecticide that, in a standard period of exposure, is used to discriminate the proportions of susceptible and resistant phenotypes in a sample of a mosquito population.

²² 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>

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

- 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.
- Resistance intensity assays should be performed with pyrethroids for which resistance was detected.

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: Resistance intensity assays should be conducted if susceptibility falls below 98%.

4. Mechanism of resistance

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 will inhibit mixed function oxidases, s,s,s-tributyl, phosphorotriothioate 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. Alternatively, biochemical assays can 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, decay rates should be measured monthly.

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 4th or 5th month after spraying should be attempted.

6. Vector behavior: 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.

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 advanced 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 measuring 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 versus. 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. Estimates of host feeding rates are strongly affected by host availability and by the sampling strategy and therefore, this is not generally recommended for PMI.

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.

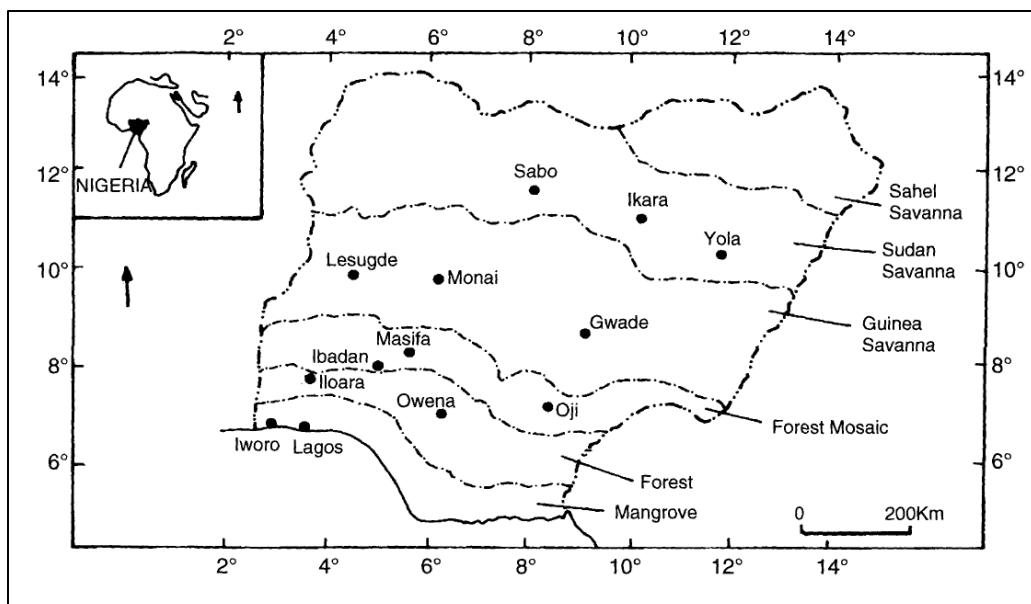
Monitoring Sites

Countries should do an initial stratification of their territory into eco-epidemiological zones and then establish at least one vector monitoring site per zone (see **Figure 2** 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 vectors' species distribution, abundance, seasonal 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).**

Because the full package of entomological monitoring requires a considerable amount of resources and human capacity, PMI recommends limiting more intensive monitoring to fewer than 8 sites, determined by programmatic questions in the country. A site may consist of several villages in close proximity. Insecticide resistance monitoring can be conducted in more sites, as resistance monitoring may be done once yearly or every other year at any given site, and resistance status may vary widely across a country. Should intense resistance be detected, an effort should be made to map the geographic extent of the focus of intense resistance. As an approximate guide, **Figure 2** shows an example of site selection in Nigeria, with 3-5 sites within each eco-epidemiological zone.

The exact number and location of sites should be discussed and approved by the PMI CDC and USAID Entomology backstops. 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 Zones²³



Entomological monitoring in 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 elimination settings, there should be a subset of sites used for longitudinal monitoring of insecticide resistance (e.g., in addition to a subset that can be chosen yearly in response to changing epidemiology). Foci investigations in response to malaria outbreaks and case follow-up are also recommended. These 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.

Reporting

23 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.

Periodic reports of findings in a standardized format should be provided to both the NMCP and PMI headquarters (including entomology team members from both agencies supporting PMI) 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. 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 basic 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 (the latter 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 Programs²⁴

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.
- 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).

²⁴ 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 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 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.
- Entomology staff should follow the best practices for entomological monitoring and data collection, as outlined by WHO,²⁵ with oversight and follow-up from PMI.

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.

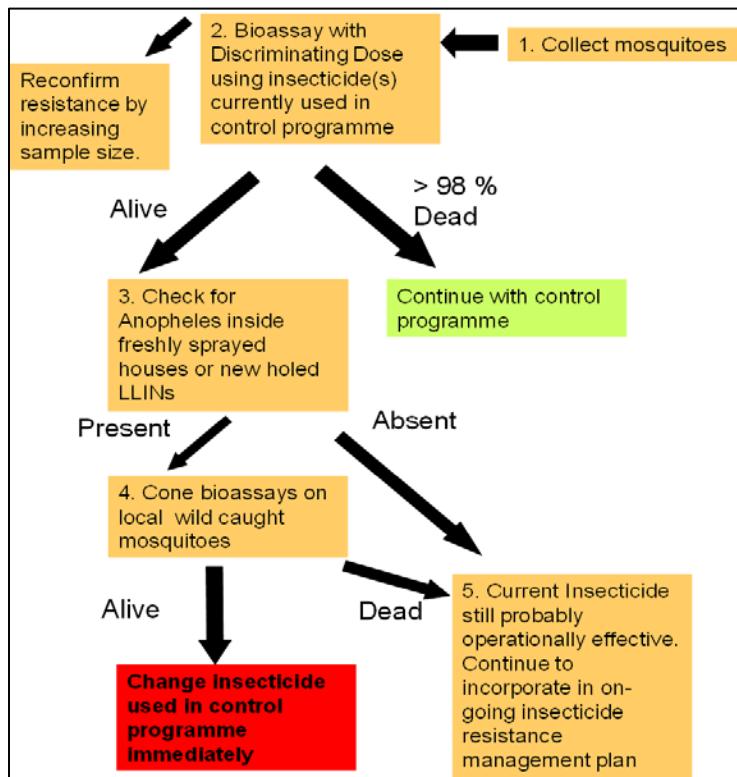
²⁵ <http://www.who.int/malaria/publications/atoz/9789241505819/en/>

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.²⁶ 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.

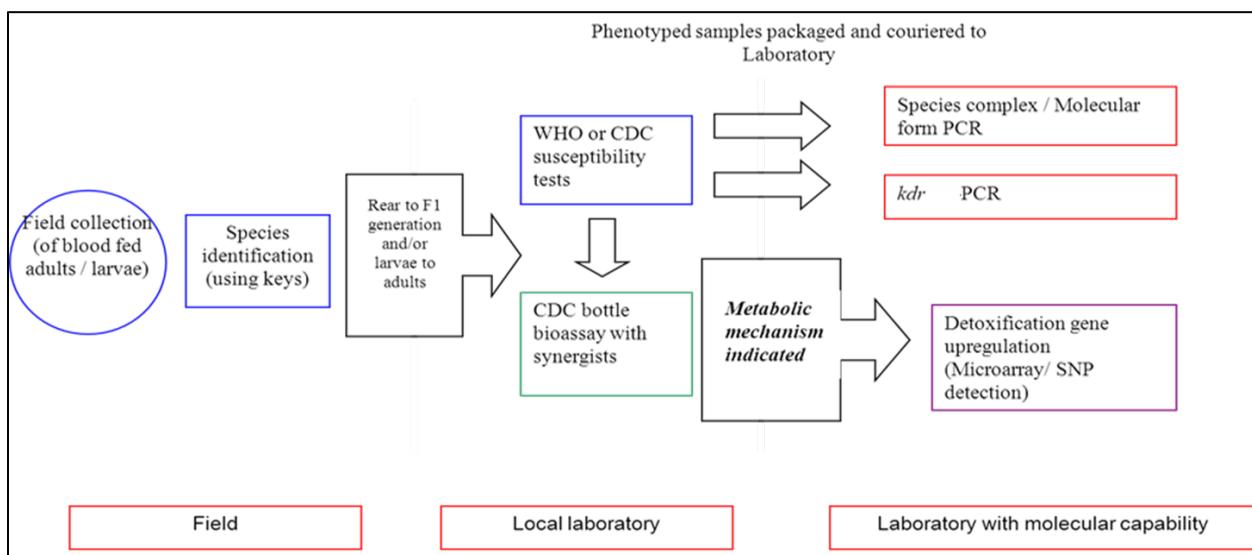
Step 2 – Conduct bioassays

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 tested with either the WHO or CDC assays. If resistance is detected in the *in vivo* assays (i.e.,

²⁶ This flow chart was developed by Maureen Coetzee and Janet Hemingway at the RBM Insecticide Resistance meeting held in Liverpool, October 2010.

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,²⁷ 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 using local field-caught mosquitoes

This step is recommended to ensure that IRS and LLINs 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 LLINs, mosquitoes should be exposed to new nets for 3 minutes in cones, using 10 mosquitoes per cone. Knockdown should be recorded after 60 minutes and mortality 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 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

²⁷ <http://www.malariajournal.com/content/12/1/57/abstract>

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.

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. IRS programs operating under the central mechanism implement clear protocols to ensure the quality of IRS, including robust training of spray operators, supervisors, and all relevant spray personnel and “directly observed spraying” whereby supervisors are required to observe spray operators’ technique while spraying houses and to provide on-the-spot correction as needed. 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*²⁸ 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

²⁸ <http://www.who.int/malaria/publications/atoz/gpirm/en/>

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, albeit a growing number, of options for non-pyrethroid, long-lasting insecticides. 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.

Insecticide Treated Nets

New/Key Messages

- **PMI Guidance on ITN Durability Monitoring:** PMI has developed new guidance for how to interpret durability monitoring data, and actions to be taken if nets perform poorly (posted on www.durabilitymonitoring.org). For more information, contact the PMI Headquarters ITN Technical team and your country team entomologist.
- **PMI Guidance on PBO LLINs:** In September 2017, the WHO Global Malaria Programme provided an interim endorsement of PBO ITNs as a new class of vector control products, with full confirmation dependent on additional epidemiological data. **PMI will consider procurement and targeted deployment of these higher cost nets according to key criteria** (e.g., moderate levels of pyrethroid resistance, evidence that PBO restores pyrethroid susceptibility, and moderate to high malaria prevalence).
- **Catalytic Funding for Next-Generation Nets:** One dual-insecticide ITN, the Interceptor G2, has received WHOPES recommendation as a pyrethroid ITN. There is currently no WHO policy on when and where to deploy these nets. However, PMI is collaborating with a UNITAID and Global Fund catalytic initiative that will provide funding to generate evidence for the needed policy recommendation, as well as subsidize procurement of next-generation nets. This subsidy may be available for select PMI focus countries which receive approval from HQ to procure next-generation ITNs. More details will be shared as the UNITAID project advances.
- **ITN Access and Use Report:** PMI has funded a secondary analysis of DHS and MIS data from all focus countries to calculate the ratio of use to access, to provide insight into how ITN use may be linked to access, or to other behaviors. This report is available at <http://www.vector-works.org/resources/itn-access-and-use/> (the report is updated within 30 days of the release of new DHS/MIS datasets (not just preliminary report) and circulated to PMI field and HQ teams).

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%.²⁹ These results were reported in five large trials, one using insecticide-treated

²⁹ 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>.

screening³⁰ material and four using ITNs.^{31,32,33,34} ITN coverage in these studies was maintained 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 1-4.³⁵

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%. 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.³⁶

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 the only type of net supported by PMI.³⁷ PMI does not support retreatment for conventional or untreated nets in Africa. In addition, PMI is

³⁰ 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.

³¹ 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.

³² 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.

³³ 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.

³⁴ Phillips-Howard PA, Nahalen 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.

³⁵ 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.

³⁶ 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>

³⁷ 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_April_2016.pdf?ua=1

procuring long-lasting insecticide-treated hammocks for distribution in the Mekong region to reach and protect migrant mobile populations.

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.³⁸

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.³⁹ 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 on a routine basis 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 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.

ITN Ownership: Key Distribution Channels

³⁸ The WHO press release can be found at: <http://www.who.int/mediacentre/news/releases/2007/pr43/en/>. The official statement can be downloaded at: <http://www.bvsde.paho.org/bvsacd/cd66/ITNspospaperfinal.pdf>

³⁹ http://www.who.int/malaria/publications/atoz/who_recommendations_universal_coverage_llins.pdf

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. Campaigns usually require logistics and planning expertise as well as time commitments that significantly strain national program capacities. Providing external technical assistance to NMCPs from implementing partners experienced in conducting campaigns is most often an excellent investment in ensuring that mass campaigns are successfully implemented in a timely manner. If needed, the Alliance for Malaria Prevention has trained expert consultants to support planning mass campaigns in countries, to supplement NMCP and implementing partner capacities. For countries where external TA is needed and desired for their campaign, PMI recommends planning for consultant TA visits at least one year in advance of upcoming mass campaigns to ensure planning stages are not delayed.

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” (i.e., selectively replacing older nets, rather than universally providing new nets) are logically 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.⁴⁰ 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://allianceformalaria-prevention.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

⁴⁰ http://www.who.int/malaria/publications/atoz/who_recommendations_universal_coverage_llins.pdf

below falls well short of maintaining ITN coverage at sufficiently high levels that will provide community protection. Therefore, a mix of several 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.

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.

The PMI VectorWorks project conducted a meta-analysis of costs of the following distribution channels in 2017: mass campaigns, ANC, EPI, school-based, and community-based. The analysis found that in terms of cost-effectiveness, conducting universal coverage campaigns every three years plus ongoing ANC/EPI distribution is equally cost-effective as full-scale school or community distribution plus ongoing ANC/EPI, in terms of cases averted. Conducting mass campaigns every three years with ongoing ANC/EPI and with school distribution in non-campaign years is more costly, but may provide additional health benefits in historically high transmission settings (EIR >32). Results will be disseminated and used to inform/update FY 2020 PMI Technical Guidance, ultimately helping countries in making the most strategic decisions on the best combination of distribution channels.

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

Routine distribution of ITNs through public-sector⁴¹ 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 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. Ghana, Nigeria, Tanzania, and Senegal have carried out school-based ITN deliveries at scale. Some smaller school-based distributions have also been conducted (e.g., Mali and Kenya). School-based distribution should be considered a viable channel in certain circumstances (including high gross school attendance rate and strong commitment of local health and education officials) 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. A school-based channel requires a large amount of coordination between the ministries of health and education (among others) and may not be appropriate or feasible in some countries or sub-regions. In addition, PMI does not recommend conducting both school and community-based distribution due to potential oversupply (see below).

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

⁴¹ 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.

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>). As mentioned above, 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 distribution approaches

Other potential continuous approaches may be needed to maintain high coverage and to keep ITNs in targeted communities 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. 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 toward maintaining universal coverage. 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 they do occur. Resources for organizing and designing continuous distribution efforts can be found on the Continuous Distribution Toolkit at: <http://www.continuousdistribution.org>.

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

ITN indicators measure access to an ITN

In 2013, the RBM Monitoring and Evaluation Reference Group adopted four indicators for ITN ownership and use to better reflect the universal coverage strategy. The following indicators (the supplemental indicator is optional) are currently included in all household surveys (MIS and DHS):⁴²

- 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 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. PMI has funded a secondary analysis of DHS and MIS data from all focus countries to calculate the ratio of use to access, to provide teams with insight into how ITN use in their country may be linked to access, or to other behaviors.⁴³ This report will continue to

⁴² Household Survey Indicators for Malaria Control; <http://www.malaria-surveys.org/documents/Household%20Survey%20Indicators%20for%20Malaria%20Control.pdf>

⁴³ ITN Access and Use: <http://www.vector-works.org/resources/itn-access-and-use/>

be updated as datasets from new surveys becomes available. 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 2009⁴⁴ 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.^{45,46} 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%)⁴⁷ masked very divergent regional characteristics. The study found distinct differences between the three Northern and the three Southern geopolitical zones.⁴⁸ 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 is critical. Studies confirm that communication programs are effective at increasing use of ITNs among targeted populations. The *Malaria SBCC Indicator Reference Guide*⁴⁹ 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

⁴⁴ 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

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 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.

⁴⁷ Nigeria Malaria Indicator Survey 2010.

⁴⁸ 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.

⁴⁹<http://www.rollbackmalaria.org/files/files/resources/Malaria-BCC-Indicators-Reference-Guide.pdf>

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.⁵⁰ 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.

WHO-Recommended Long-Lasting ITNs (LLINs)

In its most recent report, June 2017, WHO has provided interim or full (phase 3) recommendation for 19 long-lasting ITN products:⁵¹

- A to Z Textiles: *MiraNet*[®]
- BASF: *Interceptor*[®] and *Interceptor G2*[®]
- Bayer: *LifeNet*[®]
- Fujian Yamei Industry: *Yahe*[®]
- Life Ideas Textiles: *Panda Net 2.0*[®]
- Shobika: *Duranet*[®]
- Sumitomo: *Olyset Net*[®] and *Olyset Plus*[®]
- Tana Netting: *Dawaplus 2.0*[®], *Dawaplus 3.0*[®], and *Dawaplus 4.0*[®]
- Vector Control Innovations: *Veeralin*[®]
- Vestegaard Frandsen: *PermaNet*[®] 2.0 and *PermaNet*[®] 3.0
- *Mainpol GmbH: *SafeNet*[®]
- *V.K.A. Polymers: *MAGnet*TM
- *Disease Control Technology: *Royal Sentry*[®]
- *Yorkool: *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

⁵⁰ Kilian A, Balayo C, Feldman M, Koenker H, Lokko K, Ashton RA, et al. (2015) The Effect of Single or Repeated Home Visits on the Hanging and Use of Insecticide-Treated Mosquito Nets following a Mass Distribution Campaign - A Cluster Randomized, Controlled Trial. PLoS ONE 10(3): e0119078. doi:10.1371/journal.pone.0119078

⁵¹ http://www.who.int/whopes/Long-lasting_insecticidal_nets_April_2016.pdf?ua=1

in the WHOPES protocol (<http://www.who.int/whopes/guidelines/en/>). In line with the 2007 WHO position statement,⁵² PMI only supports the purchase of WHOPES-recommended ITNs.

PMI Policy on WHO Equivalency Policy

The WHO follows an equivalency process that allows new long-lasting ITN products to receive WHO recommendation status (interim or full) based on their chemical equivalency to the innovator net product. These “comparator” products are granted WHO interim or full recommendation status based only on results from WHO 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 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.)

Transition from WHOPES to WHO Prequalification Program

WHO has established a vector control unit within its Prequalification program. WHOPES will no longer review and recommend vector control products. Instead, products will submit to WHO PQ for approval. All current ITNs that have WHOPES full or interim recommendation will receive an interim approval from WHO PQ upon submission of a conversion package. The deadline for submission of a conversion package to WHO PQ was December 31, 2017. WHO PQ will begin inspecting manufacturers to ensure that they comply with good manufacturing practices (ISO) and can consistently manufacturer ITNs to meet quality standards. At this point, comparator nets will transition to WHO PQ with interim status. PMI is closely engaging with WHO PQ and encouraging them to prioritize site visits to comparator net manufacturers. Until additional data is available, PMI’s requirement for Phase 2 testing remains. PMI in-country teams will ensure that NMCPs are aware of this transition and will find the most updated list of prequalified products at: <http://www.who.int/pq-vector-control/prequalified-lists/en/>.

⁵² <http://www.bvsde.paho.org/bvsacd/cd66/ITNspospaperfinal.pdf>

Cost of ITNs

Cost assumptions for FY 2019 ITN procurements are provided in the **Commodity Procurement and Supply Chain chapter (Appendix 2)**. 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, 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,⁵³ 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.⁵⁴ 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 has funded operational research in Nigeria and Uganda to understand the knowledge, attitudes, beliefs, and practices that motivate or impede net care and repair behaviors used findings to test the effectiveness of a behavior change communication intervention. Based on these results,^{55,56} PMI will not support repair activities (e.g., distribution of ITN repair kits, social mobilization promoting ITN repair efforts, etc.).

⁵³ 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>

⁵⁴ ibid

⁵⁵ 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>

⁵⁶ 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>

PMI will support SBCC activities focused on comprehensive ITN care and consistent use (not repair) 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 from playing near the net, avoiding storing food or crops in the same room, and storing the net safely when not in use. SBCC should promote improving overall care of ITNs at the household level and delaying 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. The Nigeria and Uganda studies showed that these simple messages are very likely to result in longer life of nets and better protection of families.

Implications of Pyrethroid Resistance for ITNs

Pyrethroid resistance is a serious threat to vector control, as pyrethroids are the primary class of insecticides used on ITNs. Despite widespread resistance to pyrethroids, there is little epidemiological evidence to date that the personal protective effect of long-lasting ITNs has been compromised.⁵⁷ Nevertheless, PMI is concerned that intensification of pyrethroid resistance could begin to undermine the gains made in reducing the burden of malaria. Because of the threat of expanding and intensifying insecticide resistance, resistance monitoring should be an essential part of every PMI focus 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.

In response to increasing pyrethroid resistance, manufacturers have developed new ITNs with additional active ingredients to combat pyrethroid resistance. There are two new types of ITNs that have interim WHO PES recommendations and will be transitioning to Prequalification: piperonyl butoxide (PBO) synergist nets, and dual-insecticide nets. WHO has issued interim policy guidance for PBO nets, but has not issued guidance on when to deploy dual-insecticide nets, therefore PMI has separate guidance for each (see below). According to the data available,

⁵⁷ 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>

the unit cost of the new type of ITNs is greater than pyrethroid-only ITNs, although these unit costs may decrease in the future with economies of scale.

PBO Synergist ITNs

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 is some evidence to indicate that mosquito populations with high pyrethroid resistance have multiple resistance mechanisms, making PBO less useful against these populations.

In 2015, the WHO Global Malaria Program convened an Evidence Review Group on PBO ITNs to review data from numerous laboratory studies, nine experimental hut trials, and six village-level trials with entomological endpoints. The studies provided mixed results, and the Evidence Review Group concluded that the limited evidence did not justify a switch to PBO nets, but was sufficient to justify limited, pilot “exploratory” implementation of PBO nets accompanied by robust evaluation of impact with both entomological and epidemiological indicators. This evidence was recently supplemented by a cluster-randomized trial in Tanzania with epidemiological endpoints. Based on the positive results of this trial, in September 2017 WHO/Global Malaria Programme provided PBO ITNs an interim endorsement as a new class of vector control products.⁵⁸ Full confirmation of the class will require data from a second epidemiological trial; a cluster-randomized trial is currently underway in Uganda. Meanwhile, as stated by WHO’s policy guidance, “all pyrethroid-PBO nets that have a WHOPES recommendation or WHO prequalification listing (Permanet 3.0, Olyset Plus, Dawa 3.0, Dawa 4.0, and Veeralin) will be considered to be at least as effective at preventing malaria infections as pyrethroid-only ITNs, and possibly more effective in areas of low-to-moderate pyrethroid resistance.” Thus far, evidence has shown that PBO is not as effective at restoring pyrethroid susceptibility in areas with high or very high insecticide resistance (i.e., <35% mortality). However, WHO’s policy recommendation does not consider PBO ITNs to be a tool to effectively manage insecticide resistance in malaria vectors.

Based on this September 2017 WHO policy guidance, PMI will consider procuring PBO ITNs on a case-by-case basis, for use on a sub-national scale, following the data and program requirements outlined below. In the majority of cases, pyrethroid-only ITNs will

⁵⁸ Conditions for deployment of mosquito nets treated with a pyrethroid and piperonyl butoxide, September 2017. Geneva: World Health Organization; 2017. (<http://apps.who.int/iris/bitstream/10665/258939/1/WHO-HTM-GMP-2017.17-eng.pdf>)

continue to be the standard for PMI ITN procurements for continuous or mass campaign distribution. If NMCPs or country teams are considering procuring PBO ITNs, the country teams should engage with the PMI Vector Monitoring and Control Technical (VMCT) team for further guidance.

Key data needed to justify procuring PBO ITNs

The following data should be collected at the district or regional level where PBO ITNs are being considered:

- Current insecticide resistance data (collected within the past year) confirming moderate levels of pyrethroid resistance (35-80% mortality) in the main malaria vector.
- Evidence that PBO restores pyrethroid susceptibility. This could be from:
 - Susceptibility assays combining pyrethroid + PBO
 - ITN cone bioassays with standard and PBO ITNs
- Documented moderate to high malaria prevalence (>20%) in children 2 – 10 years old using existing data sources.

Requirements for deploying PBO ITNs

- Ability to collect entomological data and routine health facility data in the geographic areas of deployment.
- PBO ITNs should not be deployed in the same area as IRS, as there is currently no evidence of added benefit of PBO ITNs in addition to IRS.
- As PBO ITNs are currently more expensive than pyrethroid-only ITNs, the benefit of the PBO ITNs must be weighed against a potential loss of overall ITN coverage. The cost of procuring PBO ITNs must be weighed against the effect of reduced resources for other malaria program priorities—they will not be procured if there are key malaria commodity gaps (e.g., ACTs, RDTs) or significant malaria control programmatic gaps.

These criteria must be discussed with the PMI VMCT team in conjunction with country stakeholders (i.e., NMCPs, implementing partners, entomology institutions), using the best available technical evidence, and HQ must provide approval for a PMI focus country to procure PBO nets. If NMCPs or malaria partners are procuring PBO nets with non-PMI funding, please contact the PMI VMCT team to identify the appropriate partnership role PMI may play.

Dual-insecticide ITNs

Dual-insecticide nets are ITNs that have both a pyrethroid, plus a second insecticide of a different class. Unlike PBO, which is only a synergist, both active ingredients are insecticides that can individually kill a mosquito. The combination of two insecticides can potentially decrease the emergence of resistance, as mosquitoes resistant to one insecticide may still be susceptible to the other. There is currently one dual-insecticide ITN that has a WHO PQ interim recommendation, the Interceptor G2. This net has a combination of alphacypermethrin, a

pyrethroid, and chlorfenapyr, a slower-acting insecticide that targets energy production in the mitochondria.

Although the Interceptor G2 has a WHO PQ recommendation as an ITN, there is currently no WHO policy guidance on when these ITNs should be deployed instead of pyrethroid-only nets. Next-generation nets are expected to be more expensive than pyrethroid-only nets, so targeting their use to the appropriate settings will be crucial for maximizing impact. In the coming year, the WHO Vector Control Advisory Group is expected to provide technical guidance on acceptable methodologies to generate epidemiological evidence for next-generation nets that will inform future WHO policy guidance. Additionally, a UNITAID and Global Fund catalytic initiative⁵⁹ is expected to provide funding to generate evidence for the needed policy recommendation, as well as subsidize procurement of next-generation nets. Through a partnership with UNITAID and Global Fund, the future subsidy may be available for select PMI focus countries which receive approval from HQ to procure next-generation ITNs procurements. **(Currently, PMI will not procure G2 unless through the co-payment initiative or for OR purposes.)** PMI will also collaborate closely in the evidence generation aspects of this initiative. If NMCPs or country teams are considering procuring next-generation ITNs, they should engage with the PMI VMCT team for further guidance.

Environment Risks of ITN Disposal, Misuse, and Repurposing

Disposal

It is estimated that 1 billion ITNs were distributed in Africa since 2000. 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.

⁵⁹ <https://unitaid.eu/call-for-proposal/catalyzing-market-introduction-next-generation-long-lasting-insecticidal-nets-llins/#en>

- 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 2010.⁶⁰

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 use 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

⁶⁰ 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 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

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.”^{61,62}

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. The only alternative use that is never acceptable is 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.

While there is no current WHO guidance for the stage between use and disposal, the following three categories of repurposing may help in developing SBCC messaging:

4. **Beneficial repurposing** is the use of expired ITNs for purposes other than as a bednet to protect against malaria infection, such as curtains, patches for holes in viable nets, stuffing eaves, and constructing window or door screening.
5. **Neutral repurposing** is the use of expired ITNs for household uses that do not prevent mosquito bites, such as covering latrines, protecting seedlings, fencing, transporting/storing crops, screening of poultry or animal enclosures, soccer goals, tearing into strips for tying objects, and other household uses.
6. **Misuse** is the use of a non-expired ITN for purposes other than its intended use as a bednet to protect against malaria infection. Using a new or old ITN – one that is still useful for sleeping under – for another purpose is misuse. Using any ITN, whether new, old, or expired, for fishing, is the prime example of misuse.

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

⁶¹ 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

⁶² 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

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 some 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 lower overall mosquito abundance due to exposure to pyrethroids in ITNs.^{63,64,65,66,67,68,69,70}

⁶³ 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.

⁶⁴ 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>

⁶⁵ Gimnig J, Vulule J, Lo T, et al. Impact of permethrin-treated bed nets on entomologic indices in an area of intense year-round malaria transmission. *The American Journal of Tropical Medicine and Hygiene.* 2003;68:16-22

⁶⁶ Ilboudo-Sanogo, N. Cuzin-Ouattara, D. A. Diallo, S. N. Cousens, F. Esposito, A. Habluetzel, S. Sanon, A. P. Ouédraogo Insecticide-treated materials, mosquito adaptation and mass effect: entomological observations after five years of vector control in Burkina Faso. *Trans R Soc Trop Med Hyg.* 2001 Jul-Aug; 95(4): 353-360.

⁶⁷ Indome, F., Smith, T., Impact of spatial distribution of permethrin-impregnated bed nets on child mortality in rural northern Ghana. *American Journal of Tropical Medicine and Hygiene.* 1998 Jul;59(1):80-5.

⁶⁸ Howard SC, Omumbo J, Nevill C, Some ES, Donnelly CA, Snow RW. Evidence for a mass community effect of insecticide-treated bednets on the incidence of malaria on the Kenyan coast. *Trans R Soc Trop Med Hyg.* 2000 Jul-Aug;94(4):357-60.

⁶⁹ Maxwell, C. A., Msuya, E., Sudi, M., Njunwa, K. J., Carneiro, I. A. and Curtis, C. F. (2002), Effect of community-wide use of insecticide-treated nets for 3–4 years on malarial morbidity in Tanzania. *Tropical Medicine & International Health,* 7: 1003–1008.

⁷⁰ Magesa SM, Wilkes TJ, Mnzava AEP et al. (1991) Trial of pyrethroid impregnated bednets in an area of Tanzania holoendemic for malaria vector population. Part 2. Effects on the malaria vector population. *Acta Tropica* 49, 97–108.

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), a community effect may be achieved when more than half of the people (all age groups) in the community use an ITN every night.

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 or alphacypermethrin, 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.⁷¹ 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.

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 are thoroughly evaluated in USAID’s *Integrated Vector Management Programs for Malaria Vector Control: Programmatic Environmental Assessment*

⁷¹ Malaria and HIV/AIDS interactions and implications: conclusions of a technical consultation convened by WHO, 23-25 June 2004

(PEA); the PEA is routinely updated and the 2017 version is available on [pmi.gov](https://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/integrated-vector-management-programs-for-malaria-vector-control-programmatic-environmental-assessment-2017.pdf?sfvrsn=5). The PEA found that 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, and SBCC on appropriate use during distribution efforts. The current, full PEA can be downloaded at:

<https://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/integrated-vector-management-programs-for-malaria-vector-control-programmatic-environmental-assessment-2017.pdf?sfvrsn=5>

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 section 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 durability monitoring be carried out?

Factors affecting whether LLIN durability 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 numbers of LLINs. It is less useful for a program approaching elimination 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. If a country team proposes more than two sites, justification must be provided to the HQ ITN team as to how these data will be used and to ensure that other elements of the overall PMI portfolio are adequately funded.
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 specifications⁷² 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 cohort sample of 250 marked nets followed longitudinally and examined yearly for three years. With this sample size, using 15 clusters of 10 households each where all nets are marked in selected households, 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.

⁷² 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 at 12 and 24 months should be done on nets from outside the main cohort of ITNs being monitored and at 36 months from the main cohort, whereby 30 nets are taken from the field for laboratory testing each year for three years. Nets collected at the 12 and 24 months may be identified through one of two methodologies, either: a) random selection from outside the study cohort; or b) tagging a separate bioassay net cohort at baseline. Each methodology has pros and cons and should be selected based on what is most appropriate within the country specific context. 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.⁷³

Measurement of insecticidal content is done by PMI at baseline for all PMI-procured LLINs. The Global Fund has put in place an analogous program so there is no need for PMI to fund baseline measurement of insecticide content in Global Fund-procured nets. However, it is recommended to retain 30 nets before distribution for confirmation in the event that unexpected results are obtained from bioassays. At subsequent follow ups, 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

⁷³ 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)

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.

Interpretation and use of the results of LLIN monitoring

WHOPES has provided clear cut-off points for WHO cone tests. Nets are considered effective if they cause >80% mortality or >95% knockdown in the WHO cone test. For nets that fall below these criteria, WHO recommends the use of the tunnel test to assess feeding inhibition caused by sub-lethal doses of insecticide. However, the tunnel test requires special capacity that is unlikely to be present in most PMI countries. Therefore, as an alternative, nets are considered minimally effective if they cause >50% mortality or >75% knockdown in the cone test. 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. Nets should be considered in need of replacement if they have at least 1000cm² of damage (i.e., 642 pHI) (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

Durability monitoring results can help PMI identify when an ITN product does not meet acceptable standards for integrity and insecticidal effectiveness. It is NOT powered to identify a product that is significantly superior in quality as to justify preference for procurement. PMI teams should explain this carefully to NMCP and malaria partners when results are presented. PMI has recently developed guidance documents on what levels of ITN attrition, physical damage, and bioefficacy would constitute poor performance, and actions to be taken in response, posted on www.durabilitymonitoring.org.

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

- A new IRS insecticide, clothianidin, recently obtained a WHO PQ listing. In 2017, WHO's process for evaluation of vector control products transitioned from WHOPES to WHO PQ and all new products that receive a favorable review will be listed by PQ going forward, which replaces the previous WHOPES recommendation process. The expected residual efficacy of this new product, according to the WHO-approved label, is up to eight months (PQ does not include the expected duration with the listing). Clothianidin is repurposed from the agriculture industry, and is a slower-acting insecticide from the neonicotinoid class with a different mode of action than existing IRS insecticides. Sumishield is the trade name of the clothianidin product from Sumitomo which received the listing, and it is eligible for the UNITAID NgenIRS co-payment. All countries considering use of this new product should be conducting resistance testing to ensure full susceptibility of the insecticide prior to its use (see **Entomologic Monitoring and Insecticide Resistance** chapter).

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 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, no PMI-supported IRS programs have used pyrethroids since 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). These formulations are not yet compromised by insecticide resistance, and increase the effective lifetime of IRS products. There are multiple NgenIRS-eligible IRS formulations that either have a WHO PQ recommendation (Actellic CS and Sumishield), or are expected receive one in the last quarter of 2018 (Fludora Fusion). 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% co-payment 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 is expected to decrease the price of 3GIRS, so that the co-payment 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 country 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, began with four countries in Year 1 (Ethiopia, Mali, Rwanda, and Zambia), added eight countries in Year 2 (Benin, Ghana, Kenya, Madagascar, Mozambique, Tanzania, Uganda, and Zimbabwe), and will increase steadily to include the majority of PMI-supported countries by Year 4. Criteria for country inclusion include:

- 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

Selection of future countries will be made jointly by project stakeholders, including PMI Headquarters, with ultimate approval coming from UNITAID.

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. All decisions about the choice of insecticide should be done in consultation with the NMCP. 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. The choice 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	<ul style="list-style-type: none">• Low toxicity• Low cost• >7 months duration for longer-lasting formulations	Resistance	\$2-3
Carbamates	<ul style="list-style-type: none">• Medium toxicity Profile• Less resistance	<ul style="list-style-type: none">• High cost• < 4 month duration	\$11*
Organophosphates	<ul style="list-style-type: none">• Less resistance• CS formulation >6 months duration	<ul style="list-style-type: none">• Higher relative toxicity• Higher costs	\$23.50 for CS formulation (\$15 with UNITAID copayment)
Organochlorines (DDT)	<ul style="list-style-type: none">• Low cost• >7 months duration	<ul style="list-style-type: none">• Management costs• Resistance• Supply	\$4 to \$6.70
Neonicotinoids	<ul style="list-style-type: none">• Less resistance• Residual efficacy predicted to be 7 months	<ul style="list-style-type: none">• Higher costs	TBD, expected to be similar to organophosphates

*The number of structures sprayed per bottle/sachet is approximately equivalent for all insecticides, however, the short residual life of current WHO PES-recommended carbamate formulations means that in areas of year-round transmission, two rounds of spraying are required, effectively doubling the price of carbamates.

The five classes of insecticides currently recommended by WHO for IRS are 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. Carbamates and 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. The most recent class to receive a recommendation by WHO for IRS are neonicotinoids. These nicotine-like compounds mimic acetylcholine, tightly binding the acetylcholine receptor to cause high levels of activation and overstimulation. Neonicotinoids are

slow-acting insecticides that cause mosquito mortality at 72 hours, rather than the typical 24 hours observed for other classes. Another potential new class of public health pesticide, the pyrroles, is currently registered by the U.S. Environmental Protection Agency for some indoor uses (e.g., commercial kitchens). Pyrroles are not neurotoxins, but act by disrupting mitochondrial ATP, leading to cellular death and eventual insect mortality. One member of this class, chlорfenapyr, has been evaluated by WHO for use on ITNs, and may be evaluated for use in IRS in the future.

The WHO-specified duration of effective action in Table 1 corresponds to results from WHO supported trials. However, PMI's operational experience has generally demonstrated effective action for the longer-lasting OP (pirimiphos-methyl CS) of at least 6 months on cement, mud, and wood surfaces. 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. However, a small number of countries in West Africa have shown significantly shorter residual life for all insecticides, with 1 month residual efficacy for bendiocarb and 2-3 months for pirimiphos-methyl.

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.** **The updated PQ listing can be found at: <http://www.who.int/pq-vector-control/prequalified-lists/en/>.**

The WHO Global Plan for Insecticide Resistance Management⁷⁴ recommends rotations, mosaics, and mixtures to slow selection of resistant vectors. As there are now multiple, similarly-priced insecticide formulations available for IRS, PMI supports rotating between insecticides with susceptibility, where possible. As a practical option to manage buffer stocks, it may be possible to spray some districts with insecticide A, and others with insecticide B, and switch annually. Country teams should engage the PMI Headquarters IRS Team and their entomology backstop to discuss insecticide resistance management plans in light of new products that have recently become available.

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. For additional information on the

⁷⁴ http://apps.who.int/iris/bitstream/10665/44846/1/9789241564472_eng.pdf

combination of IRS and ITNs, please see the **Vector Monitoring and Control** chapter of the PMI Guidance. 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 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, if there are unique circumstances (e.g., delayed LLIN 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 (sub-district, district, region, or other administrative unit) to be sprayed, although WHO guidelines state that coverage above 85% 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 spraying of living structure within selected, discrete geographic areas within an area targeted for IRS activities, based on epidemiologic or ecological parameters. Focal IRS requires precise epidemiological, environmental, 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 most suitable for spraying.
- Although 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 are 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 (anticipated the last quarter of 2018), 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 of high transmission, and 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, and the availability of new, longer-lasting insecticides, 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 (i.e., IRS is used to reduce or “knock-down” the malaria burden, and then ITNs are used to maintain or “keep-down” the burden), 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 as 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 2016,⁷⁵ in the majority of PMI-supported countries, insecticide costs average 39% of the IRS budget, ranging from 27% to 50%, depending on the insecticide class used. 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 increased 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,

⁷⁵ Accessible at <https://www.pmi.gov/docs/default-source/default-document-library/implementing-partner-reports/africa-indoor-residual-spraying-project-pmi-irs-country-programs-2016-comparative-cost-analysis.pdf?sfvrsn=4>

differing efficacy periods, variation of the programmatic impact of resistance on the interventions, and LLIN durability.

- For FY 2019 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.
- Due to the availability of multiple WHO approved classes of insecticides for IRS implementation, IRS is seen as a potential resistance management tool. 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 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).
- 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 WHO. Typically, insecticides will arrive in country with quality assurance documents from the manufacturer. However, to ensure due diligence, PMI requires its IRS partner to conduct independent, pre-shipment quality control evaluations. In countries where PMI conducts IRS but the insecticide was not 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 confirmed resistance, as defined by the WHO guidelines, 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 four of five classes of insecticide (but not necessarily all active ingredients in each class). 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

- With the release of the 2016 WHO ANC Guidelines, and as countries begin to adopt them for their specific country context, PMI country teams should work with the NMCP counterparts and actively engage in the adaptation of these guidelines and revision of national ANC policies to ensure the timing of ANC visits promotes optimal dosing of IPTp. This will likely require an **additional ANC contact** at 13-16 weeks, as recommended by WHO. A contact with a health provider between 13 and 16 weeks gestation is critical to ensuring timely access to the first dose of IPTp-SP for maximum impact. See below for further details and clarification.
- IPTp3+ is now the primary indicator recommended by the RBM MERG. PMI recommends tracking both IPTp3+ and IPTp2+ for MIP programming results, to provide continuity in reporting.
- In July 2017 the WHO MPAC reviewed recent studies on MIP in low transmission settings. No new recommendations came out of this meeting. Until further data are made available, IPTp-DP is still not recommended for malaria prevention in pregnant women. In low transmission settings where Single Screening and Treatment is routinely implemented for all women presenting at ANC, Intermittent Screening and Treatment did not result in detection of significantly more malaria infections and is still not recommended.

Introduction

Each year, approximately 125.2 million women living in malaria-endemic countries,⁷⁶ 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.⁷⁷

⁷⁶ 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

⁷⁷ <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 antenatal care service delivery platform in collaboration with both NMCPs and Reproductive/Maternal Health Programs. To facilitate this collaboration and to ensure improvements in delivery and uptake of IPTp, PMI encourages countries to establish a national technical advisory body, such as an MIP or ANC 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.⁷⁸

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 (13 weeks), provided that there has been an interval of approximately one month since the last dose of SP.^{79,80,81} 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.^{82,83,84,85}

⁷⁸ 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.

⁷⁹ 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.

⁸⁰ http://www.who.int/entity/malaria/iptp_sp_updated_policy_recommendation_en_102012.pdf

⁸¹ http://www.who.int/malaria/mpac/sep2012/iptp_sp_erg_meeting_report_july2012.pdf

⁸² 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.

⁸³ 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.

⁸⁴ 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.

⁸⁵ 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.

Current WHO IPTp Policy Recommendations

- In areas of moderate-to-high malaria transmission, IPTp with SP is recommended for all pregnant women at **each** scheduled antenatal care visit starting as early as possible during the second trimester of gestation, provided these visits are at least one month apart. 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.

New 2016 WHO ANC Guidelines

The new WHO ANC Guidelines, released in late 2016, call for a minimum of 8 contacts with a health provider, with one contact during the first 12 weeks gestation, and subsequent contacts at 20, 26, 30, 34, 36, 38 and 40 weeks gestation.⁸⁶ The ANC guidance also notes that “frequency and exact timing of some of these ANC practices and interventions – especially related to malaria, tuberculosis and HIV – may need to be adapted, based on the local context, population and health system.” As highlighted in the RBM ANC brief, developed in close collaboration with WHO Reproductive Health and Global Malaria colleagues, in malaria endemic areas, **an additional visit at 13-16 weeks is recommended to allow for early provision of IPTp.**⁸⁷ Ideally, this would mean that women would be given IPTp at **each** visit starting from 13-16 weeks, provided that the last dose of IPTp-SP was at least 4 weeks prior, as follows:

Table 1. Adaptation of WHO Recommended ANC Contact Schedule to Include IPTp	
Timing of Contact	Dose #
1: Up to 12 weeks	ITN provided
1a: 13-16 weeks	IPTp-SP dose 1 (additional contact)
2: 20 weeks	IPTp-SP dose 2
3: 26 weeks	IPTp-SP dose 3
4: 30 weeks	IPTp-SP dose 4
5: 34 weeks	IPTp-SP dose 5
6: 36 weeks	No SP, if last dose received <1 month ago
7: 38 weeks	IPTp-SP dose 6 (if no dose in past month)
8: 40 weeks	

⁸⁶ <http://apps.who.int/iris/bitstream/10665/250800/1/WHO-RHR-16.12-eng.pdf?ua=1>

⁸⁷ www.rollbackmalaria.com/organizational-structure/working-groups/mipwg/

When implementing these recommendations, care should be taken to preserve flexibility- i.e., it should be made clear to providers that the 20 week visit can be conducted over a range of weeks, and not only at exactly 20 weeks, and that IPTp can be given at each visit, provided that the woman is at least 13 weeks, and at least 4 weeks has elapsed since the prior dose was administered. In training documents, one could consider highlighting that the visits should occur approximately monthly starting at 26 weeks, with biweekly visits starting at week 34 until the end of pregnancy.

Due to the revised WHO policy of giving IPTp at every ANC visit starting early in 2nd trimester, the **RBM MERG has recommended tracking the percentage of women receiving the 3rd dose (IPTp3)**. While PMI has historically tracked the 2nd dose, and will continue to do so in order to continue monitoring trends over time, PMI will also track the 3rd dose of IPTp (and potentially additional doses as well) as countries start implementing the new policy.

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.

Women can and should receive IPTp each month starting in the 2nd trimester; 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 SRA⁸⁸ can be procured. In cases where countries are

⁸⁸This 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/>.

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 manufactured 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,⁸⁹ and in one study in Kenya, 45% of SP was found to be substandard.⁹⁰ Depending on the manufacturer, SP has a reported shelf life of between 36 and 48 months.

Due to consistent demand and long lead times, PMI continues to look at options to improve procurement processes for SP. Importation issues and registration policies continue to be key challenges to ensuring access to SP in sub-Saharan African countries. The variety of SP presentations available for procurement (i.e., numerous different-sized unit bottles and various blisters pack options) has added an additional obstacle to the in-country registration processes, providing little incentive for manufacturers to register any one product over another. PMI-supported countries should plan on longer lead times (8-12 months) for SP commodity orders from quality-assured manufacturers and work with their in-country supply chain technical assistance partners to obtain importation waivers, if necessary. Currently, there are no WHO prequalified single-unit dose presentations of SP indicated for IPTp; PMI procures non-pre-qualified SP from wholesalers. To ensure only good quality products are sourced from reliable vendors, PMI continues to apply a robust QA/QC policy to every consignment of SP. Please refer to the Sulfadoxine-Pyrimethamine and Lot Quality Assurance/Quality Control subsections within the **Commodity Procurement and Supply Chain Management** chapter for more information.

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 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

⁸⁹ 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.

⁹⁰ Amin A, et al. The quality of sulfadoxine-pyrimethamine and amodiaquine products in the Kenyan retail sector. *J Clin Pharm Ther*, 30:6 (2005).

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 has recommended 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 is supporting a study to further assess IPTp with DP in Malawi. In addition, a multi-country study (Tanzania, Kenya, Malawi) funded by the European and Developing Countries Clinical Trials Partnership is expected to begin in early 2018 to definitively address this question.

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 East and West Africa, and ISTp was not superior to IPTp-SP even in areas with significant SP resistance. ISTp has also been evaluated against IPTp in Indonesia, where IPTp was more effective, except in the lower transmission setting, where IPTp was not significantly different from ISTp. In Africa, 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.”⁹¹

⁹¹ WHO Regional Office for Africa: A Strategic Framework for Malaria Prevention and Control During Pregnancy in the African Region (2004).

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 (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.^{92,93} 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.^{94,95} 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.⁹⁶ 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 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 studies in Burkina Faso and Malawi to assess the feasibility and effects of community level delivery of IPTp on both IPTp uptake and ANC attendance. Also, UNITAID has launched a new 4-country study to pilot community-delivery of IPTp with SP in DRC, Nigeria, Madagascar, and Mozambique. These studies will generate evidence for WHO's policy on c-IPTp. 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

⁹² 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>.

⁹³ Richard Ndyomugenyi, 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.

⁹⁴ 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.

⁹⁵ 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.

⁹⁶ 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.

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.

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.⁹⁷ The provision of ITNs to pregnant women is part of the essential package of ANC 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; PMI teams are encouraged to identify additional novel distribution channels to ensure high coverage of nets to women of reproductive age, particularly adolescent girls. **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 published a joint statement detailing the importance of maintaining LLIN coverage of vulnerable populations via ANC and EPI distribution.⁹⁸

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.

⁹⁷ 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*.

⁹⁸ http://www.rollbackmalaria.org/files/files/partnership/4_FLLIN_E.PDF

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 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 continues to recommend that women in the first trimester should be treated with oral quinine for seven days (with or without clindamycin), however, the Technical Expert Group on Malaria Chemotherapy is expected to review the safety data and make a recommendation on whether ACTs can be considered equivalent to quinine for treatment of acute malaria in the 1st trimester of pregnancy in early 2018. Until the recommendation is changed, however, ACTs should be used for treating uncomplicated first trimester malaria infections only if no other efficacious antimalarial treatments are available. 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).⁹⁹

Table 2. 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.

⁹⁹ WHO, 2012. Management of severe malaria: a practical handbook – 3rd ed.

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.

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.¹⁰⁰ 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.¹⁰¹ 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.¹⁰² In contrast, the 0.4 mg/day 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

¹⁰⁰ 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.

¹⁰¹ http://www.who.int/maternal_child_adolescent/documents/924159084x/en/index.html

¹⁰² 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.

teams should work with the MOH to procure (or consider procuring) low-dose folic acid (or iron and folate combination tablets, with 60 mg/day iron and 0.4 mg/day of folate), which is recommended by WHO for use in pregnancy.

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 (please see **Table 3** for a list of remaining barriers by health system component and possible solutions).

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 (i.e., IPTp3, IPTp4, etc.)
- 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 and stock management, training, and logistics and procure SP in case of gaps
- Explore innovative means to reach out to CHWs, including the use of cell phone messaging to promote ANC attendance and IPTp awareness.
- 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, engaging men, 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.

Table 3. Improving IPTp Uptake: Addressing Remaining Barriers

Policy	Provider	Client	Product	Data
Contradictory and restrictive language: -Revisions to country guidance based on WHO IPTp policy recommendations issued in 2012 -Advocacy MIP infographic developed to target policy makers (see #1 below)	Incorrect practices and perceptions: -SBCC strategy targeted to providers attitudes and behaviors. -Implement quality assurance tool developed for improving provider practices on IPTp, which promotes provider monitoring. (see #2 below)	Lack of early or frequent ANC visits : -Most countries have high ANC 1 (over 90%) attendance but low ANC4. -Most pregnant women come at ~4-5 months gestation for their first ANC; ideal for first dose to be given at 13-16 weeks. -Use of IPTp tool to determine gestational age (#5 below)	SP facility level stock-outs: -SP is a tracer drug -Support EUV tracking - ensure timely orders of SP submitted (with longer lead times) -support stock management trainings to ensure facilities are equipped to manage a stock out.	Lack of quality facility level data on IPTp – -Ensure IPTp3 is tracked in HMIS and ANC registers are updated. -Ensure correct denominator used in HMIS to track # of IPTp treatments. -Improve MIP indicators used in health facility surveys.
Lack of coordination between Malaria and Maternal Health Programs: -Establish a national MIP technical working group. - Ensure MH guidelines are consistent with new IPTp recommendations; particularly if ANC guidance is revised.	-Developed a Gestational Age job aid for correctly identifying and initiating the first IPTp treatment (#5 below) -Refresher training for providers that includes country MIP guidelines and promotes IPTp uptake	Knowledge of MIP and IPTp: -Percentage of pregnant women who know importance of taking IPTp during pregnancy.	- support development of logistics management information systems	Validity of self-reported IPTp2 data in national household surveys: -Include tracking of malaria cases among pregnant women in HMIS
Ensure IPTp and ITN policies are clarified in the context of the new WHO ANC Guidelines (2016)	Lack of DOT administration -Ensure cups and clean water are available at ANC. Confusion over number and timing of doses (as a result of policy language) -Use of memo from District Health Officer stating correct policy (Example from Kenya). - Training on updated policy should address this Perception of SP resistance -Malawi study, in an area of high SP resistance, with fixation of the quintuple mutant, showed benefit of IPTp on LBW and SGA outcomes. -Mounting evidence that SP has beneficial effects aside from antimalarial effects	-Work with Peace Corps Volunteers to improve health education in MIP. -providers should explain and promote IPTp and ITN use at every ANC visit SBCC MIP strategy development tool kit developed (#6 below)	Availability of low dose folate (0.4mg): -Ensure low dose folate available. (Links to technical briefer on controlling anemia and RBM MIP consensus statement below, #3 and #4)	-2014 Ghana DHS pilot found: a relatively small percentage of women had an ANC card that was seen by interviewers (36%) even though the vast majority reported having a card (97%). Exclusion of HIV+ women on daily CTX from IPTp: -Collect data on number of HIV+ women excluded from IPTp
		Inability to pay client fees for ANC and SP (and/or ANC card): -Explore health insurance or financing schemes. -Ensure ANC and IPTp are provided free per national policies.		
		Young adults and first/second pregnancies less likely to receive IPTp2: -Ensure ANC services target this group to increase ANC and IPTp coverage.		
		Can c-IPTp increase coverage? -Testing whether community-based IPTp can increase IPTp2 coverage and ANC attendance in		

		Burkina Faso.		
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#1 MIP info-graphic: <https://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/malaria-infographic-english-508.pdf?sfvrsn=8>

#2 IPTp Quality Assurance tool:

http://www.africanstrategies4health.org/uploads/1/3/5/3/13538666/iptp_technical_brief_final.pdf

#3 technical briefer on controlling anemia: <https://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/controlling-maternal-anemia-and-malaria.pdf>

#4 RBM MIP consensus statement: <https://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/consensus-statement-folic-acid-supplementation-during-pregnancy.pdf>

#5 PMI MCSP IPTp Tool for determining gestational age and early timing of IPTp:

<<http://www.mcsprogram.org/resource/toolkit-improve-early-sustained-iptp-uptake-english/>>

#6 PMI HC3 SBCC MIP Strategy Development Guidance I-Kit Tool:

<https://healthcommcapacity.org/hc3resources/sbcc-malaria-pregnancy-strategy-development-guidance-kit/>

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. Updated ANC guidance:
www.who.int/reproductivehealth/publications/maternal_perinatal_health/anc-positive-pregnancy-experience/en/
- ANC guidance executive summary, including the list of the recommendations: <http://apps.who.int/iris/bitstream/10665/250800/1/WHO-RHR-16.12-eng.pdf?ua=1>

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 for treating uncomplicated malaria, it remains effective for IPTp (which is not a case management strategy). It is thought that pregnant woman's pre-existing immunity amplifies the effectiveness of SP in IPTp, whereas young children have no such immunity.¹⁰³ 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.^{104,105,106} 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.¹⁰⁷ 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.¹⁰⁸ 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

¹⁰³ 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.

¹⁰⁴ 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.

¹⁰⁵ 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.

¹⁰⁶ 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.

¹⁰⁷ 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.

¹⁰⁸ 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.^{109,110} Studies in areas with lower levels of SP resistance (West Africa) have found that IPTp with SP remains effective.^{111,112} In addition, a recent meta-analysis of national survey data has shown that SP provides protection in a programmatic context.¹¹³ 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.¹¹⁴ Consequently, WHO recommends continuing 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)

¹⁰⁹ Menendez, C., A. Bardaji, et al. (2010). "Malaria Prevention with IPTp during Pregnancy Reduces Neonatal Mortality." *PLoS ONE* 5(2): e9438.

¹¹⁰ 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.

¹¹¹ 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

¹¹² 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

¹¹³ 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.

¹¹⁴ 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.

Seasonal Malaria Chemoprevention

New/Key Messages

- Seasonal malaria chemoprevention has been shown to be an effective strategy in reducing malaria morbidity in eligible countries of the Sahel and feasible to implement on existing platforms.
- Planning for procurement of commodities should be done at least a year in advance given long lead times for delivery.

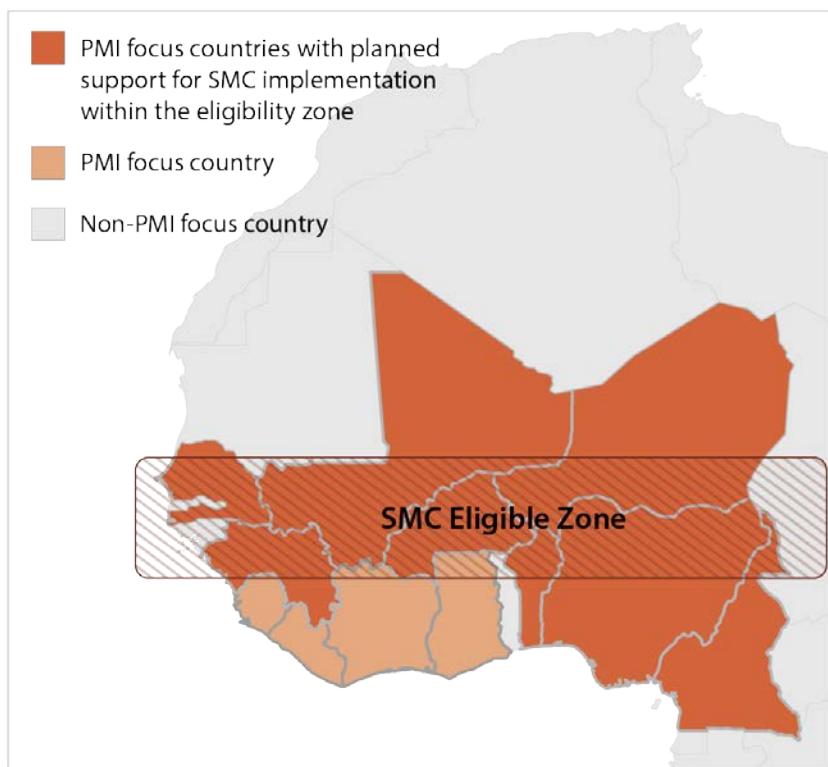
Introduction

WHO issued a recommendation for the implementation of seasonal malaria chemoprevention (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 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 duration of the malaria transmission season is four months or less. Seasonal malaria chemoprevention 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. WHO recommends that countries implementing SMC should not also implement intermittent preventive treatment in infants (IPTi, which is the administration of a full treatment dose of SP to infants less than one year of age) in the same areas. PMI currently supports SMC activities in Senegal, Mali, and Burkina Faso, and will be initiating activities in Benin, Cameroon, Niger, Guinea, and northern Nigeria with FY 2017 resources. 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.

Seasonal malaria chemoprevention programs require a community-based structure to deliver this intervention. Many successful programs are 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, distribute the medications, and follow-up to ensure adherence to dosing regimens throughout the rainy season. Results from the PMI-funded pilot implementation and evaluation of SMC in Mali and Senegal showed a 66% drop in parasite prevalence and a 50% drop in cases of uncomplicated malaria among children <5 following four rounds of SMC. The studies also demonstrated the feasibility of implementing through existing community-based 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.



Considerations

A number of technical and logistical considerations exist when supporting an SMC program.

Age groups

The current WHO recommendation is for SMC to target children aged 3-59 months. These recommendations are based on several clinical trials and pilot SMC projects which documented the effectiveness of the intervention to reduce malaria morbidity in this age group. A few countries are currently piloting extending the age range for SMC up to age 10, including a PMI-funded OR project. However, these studies are ongoing and the results regarding feasibility and

effectiveness in the older age group are not yet known. For this reason, PMI-funded programs should adhere to the current WHO age definitions.

Time frame

Seasonal malaria chemoprevention should be delivered once a month during the peak transmission season, not to exceed four months of implementation in a given year. Some countries have questioned whether three rounds would be sufficient to provide a desired level of protection, while others have considered extending the season to five months or more. Currently, WHO does not recommend extending the SMC season beyond four months to prevent accelerated development of resistance to the drugs. Countries or geographic areas with a documented transmission season shorter than four months may consider only covering the duration of the transmission season. However, shortening SMC to fewer than four months should not be considered as a cost-savings activity as sufficient data do not currently exist on the effectiveness of a shortened period of implementation.

Implementation issues

The current WHO guidance does not provide details on the best strategies for delivery of SMC in the field. In many countries, the first dose SMC is delivered door-to-door by community health workers, and the doses for the second and third day are left with the child's caregiver, along with instructions for administration. In other countries, a fixed-point approach is used for the first dose, with caregivers taking the additional doses for home administration. In fixed-point sites, there may also be community level 'mop-up' to reach children not seen at the distribution points. Some programs couple other interventions, such as nutritional supplementation, to SMC delivery. In most programs, SMC is given to all children who present, but there are exceptions. For example, in Mali, malaria screening and testing is done prior to SMC delivery and children who test positive are treated with ACTs and do not receive SMC drugs. Countries have adopted different delivery approaches that are adapted to the specific country context. While no official guidance exists, the individual experiences of different countries have been documented in the scientific literature. For example, a PEER study funded by PMI documented that door-to-door distribution achieved higher coverage levels, but also increased costs for the program. PMI countries teams are encouraged to reach out to the Resident Advisors, and NMCP staff, in other countries implementing SMC to better understand best practices.

Resistance monitoring vs. pharmacovigilance

The deployment of a novel drug-based strategy such as SMC, even though it uses well-tested drugs, raises questions of efficacy and pharmacovigilance. The current WHO guidelines stress that systems to monitor both these issues should be instituted or strengthened in SMC zones. As with other malaria medications, PMI does not prioritize support for pharmacovigilance due to the well-established safety profile of AQ and SP. On the other hand, PMI does support monitoring of therapeutic efficacy for first-line malaria treatments, which can include testing for molecular

markers of drug resistance for ACTs as well as AQ and SP. Therapeutic efficacy monitoring of AQ and SP is not conducted as it would be unethical to use either of these drugs for treatment of clinical malaria in a standard TES protocol. PMI is working with WHO and other partners to develop and implement molecular methods to monitor for resistance to these two drugs. Country teams interested in supporting resistance monitoring activities should consult with the Case Management team for guidance.

Commodities

One significant issue for implementing an SMC program is having the necessary quantities of quality-assured SP+AQ available in advance of the malaria transmission season. In the past, individual tablets for SP and AQ were purchased separately, necessitating relatively complicated cutting to prepare the appropriate age-based combination treatment dosages, especially for children under one year of age who require smaller doses. In 2014, one manufacturer received approval from the WHO Prequalification Program for non-dispersible formulated co-blister presentation of SP+AQ. Additionally, there is a dossier for a dispersible co-blister formulation of SP+AQ currently under review by the WHO PQ Program; PMI can procure both the dispersible and non-dispersible coblisters, and these products are preferable over the loose pills used in the past. Regardless of formulation, lead times are long (approximately 10 months) and countries considering drug procurement in support of 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 to the intended point-of-care distribution locations. All PMI country teams planning to support SMC should work closely with the PMI Headquarters Supply Chain Team to ensure sufficient quantities of SMC 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 recommended that countries do specific quantification for RDT and ACT needs during the SMC distribution rounds as part of the logistics planning, as the additional testing of febrile children during these rounds (in countries where active screening and treating is part of the SMC protocol) might result in a seasonal increase in the needs for ACTs and RDTs.

Surveillance, monitoring, and evaluation

As a geographically targeted program, SMC presents some unique challenges for surveillance, monitoring, and evaluation. The first challenge is enumerating the target population of children 3-59 months. While most districts (or health zones, etc.) have estimates for this figure, precision

is often difficult; some children will age into, and out of, this range during the period of implementation and older siblings or children from outside the SMC geographic area may present for treatment. Enumeration of the eligible population has implications for planning and procurement of drugs as well as for estimates of SMC coverage.

Tracking actual administration of the drugs is also a major challenge. The community health workers or other implementers tasked with delivering the drugs generally record the child's information and any reasons for non-administration of SMC in a standardized register. Most programs also provide caregivers with individual cards for each child, and each administration of SMC is recorded on the card. This allows tracking of the children over each month of SMC implementation. These data can then be aggregated by district to calculate coverage rates. However, these systems are fairly new and can be subject to incomplete data, especially in regards to why a child did not receive SMC during a particular round.

Currently, WHO recommends that countries collect only one indicator on SMC programs:

Proportion of children aged 3–59 months (of those targeted) who received the full number of courses of SMC per transmission season

This indicator is intended to be derived from routine systems such as those mentioned above. Despite this being the official WHO-recommended indicator, the measurement details have not been fully finalized. Ideally, coverage would mean each child has received all three daily doses of medication each month, over the three or four months of the transmission season. In reality, the routine data generally just reflect the children who received the first dose through directly-observed treatment and whose caregivers were given the remaining two doses to administer at home. Most routine information systems are not able to capture actual administration of the second and third dose. However, PMI's pilot studies indicated that if a child received the first directly observed therapy dose, there was a very high likelihood of receiving the additional doses at home. The number of rounds (months) of administration can vary by country and even by sub-national zone depending on a range of planning factors. Thus, countries should also report on the target number of courses (3 or 4) and calculate this indicator accordingly.

In addition, it will be important to monitor the proportion of children who meet the eligibility criteria (including residence in eligible zones) but who did not receive SMC due to refusals, presenting with malaria (in the case of Mali), etc. During the pilot phases of SMC scale-up, a number of programs used pre- and post-coverage surveys to capture direct data on coverage of the intervention. However, now that SMC has moved beyond the pilot phase, such surveys can be prohibitively expensive and can increase the overall costs of the intervention. For this reason, PMI does not recommend using coverage surveys as a means to monitor the intervention. Similarly, PMI does not recommend tracking coverage of SMC through national household surveys such as the DHS or MIS. Instead, PMI will work with NMCPs to report SMC

implementation results using program data. The reason is that SMC programs are often only implemented in select districts and the sampling frame for these surveys is not representative at the district or lower levels (similar issues arise with IRS programs). In addition, the timing of the survey work is not linked to the timing of the SMC activities. If data collection occurs before or during SMC implementation in a given year, the results could underestimate actual coverage.

A number of national programs and implementing partners have developed data collection tools to monitor program progress in their countries. The RBM Monitoring and Evaluation Reference Group (MERG) has convened an SMC Task Force to review these tools and make recommendations on a consistent approach to program monitoring.

Additional information on the WHO policy recommendation can be found at:

http://www.who.int/malaria/publications/atoz/smcpolicy_recommendation_en_032012.pdf

A field guide for SMC implementation from WHO is available here:

<http://www.who.int/malaria/publications/atoz/9789241504737/en/>

An additional toolkit from MMV is available at:

<https://www.mmv.org/access/tool-kits/seasonal-malaria-chemoprevention-tool-kit>

Vaccines and Other Preventive Approaches

New/Key Messages

- WHO is conducting a pilot evaluation of RTS,S in three countries to assess feasibility, safety, and impact (mortality) in programmatic conditions. The vaccine implementation evaluation is likely to start in Kenya in mid-2018, in Ghana in late-2018, and in Malawi in 2019.
- No changes have been made to the 2015 WHO's Malaria Policy Advisory Committee recommendations on mass drug administration (MDA) and mass screen and treat (MSAT) strategies. PMI will consider OR proposals to test these strategies on a case-by-case basis, which will require approval by the OR committee.
- Proactive community treatment (ProACT) is a community-based intervention where community health workers actively seek out persons with fever, test them, and treat those that test positive for malaria. ProAct is being scaled up in Senegal (after operational research demonstrated its effectiveness in identifying malaria cases and reducing severe malaria and deaths). PMI is currently planning operational research to assess whether ProACT can have an impact on reducing malaria transmission. Other OR proposals could be considered on a case-by-case basis. PMI is not yet supporting its implementation outside of Senegal.

Introduction

Although much progress has been made with the scale-up of PMI's core 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— their intended role, targeted settings, and level of current evidence. It is important to note that these interventions are intended to complement, not replace, core interventions in case management and vector control and should only be considered for PMI support once requirements for these core interventions have been addressed. Some of these interventions are appropriate for control/transmission reduction settings and others are intended as tools for elimination.

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 piloted by other groups 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) have been evaluated in various transmission settings. The evidence to date was reviewed by WHO in 2015. 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 Elimination Working Group.**

Intermittent Preventive Treatment in Infants (IPTi)

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 a sub-national level (e.g., at the regional or district level) when the extent of SP resistance is only known for a smaller geographic area.

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 in any country except Sierra Leone. Sierra Leone has piloted IPTi in two of its 14 districts and plans to scale up IPTi nationally. WHO recommends that countries implementing SMC should not also implement IPTi in the same areas. Any requests from NMCPs to support IPTi 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 secured funding to support the initial phase IV pilot with support from the Global Fund, GAVI, and UNITAID and put out a call for proposals (June 2017) to assess feasibility, safety, and impact (mortality). The selection of the grant recipients is in the final stages and these pilots are due to begin in mid-2018. 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 of any developments as these pilots are implemented. 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 rapidly 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. A recent consensus modelling study¹¹⁵ noted that despite differing magnitude of effect depending on the transmission model used, all models predicted the percentage reduction in transmission to be temporary. The underlying assumption and the rationale for MDA is that subpatent parasitemia contributes substantially to malaria transmission and, therefore, must be treated if malaria is to be eliminated.

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 remain unanswered, 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.¹¹⁶ 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, have funded pilot studies in the Greater Mekong Subregion and other areas in Africa to assess the effectiveness of MDA, particularly in the context of elimination efforts.

Preliminary results of these studies have been mixed, both in terms of the coverage achieved (which often was well below the target) and in overall effectiveness. Some of the variation in study results appears to be related to transmission level and the coverage achieved and ongoing importation of malaria infections from outside the targeted area. In addition, initial results from southern Zambia showed marked reductions in malaria prevalence and incidence across both

¹¹⁵ Brady, O. J., et al. (2017). Role of mass drug administration in elimination of Plasmodium falciparum malaria: a consensus modelling study. *Lancet Glob Health* **5**(7): e680-e687

¹¹⁶ Aregawi, M., et al. (2016). Impact of the Mass Drug Administration for malaria in response to the Ebola outbreak in Sierra Leone. *Malar J* **15**: 480.

control and MDA arms following aggressive efforts to achieve universal coverage of LLINs, IRS, and effective community case management.¹¹⁷ In addition, focal MDA (MDA targeting households or small-scale foci) was not as effective or cost-saving compared to MDA.

In 2015, WHO convened an Evidence Review Group to review all available evidence on MDA and presented their draft recommendations to the Malaria Policy Advisory Committee. In November 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. PMI support for MDA will only be considered in the context of operational research. PMI will be supporting operational research to compare targeted MDA versus reactive case detection in response to index cases in the elimination settings of Ethiopia. Any country teams considering supporting an MDA intervention should consult with the PMI Headquarters 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-md-and-primaquine.pdf>

Mass Screen and Treat

Mass screen and treat refers to screening all persons 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

¹¹⁷ Eisele, T.P. et al. (2016). Short-term Impact of Mass Drug Administration with Dihydroartemisinin Plus Piperaquine on Malaria in Southern Province Zambia: A Cluster-Randomized Controlled Trial. *J Infect Dis*, 214(12):1831-1839.

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. Evidence from Burkina Faso and Zambia, and from a PMI-supported study in Kenya, indicate that MSaT with conventional RDTs is insufficient to significantly reduce the human infection reservoir. While work to develop more field-friendly molecular tests are underway and a highly-sensitive *hrp2*-based RDT is commercially available, there is currently no evidence to indicate that such more sensitive diagnostic tests will improve the effectiveness of the MSAT approach. Evaluation of the performance of the high-sensitivity RDT for *P. falciparum* malaria in asymptomatic individuals from Uganda, Myanmar, and naïve human challenge infections showed a greater than 10-fold lower limit of HRP2 compared with conventional RDT.¹¹⁸

The 2015 Malaria Policy Advisory Group concluded that mass screening and treatment and focal screening and treatment for malaria are not recommended as interventions to interrupt malaria transmission. PMI is not currently supporting MSaT activities; however, the role of highly-sensitive RDTs in reactive case detection is being evaluated in Burma and Cambodia. Any country teams considering supporting an intervention involving MSaT should consult with the PMI Headquarters Elimination Working Group and Case Management Teams in advance of any consideration of MOP support.

Pro-active Community Treatment

Proactive community treatment (ProACT) is deployed to identify persons of all ages with fever or other symptoms consistent with malaria on a routine basis (generally weekly) in a targeted community. With this approach, persons with fever are actively identified in the community, often by door-to-door sweeps through the catchment area, and tested with a malaria RDT. Those that are positive are treated with the appropriate first-line treatment (or referred if signs of severe disease are present). Such community sweeps are often restricted to the high transmission season.

The most well-established example of this approach is the PECADOM Plus program in Senegal. Community health workers conduct weekly visits to all households in their catchment areas during high transmission season for malaria. They interview residents to identify anyone with recent fever or symptoms related to malaria. Those reporting such symptoms are tested with an

¹¹⁸ Das, S., et al. (2017). Performance of a High-Sensitivity Rapid Diagnostic Test for Plasmodium falciparum Malaria in Asymptomatic Individuals from Uganda and Myanmar and Naive Human Challenge Infections. *Am J Trop Med Hyg*

RDT. Treatment is provided to those who test positive. In villages where PECADOM Plus has been implemented, there have been significant reductions in weekly prevalence of symptomatic, parasitologically confirmed malaria infection over the course of the transmission season, even while total numbers of cases identified and treated at the community level increased.¹¹⁹ The approach, started in the highest transmission districts, was scaled to 40 of Senegal's 76 health districts in 2016, including some zones of low transmission.

To date, studies of ProACT have been limited, though the approach has been seen to have positive results in Senegal. The ProACT approach may be most appropriately deployed in areas with low to moderate transmission where core vector control and passive case management interventions have been fully scaled up and where an existing iCCM program is in place.

Evidence as to feasibility/effectiveness in other settings is currently unavailable and thus PMI does not recommend ProACT to be deployed outside of OR at this time.

PMI is exploring whether the ProACT approach might be feasible and effective, both as a means of reducing severe disease and death and as a transmission reduction strategy, in other settings. A number of studies in different contexts are underway or planned, funded both by PMI and by other partners, and more evidence is likely to become available in the next few years. Any country considering deploying ProACT should consult with the PMI Headquarters Case Management Team. Such pilots should be considered OR and have clear study questions related to effectiveness and/or feasibility.

¹¹⁹ Linn A, et al. Reduction in symptomatic malaria prevalence through proactive community treatment in rural Senegal. *Trop Med International Health* 2015.

Case Management

New/Key Messages

- Infections with parasites containing deletions in the *hrp2* gene, which produces the main antigen detected by *P. falciparum* RDTs, have been identified in a few sites in Africa. In accordance with WHO, PMI does not support surveillance for *hrp2* deletions unless strong suspicion of false-negative RDTs has been identified and the presence of deletions validated by *hrp2* testing. Further guidance from WHO and PMI will be shared over the next few months. Please contact the PMI Headquarters Case Management (CM) Team with any questions or concerns.
- Multi-species RDTs will only be procured in countries with co-endemic *P. vivax* (Ethiopia, Madagascar, and Greater Mekong Subregion). PMI does not procure two line multi-antigen RDTs for *P. falciparum* or highly sensitive RDTs for case management.
- A new checklist is available that will assist PMI country teams in reviewing new or updated case management guidelines created by NMCPs. Reach out to the HQ CM team for more information.
- Many African countries are receiving donations of Artequick, an ACT not approved by WHO. Please notify the HQ CM team if this issue arises in your country.
- Many national policies on the use of pre-referral rectal artesunate deviate from the most recent WHO Malaria Treatment Guidelines, which recommend use only for those less than six years of age. Before PMI will procure rectal artesunate, a country must update their training materials and/or case management guidelines to be consistent with WHO guidelines.

Introduction

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

- 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
- Practices for accurately recording and reporting malaria test and treatment results
- 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 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 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 for severe malaria. 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 the 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 are the best option in settings where a laboratory is not available (e.g., at lower level health facilities and the community level).

Case Management

Treatment of uncomplicated malaria

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

For uncomplicated malaria, WHO recommends ACTs as the first-line treatment.¹²⁰ 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 widely used 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 most countries.

¹²⁰ WHO Guidelines for the treatment of malaria, 3rd edition, 2015

Treatment of severe malaria

Severe malaria is characterized by any 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, or *P. falciparum* parasitemia greater than 10%. The definition of severe vivax malaria is the same as for falciparum, but without a parasite density threshold.

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.**¹²¹ 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. PMI supports country-level policy changes and planned transitions to parenteral artesunate or artemether, which includes a strategy for training health care workers in administration of the drugs and monitoring and management of patients with severe malaria. PMI recommends that countries try to match the distribution of severe malaria commodities to the rollout of updated case management training closely in time, so that health care workers are equipped and ready to use them upon receipt. In addition to in-service training and supervision, course materials and instructors at pre-service institutions should be updated as well. Toolkits and other helpful information about severe malaria are available at <https://www.severemalaria.org/>.

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.

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 administration of pre-referral

¹²¹ 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.sciedirect.7.

treatment (to reduce disease severity until the patient can receive parenteral therapy at a higher-level facility) and rapid referral to an appropriate health facility. NMCPs from nearly all PMI countries have incorporated rectal artesunate into their case management guidelines, although the vast majority deviate from the most recent WHO Malaria Treatment Guidelines, which recommend use only for those less than six years of age. A WHO information note was recently published reiterating these guidelines.¹²² Before PMI will procure rectal artesunate, a country must update their case management guidelines to be consistent with WHO guidelines (e.g., indicated only for those younger than six years), update their training material to reflect WHO guidelines, or (preferably) both. The WHO information note also recommends the newly available 100-mg formulation (available from two manufacturers) over the 50- and 200-mg formulations, and indicates that ‘as severe malaria is a life-threatening medical emergency, children should rather be over- than under-dosed, so that children weighing up to 10 kg should receive one suppository of 100 mg artesunate, and children weighing up to 20 kg should receive two 100 mg suppositories.’³ Although none of the formulations are currently approved through WHO pre-qualification, both 100-mg formulations have received Expert Review Panel approval by the Global Fund and are expected to receive WHO pre-qualification status.

Obstacles to widespread roll-out include inadequate pre-referral training (not only for rectal artesunate but IM treatments also) and underdeveloped or non-existent community-based platforms for delivery and referral systems. Lack of follow up to the referred level of care can result in not obtaining a definitive diagnosis, 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 workers and SBCC materials. Groups such as Medicines for Malaria Venture and the Clinton Health Access Initiative have started to identify countries where “landscaping” evaluations will be performed to better characterize these obstacles and identify potential solutions.

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 could 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.

¹²² [Rectal artesunate for pre-referral treatment of severe malaria](#). WHO October 2017.

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 women 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 all trimesters.

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.

In women who are pregnant or breastfeeding and diagnosed with and treated for *P. vivax*, WHO recommends countries to consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed following the initial schizonticidal treatment, then, on the basis of G6PD status, treating with primaquine to prevent future relapse.¹

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, processing, and reporting 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. UNICEF and USAID MCH do support procurement of these commodities in some countries; however, at present, no other donor has committed to consistently buying these medicines. Thus NMCPs should discuss and collaborate with their Ministry of Health MCH and/or Community Health counterparts to encourage prioritizing domestic resources. PMI recognizes that this can unfortunately result in malaria CCM, and not an iCCM program, when these gaps in non-malaria commodities exist. 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 '***Incentives and Retention Strategies for CHWs***' section below.

PMI generally supports iCCM for children younger than five years of age as recommended by WHO and UNICEF.¹²³ In countries that are moving towards elimination or are implementing activities such as proactive case detection on top of a strong iCCM platform, PMI support for the expansion of malaria testing and treatment of older age groups by CHWs may be considered.

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

¹²³ WHO/UNICEF Joint Statement: Integrated Community Case Management (iCCM) 2012

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-procured commodities must be provided free of charge to patients/beneficiaries.** Where approved, when working with the private for-profit sector, PMI teams should engage the PMI Headquarters Case Management Team to ensure that PMI-supported private sector activities (using commodities procured by other sources) are in line with PMI Technical Guidance. Finally, 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 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. An analysis of 12 studies on the introduction of RDTs in the private sector is available for more information, and includes lessons learned and recommendations for consideration.¹²⁴

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

¹²⁴ Visser T et al. [Introducing malaria rapid diagnostic tests in private medicine retail outlets: A systematic literature review](#). PLoS One. 2017 12(3).

Conducting therapeutic efficacy studies (TES)

In Southeast Asia, artemisinin resistance—which manifests as delayed clearance of parasitemia and is associated with mutations to the *k13* gene – has now been reported from multiple areas throughout the Greater Mekong Subregion.^{125,126} 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.

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.¹²⁷ WHO recommends that the efficacy monitoring be conducted once every 24 months at four to eight sites per country, with at least 88 patients enrolled per arm per site. 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 in-country 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 has piloted a (QA)/quality control (QC) checklist and protocol for assuring high quality data collection and is currently working with country teams with planned TES to implement the checklist. 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, Worldwide Antimalarial Resistance Monitoring Network, and international consortia focusing on antimalarial drug resistance.

¹²⁵ Ashley EA et al. [Spread of artemisinin resistance in Plasmodium falciparum malaria](#). *N Engl J Med*. 2014 Jul 31;371(5):411-23

¹²⁶ WHO status report April 2017: [Artemisinin and artemisinin-based combination therapy resistance](#)

¹²⁷ http://whqlibdoc.who.int/publications/2009/9789241597531_eng.pdf

Using TES results for selection of treatments

According to WHO guidelines, the first-line antimalarial treatment should be switched to another more effective alternative if therapeutic efficacy falls below 90%. Although ACT efficacy is generally high (>95%) in sub-Saharan Africa, there have been reports of some combinations reaching or exceeding 10% treatment failures in certain sites, likely due to resistance or tolerance to the partner drug. Please contact the TES/PARMA team with any concerns about TES results, their interpretation, and any follow up actions.

Monitoring Molecular Markers of ACT Resistance

Introduction

Studies have identified¹²⁸ and validated¹² 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. PMI support for K13 monitoring allows PMI to pick up any early signs that resistance is emerging or spreading before in vivo resistance becomes apparent. Molecular markers of resistance to piperaquine^{129,130} have also been detected in Southeast Asia, and markers linked to tolerance of other partner drugs have also been identified.¹³¹

The PARMA Network has been established to determine when artemisinin resistance-conferring mutations in the *k13* gene arise or appear in Africa. PMI also monitors molecular markers for resistance to ACT partner drugs, as appropriate. Activities of the network will supplement countries' routine drug efficacy monitoring efforts by characterizing molecular markers that may help to improve surveillance. In addition to the expedient testing of TES samples for the presence of molecular markers of antimalarial resistance, PMI also prioritizes training appropriate country laboratory staff in these techniques. Sample collection for molecular testing is now being carried out in fourteen countries, and many more are anticipated to join the network in the upcoming year. Beginning with FY 2018 funds, expenses related to capacity-building visits to CDC/Atlanta (i.e., a laboratory worker from the TES country learning the techniques and testing samples during a 6-week visit to the CDC) should be included in MOPs at an estimated \$12,000 per TES, if the country prioritizes this for funding. The PMI Headquarters PARMA Team is working closely with individual RAs to assess the current status of in-country

¹²⁸ Ariey F et al. A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria. 2014. *Nature*. 505(7481):50-5.

¹²⁹ <http://www.thelancet.com/journals/laninf/article/PIIS1473-3099%2816%2930409-1/fulltext>

¹³⁰ <http://www.thelancet.com/journals/laninf/article/PIIS1473-3099%2816%2930415-7/fulltext>

¹³¹ <http://www.ajtmh.org/content/91/4/833.long>

efficacy testing and how best to plan and budget for activities. Standard operating procedures covering sample collection, storage, and shipment are available upon request. Questions can be directed to the TES/PARMA team at PMI Headquarters.

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 upon request.

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 the in-country study investigators will share results within the country (with NMCP and others as appropriate), as well as with WHO. Broader sharing with groups such as the Worldwide Antimalarial Resistance Network is encouraged. The PMI Headquarters PARMA Team will work with 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.^{132, 133} 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 seven rounds of standardized product testing and prepared an information note on criteria for selecting appropriate tests.¹³⁴ 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 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 information is provided to health workers about how the tests differ. Where relevant, PMI RAs and country teams should work closely with NMCPs and other donors to harmonize procurements and trainings to ensure that health care workers have been trained on the key steps for the RDTs that are being purchased.

¹³² [Good practices for selecting and procuring rapid diagnostic tests for malaria](#):

¹³³ [Manual for quantification of malaria commodities: Rapid diagnostic tests and Artemisinin-based combination therapy for first-line treatment of *Plasmodium falciparum* malaria](#)

¹³⁴ [Information note on recommended selection criteria for procurement of malaria rapid diagnostic tests \(RDTs\)](#)

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 extremes 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”). In recent years, reports were received regarding the failure of nine different single use test kits, sourced from three manufacturers. Specifically, reports indicated buffer evaporation from the individual ampules, rendering the RDT unusable. Through collaboration with the WHO GMP, a root cause was identified and resolved.

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 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 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. Moreover, most *P. malariae* infections are detected in patients with concurrent *P. falciparum* infections, and mixed Pf/Pm infections are treated with ACTs, exactly as one would treat Pf-only 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.

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).

hrp2 deletions and multi-antigen tests

As reported in an information note published by WHO¹³⁵, malaria parasites lacking the HRP2 and/or HRP3 antigens (the antigens detected by current *P. falciparum* RDTs) have recently been identified in Sub-Saharan Africa. Parasites with *hrp2/hrp3* gene deletions were first detected in the Peruvian Amazon and have since been identified in various locations in South America as well as in India. There have been occasional reports of *hrp2/hrp3*-deleted parasites in isolated locations in Africa in the past few years.

In 2016, such deletions were documented at high prevalence in areas of Eritrea, near the border with Sudan. Different research groups have reported detection of deletions in DRC, Mali, Uganda, Rwanda, and Ghana, but the methods used and reliability of these reports are variable. As per the information note, WHO and PMI do not support surveillance for *hrp2* deletions unless strong suspicion of false negative RDT results due to *hrp2* deletions is followed by confirmation that deletions are indeed present. Rather, in countries without suspicion of false negative RDT results, reporting should be strengthened to ensure that any signals of missed infections by RDTs are identified and followed up. It should be noted that RDT failure can have multiple causes, including user error and poor efficacy due to inappropriate storage conditions. For countries where further investigation is warranted, WHO is currently developing guidance for surveillance for *hrp2* deletions. In addition to guidance, WHO is working to identify reference laboratories and to provide standard operating procedures and protocols for sampling and genotyping.

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. **Given the challenges in interpretation and the limited settings experiencing prevalent *hrp2* deletions, PMI will not procure two line multi-antigen RDTs for *P. falciparum*.** Some manufacturers also produce a single test line RDT that contains antibodies to both HRP-2 and pLDH. It is hoped that this type of test might be a programmatic solution in countries with *hrp2*-deleted parasites in limited areas. These tests,

¹³⁵ [False-negative RDT results and implications of new reports of *P. falciparum* histidine-rich protein 2/3 gene deletions](#)

though, have not yet been validated against *hrp2* deleted parasites and, therefore, cannot at this time be recommended for use in areas where *hrp2* deletions have been identified. Results of Round 8 WHO product testing will include evaluation of multi-antigen tests against parasites with *hrp2* gene deletions and will be available in March 2018.

PMI will work with countries with suspected/reported *hrp2* deletions and their neighbors to implement surveillance and will continue to share guidance from WHO as it is developed. Countries that either have evidence of *hrp2*-deleted parasites or that suspect that such deleted parasites exist in their countries should contact the PMI Headquarters Case Management Team for guidance on methods to document the presence of these parasites and for recommendations on alternative RDTs if such deletions are detected.

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 United States Food and Drug Administration (US FDA) to help evaluate handheld 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 are 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.

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.^{136, 137, 138} 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 recommendations¹ 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 TESs and other relevant investigations (e.g., acceptability studies). In particular, policies regarding treatment of severe malaria should be aligned with the

¹³⁶ WHO Malaria Diagnosis website: <http://www.who.int/malaria/areas/diagnosis/en/>

¹³⁷ Universal Access To Malaria Diagnostic Testing: An operational manual 2011: <http://www.who.int/malaria/publications/atoz/9789241502092/en/index.html>

¹³⁸ [Malaria rapid diagnostic test performance. Results of WHO product testing of malaria RDTs: round 7 \(2015-2016\)](#)

updated recommendations issued by WHO in 2015.¹ 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 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. Teams are encouraged to work with NMCPs as they develop or update national case management guidelines. PMI Headquarters has developed a checklist that can guide this process.

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, SOPs, and bench aids developed by PMI through the MalariaCare Project¹³⁹ can be adapted and tailored to country context. 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

¹³⁹ [Malariacare Toolkit](#)

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 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,¹⁴⁰ 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 (<https://www.finddx.org/malaria-rdt-qa/>).

¹⁴⁰ [Malaria microscopy quality assurance manual - version 2](#)

At this time, methods for quality control of RDTs at the point-of-service are somewhat limited, but must be considered. 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. Although PMI is not currently supporting the use of PCWs, further guidance on the appropriate piloting/use of PCWs will be issued once they are available for procurement. The following activities for QA of RDTs are **not recommended**: cross-checking RDTs with blood slide microscopy, saving RDTs for re-reading, or conducting PCR as part of clinical case management.

Rapid diagnostic tests require proper transport and storage to avoid damage that may be caused by extreme heat and humidity. Post-deployment monitoring of RDT kit performance can be conducted in cases where 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 parasite 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 updated its guidelines for QA of malaria microscopy, in January 2016 and it can be accessed at this link:
<http://www.who.int/malaria/publications/atoz/9789241549394/en/>.

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 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 is provided to partners for improving the capacities of the NMCPs and other key stakeholders in the quantification of requirements for these commodities. 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 on-site 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. Should PMI countries invest in post-deployment lot testing of RDTs?

A. Post-deployment monitoring of RDT kit performance can be conducted in cases where storage conditions are known or suspected to be poor, or if there is evidence of RDTs failure in a clinical setting. 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.

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 for vivax radical cure, which is currently the only drug available for radical cure of *P. vivax* hypnozoites, patients need to undergo G6PD testing. No G6PD testing is required for single, low-dose (0.25mg/kg) primaquine use.

In most clinical settings, 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 US FDA approved, but has not been used widely due to its requirement for venous blood collection, strict temperature range of 18°C to 25°C, and high cost of around \$25 per test. The CareStart G6PD deficiency screening test is a qualitative enzyme chromatographic test that uses blood from a finger prick and has shown test performance comparable to the fluorescent spot test in study settings. However, wide scale uptake has been limited by difficulties in interpreting a faint color change without a control line. It should also be noted that this test could not be used to guide tafenoquine therapy as a quantitative G6PD test is needed.

Several new, point-of-care G6PD tests, both quantitative and qualitative are currently under development. It is anticipated that new products may be available in the next 1-2 years and PMI plans to evaluate the test performance of these new point-of-care tests in Cambodia.

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 granulated 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).

Pyramax® has shown an acceptable safety profile but acute, reversible increases in liver enzymes were detected in some patients in early studies. A Phase IIIb/IV study is planned in five African countries to evaluate safety in patients with underlying hepatic conditions in the context of widespread use and is expected to be completed in 2019.

Pyramax® is registered in several countries already and many more are currently reviewing the dossier. Although clinical trial of AS-PYR in Cambodia did not show high (<90%) efficacy¹⁴¹, unpublished, preliminary data from Viet Nam showed very high efficacy.

At least four other drugs, as well as triple ACT therapy, are in the testing phase and not yet ready for consideration for FY 2018 MOP planning:

- **Tafenoquine (Phase 3):** Tafenoquine has been developed by Medicines for Malaria Venture (MMV) in partnership with GSK for the treatment and radical cure of *P. vivax* (relapsing) malaria. In November 2017, MMV and GSK announced the submission of a new drug application (NDA) to the US FDA, seeking approval of single-dose tafenoquine for the radical cure (prevention of relapse) of *P. vivax* malaria in patients 16 years of age and older. Shortly thereafter, they submitted a regulatory application to the Australian Therapeutics Good Administration (TGA) for the same indication as approval of tafenoquine by the TGA will help facilitate registration in countries where malaria is endemic as they will act as the reference regulatory authority. Although two Phase III (DETECTIVE and GATHER) trials have been completed, additional studies including in pediatric populations are still underway. In addition to the radical cure indication, 60 Degrees Pharmaceuticals, US Army's co-development partner, also filed their NDA for tafenoquine to the FDA with a prophylaxis indication. Once the 60 Degrees and GSK NDA's are approved, tafenoquine will have a dual role in the prevention and treatment of malaria. Medicines from the 8-aminoquinoline class, including tafenoquine and primaquine, are associated with hemolytic anemia in individuals with G6PD deficiency. Unlike with the use of primaquine for radical cure of *P. vivax*, where individual countries have set their own policy on the need for G6PD

¹⁴¹ Leang, R. et. al., *Antimicrob Agents Chemother*. 2016 Jul; 60(7): 3884–3890.

testing, tafenoquine will require testing for G6PD deficiency using a quantitative test prior to administration. 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*.

- **Artefenomel (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 ferroquine are underway in seven countries.
- **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. Because it appears that resistance develops easily to this medication, it will most likely require dosing with another antimalarial.
- **KAF156 (Phase 2):** KAF156 is the first compound from a novel class of drugs called imidazolopiperazines whose mechanism of action is still being characterized. A Phase IIa study conducted in Thailand and Vietnam showed high efficacy against *P. falciparum* and *P. vivax* infections, including artemisinin-resistant *P. falciparum* strains. Phase IIb trials are planned in combination with a new once-per-day formulation of lumefantrine in various doses, regimens, and age groups.

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

A. Please see the **Elimination** chapter ('**Case Management**' section) for guidance on single, low-dose primaquine and updates on HS RDTs

Q3. If my country is experiencing an increase in reported malaria cases, what is the best way to communicate that this is unlikely due to artemisinin resistance?

A. The NMCP has been conducting ongoing monitoring of the country's first-line antimalarials for several years, and to date no evidence of artemisinin resistance has been detected. In addition, over 20 other countries in Africa are monitoring for artemisinin resistance, and no evidence suggests this problem has emerged in Africa.

Q4: What is Artequick?

A: Artequick is an ACT (artemisinin 62.5mg + piperaquine 375mg) produced by a Chinese pharmaceutical company that is not approved by WHO. Many PMI countries in Africa (e.g.,

Uganda, Malawi, Zambia) have reported Artequick donation offers made by a Chinese university. Comoros applied a large donation of Artequick to a comprehensive, nearly island-wide MDA campaign. Countries are often encouraged to use the donated Artequick as part of MDA, even when the transmission setting is not appropriate for MDA. In addition to the MDA-related issue, WHO (along with PMI) are concerned because of the unproven efficacy, possible side effects, and lack of quality assurance of this medication. If teams become aware of Artequick donation offers in their country, they are encouraged to contact the PMI Case Management Headquarters team that have been in contact with WHO about this issue.

Health Systems Strengthening

New/Key Messages

- Health systems strengthening is one of five strategic focus areas outlined in the *PMI Strategy 2015-2010* and thus remains a priority for PMI.
- PMI continues to contribute to strengthened health systems through PMI's support for bringing and keeping at scale proven interventions. Capacitated health care workers and systems that deliver health services at facility and community level are necessary for continued progress in malaria control. Thus, PMI's investments across MOP technical intervention areas, not just as described in this section, contribute to health systems strengthening.
- USAID Administrator Mark Green has called “working ourselves out of a job” one of his highest strategic priorities, which underscores the importance of continuing to work with our implementing partners to ensure that capacity building is part and parcel to all of our activities.
- Peace Corps and Field Epidemiology Training Program (FETP) investment information are included under this section.
- Inclusion of a table cross referencing HSS activities with technical areas is no longer required in the MOP.
- PMI teams are strongly encouraged to more comprehensively and/or quantifiably describe HSS efforts throughout the MOP.

Introduction

Building capacity and strengthening 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. In addition, “working ourselves out of jobs” is one of USAID Administrator Mark Green’s highest strategic priorities. 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.

Most, if not all, PMI-supported activities – whether intervention-specific or cross-cutting – contribute to strengthening one or more of the six internationally recognized core HSS functions of human resources for health; health finance; health governance; health information; medical

products, vaccines, and technologies; and service delivery. Examples include, but are not limited to, the following:

- Strengthening quantification methods and supply chains for 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

PMI's support for HSS is aligned with USAID's *Vision for Health Systems Strengthening 2015-2019*,¹⁴² which defines four strategic outcomes to achieving **universal health coverage** (defined as a condition where all the people who need health services receive them without financial hardship):

1. **Financial protection:** reducing financial barriers to access life-saving services for the poor
2. **Essential services:** ensuring that priority maternal, newborn, infectious disease services, etc., are included in the national essential benefits packages
3. **Population coverage:** attaining coverage for people in the bottom wealth quintile and for other marginalized people
4. **Responsiveness:** improving the satisfaction of poor and marginalized people with provision of essential services.

PMI funding can be utilized to support activities that result in universal health coverage, but such activities must *directly* address key barriers to achieving PMI's goal 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

¹⁴² <https://www.usaid.gov/what-we-do/global-health/health-systems/usaids-vision-health-systems-strengthening>

supported with PMI funding related to the leadership and governance health system investment area must be directly related to an improvement in the countries' malaria program. 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). However, although PMI does not support hiring of public sector staff as mentioned above, PMI does support technical and management capacity building approaches at national level and/or regional/provincial/zonal levels in the form of technical experts seconded to the NMCP or Ministry of Health Management Teams to work as integral members of these teams transferring knowledge, and skills and building capacity. When malaria technical/management secondments are supported with PMI funds, these secondments should have communication and reporting linkages directly with the PMI team, in addition to the NMCP.

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 (e.g., within IRS, case management, etc.). Recent years' MOPs included a HSS table that cross-referenced HSS-based activities found throughout the MOP. This table is no longer required. However, PMI teams are strongly encouraged to quantify (when possible) or more comprehensively address HSS efforts throughout the MOP. For example, if supporting strengthening malaria service delivery, the MOP should contain details such as what level(s) of the service delivery system (e.g., health facility, community, national laboratory, etc.) will be strengthened, the approximate target number of health workers that will be trained or supervised, etc.

Non-intervention-specific or cross-cutting HSS activities should be described exclusively in the HSS section. Examples include:

- Training and capacity strengthening activities with NMCPs and other local government entities, including, but not limited to, Field Epidemiology Training Program (FETP) activities
- Activities to promote partnership, such as or support for coordination of malaria partners or support for U.S. Peace Corps malaria volunteers
- 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 such as policy or strategy development, quality improvement efforts focused on management systems, and interventions to improve transparency and accountability that directly contribute to improvements in malaria outcomes.

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 (GHS) activities”. These efforts can include maximizing integration with USAID programming in health or other sectors, as well as with other USG Agency health program activities including but not limited to PEPFAR and Global Health Security activities implemented by USG Agencies other than USAID.

The GHS agenda aims to develop the capacity to conduct surveillance and adequately respond to public health threats through enhancing infectious disease surveillance, laboratory, information systems and public health workforce. These activities can be leveraged with and can contribute to malaria prevention, control and elimination efforts by expanding their reach, efficiency and effectiveness. For example, GHS activities may contribute to PMI objectives by working to address artemisinin-resistance and multi-drug resistance in falciparum malaria parasites or identify the distribution of vector mosquitoes with resistance to synthetic pyrethroids and other classes of insecticide used for vector control. Where PMI aims to integrate PMI and GHS activities, the PMI team should designate an activity manager to engage regularly with the non-PMI funded aspects of the integrated efforts.

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 describing both the PMI and non-PMI (MCH) investments of the integrated effort, 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. The PMI and non-PMI investments for these systems strengthening efforts should be described in the HSS section of the MOP. 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 and describe these sources within the MOP
- For activities carried out by implementing partners with a mandate that extends beyond malaria:
 - That the 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
- For activities carried out by staff or implementing partners of USG Agency other than USAID, PMI must identify an activity manager to provide oversight to the PMI funded and non-PMI funded aspects of the integrated activity to ensure maximum benefit to malaria and to ensure coordination across PMI's overall investment.

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 and 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 are 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 PCV 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. PMI teams should assess whether it is to PMI's advantage to provide support for PCV malaria projects through a PMI implementing partner rather than through the Peace Corps SPA agreement. There may be situations where it makes greater programmatic sense to work with PCVs on a community project with the funding flowing through a PMI implementing partner to ensure the right technical expertise is available and the work is coordinated closely with PMI's overall program in country.

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 ITN 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 alone**, but any PMI-supported malaria training should be part of PMI's ongoing malaria control and elimination training efforts in country aimed at building partner country capacity. PCVs taking part in PMI supported malaria training activities should be oriented to obtaining new knowledge and skills in order to work in their communities with local counterparts to carry out malaria control work.

Training/country orientation

Peace Corps historically conducted 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 was organized and funded by PC, not by PMI funding, and PMI staff were 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). As of January 2018, Peace Corps transitioned to a new model, which prioritizes in country trainings as well as virtual, online trainings. This country-focused model will facilitate capacity building of PCVs together with host country counterparts, while also allowing for more participation by in country malaria experts. The PMI in-country team is encouraged to collaborate with the NMCP and partners to coordinate and participate in these country-specific training for new PC MVs and their counterparts, as well as to assist with more in-depth orientation of PC MVs (i.e., sharing 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 country-based 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 relevant intervention sections of the MOP (i.e., training, on site supervision to strengthen diagnosis and treatment should be described in the case management section). Training activities for NMCP staff that do not appear within the technical intervention sections of the MOP, including FETP, should be described in the HSS section.

As a part of efforts to strengthen national capacity in malaria control, PMI supports short-term training of NMCP permanent staff in areas that directly benefit the country's malaria program. 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. As mentioned earlier, PMI also supports technical and management capacity building approaches at national level and/or regional/provincial/zonal levels in the form of technical experts seconded to the NMCP or Ministry of Health Management Teams to work as integral members of these teams transferring knowledge, and skills and building capacity. When malaria technical/management secondments are supported with PMI funds, these secondments should have communication and reporting linkages directly with the PMI team in addition to the NMCP.

Direct government-to-government 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, and should be described in the MOP HSS section.

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 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.

Field Epidemiology 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 FETP national level training efforts. In 2016, CDC reconfigured their FETP program to a three-tiered pyramid model consisting of frontline (short-term 3 month training), intermediate (9-12 months of training), and advanced two-year training. PMI support can be directed to the advanced program, which consists of 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. The aim is that over time, PMI investments in FETP will 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 and that this cadre will have positive impacts of malaria program efforts following completion of training.

PMI supports trainees in the advanced level 2 year program however, in PMI-supported countries where CDC is implementing frontline programs (whether via GHSA or other funds), PMI staff and partners should look to benefit from the new capacity of the district (or district-equivalent) managers benefitting from the frontline program. Frontline FETPs are basic level field epidemiology trainings typically 3 months long with 12 days of didactic

trainings/workshops. Frontline FETPs are currently operational in the following PMI focus countries: Benin, Burkina Faso, Cameroon, Cote D'Ivoire, DRC, Ethiopia, Ghana, Guinea, Kenya, Liberia, Malawi, Mali, Nigeria, Senegal, Sierra Leone, Tanzania, and Uganda.

Approximately 20-25% of the FELTP advanced 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 advanced programs, a Master of Public Health degree.

FETPs are helping to realize the long-term health systems capacity development component of the USG's Global Health Security Agenda to which PMI aims to contribute. As of FY 2018 planning, PMI is supporting FETP advanced program trainees in twelve countries: Angola, DRC, Ethiopia, Ghana, Kenya, Burma, Mozambique, Nigeria, Rwanda, Tanzania, Uganda, and Zambia.

Field Epidemiology 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. FETP residents/participants receive financial support from a variety of funding sources with new funding now provided through the Global Health Security Agenda. PMI country MOP funding can be prioritized for support for FETP. If support for FETP is prioritized, PMI country teams should work with FETP leaders to determine the appropriate PMI financial investment for FETPs within their respective countries within the financial parameters that define maximum funding for PMI support (see further below). In addition, PMI country teams must coordinate closely with FETP leaders to ensure support for PMI malaria-specific activities and training for FETP participants. For example, the PMI RAs may provide malaria focused lectures to FETP participants, and mentorship on malaria-related projects. They also help to coordinate and promote the placement of FETP residents within the NMCP for training and field work and should take the lead in facilitating FETP resident collaboration with implementing partners on PMI-funded activities.

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

Although levels of financial support for malaria-focused FETP residents and the costs of training will vary by country, PMI has established budget guidance parameters for PMI support for FETP. PMI support for FETP trainees is external to salary provided by the Ministry of Health. PMI support contributes to the CDC program that includes 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 funding for FETP cannot be used to support salaries of FETP RAs or salaries of any FETP residents or any other staff associated with the FETP program. PMI country teams proposing support for FETP 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 FETP program in their FY 2019 MOP budgets (please use country specific cost estimates when available without exceeding the maximum threshold allowed). No more than \$300,000 per year and four trainees at a time can be supported (two trainees in the new/startling cohort and two trainees in their second and final year of the advanced FETP training program). PMI country teams need to ensure that PMI funding is not displacing CDC appropriated, Global Health Security, or other USG funding supporting FETP program activities in country. PMI country teams can explore requesting a PMI implementing partner with district level implementation focus to include support for training district level health officers through the CDC FETP frontline program in their annual workplan where CDC FETP frontline programs exist. Country teams should be careful to ensure that the training does not duplicate ongoing PMI supported training and capacity building efforts. If country teams choose to prioritize support for this training within a PMI partner's workplan, the PMI team should consult the in country FETP program for exact costs but it is expected that the implementing partner will need to budget no more than \$10,000 per student. Where PMI country team's prioritize support of trainees participating in a frontline/short-course FETP program will not be through AFENET, but through a PMI implementing partner. The majority of PMI implementing partners work at subnational levels and would be able to provide the necessary support needed for a successful partnership with the FETP Frontline programs.

PMI country teams should ensure appropriate indicators are in place to document the impact of PMI support for the FETP. PMI's decision to support FETP in the early days of PMI was taken with the expectation that graduates employment following graduation would be tracked in order for PMI to evaluate the extent to which FETP is building cadres of staff that remain within the MOH, to document how PMI investments in this program continuing to have lasting impact. Countries are expected to annually update a PMI-FETP progress tracking spreadsheet which is sent to the countries for completion and then to USAID Washington per CDC IAA reporting requirements. The following indicators will be tracked:

- total number of FETP trainees enrolled and specifically, number of malaria FETP trainees enrolled

- total number of FETP trainees graduated
- total number of FETP trainees who are employed by the NMCP or other malaria programs after graduation (title and position) (PMI in country teams are to maintain a list of graduates and track annually their continued employment with the MOH)
- list of malaria projects completed with some details about the activity or response effort if a malaria outbreak investigation
- list of products (reports, publications and presentations) from malaria-related projects that were disseminated beyond the FETP program
- list of any malaria training conducted for FETP trainees
- success stories

Social and Behavior Change Communication

New/Key Messages

Evidence: In 2017, PMI supported a multiphase review of over 4,000 peer reviewed articles and grey literature to assess the evidence for malaria SBCC. Results from this review resulted in multiple resources that can be used to help inform SBCC activities across each intervention area, including a searchable evidence database, factsheets, and infographics.

Best Practices: The evidence review also resulted in the identification of best and promising practices for malaria SBCC including (1) emphasis and reinforcement of specific health behaviors (2) use of innovative approaches; (3) use of mass media; (4) use of multi-channel approaches; (5) use of integrated multi-media SBCC; (6) use of formative research to improve program design; and (7) use of community change agents, leaders, and community engagement and mobilization efforts.

M&E: PMI should adequately plan and budget for M&E of SBCC activities including formative research, monitoring, and outcome evaluation. Where possible, existing data should be used for formative research, but additional data may be needed to address information gaps about barriers to uptake of key behaviors by the target audience. Monitoring of the target audience during implementation determines whether activities are effectively reaching the audience and having measurable effects on intermediate outcomes such as knowledge, risk perception, perceived efficacy, or attitudes. These data can inform mid-stream program adjustments and PMI encourages audience monitoring to inform effective SBCC activities. Outcome evaluation should be conducted to assess and document changes in behavior and intermediate outcomes from SBCC activities.

New tool: The Malaria Behavior Survey (MBS)¹⁴³ was designed by the Health Communication Capacity Collaborative (HC3) and Breakthrough ACTION in collaboration with the PMI SBCC team as a formative research tool to inform the design of PMI-supported SBCC activities and evaluation research tool to help determine the behavioral and intermediate outcomes of PMI-supported SBCC activities. For more information about the MBS, contact the PMI SBCC team.

¹⁴³ For more information about the MBS, please contact the PMI SBCC team.

Introduction

PMI supports a range of social and behavior change communication (SBCC) activities to increase the uptake and correct and consistent use of malaria interventions, thereby improving the overall quality of malaria control efforts that will 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 strengthening, (3) designing and implementing activities, (4) monitoring and evaluation, and (5) operational research.

Achieving and maintaining PMI and National Malaria Control Program (NMCP) goals depends on the acceptance and correct and consistent use of proven interventions (e.g., ITNs, IRS, RDTs, ACTs, IPTp, and SMC). When tailored to the specific country context and needs, SBCC activities play an important role in promoting uptake of these interventions and achieving the desired individual-level and public health impact.

SBCC Defined: SBCC for health is an evidence-based, consultative process that uses communication to promote and facilitate behavior change, optimize use of interventions, and support the requisite social change for the purpose of improving health outcomes. To achieve social and behavior change, SBCC is driven by epidemiological evidence and client perspectives and needs. SBCC is guided by a comprehensive ecological theory that incorporates both individual-level change and change at broader environmental and structural levels. Thus, it works at one or more levels: the behavior or action of an individual, the collective actions taken by groups, social and cultural structures, and the enabling environment.¹⁴⁴ For malaria, the primary behaviors of interest include correct and consistent net use; acceptance of IRS; early and frequent ANC attendance; prompt care-seeking for fever; and adherence to national guidelines for health workers (e.g., IPTp, case management).

While PMI continues to use the term SBCC, many development and public health entities, including USAID, have adopted the term social and behavior change (SBC) to encompass factors beyond communication that can influence behavior change. With SBC, the focus is on gaining a comprehensive understanding of the factors that support or prevent the practice of a behavior and developing activities that promote or address the identified factors. The activities might be communication-based or non-communication-based. SBC takes into account factors like economic barriers (e.g., consultation fees), logistical barriers including accessibility of services, and quality of goods and services. Examples of SBC activities that are not purely communication-based might include providing cups and water for directly observed IPTp, quality improvement collaboratives, and revising health worker training materials. PMI

¹⁴⁴ Adapted from <http://manoffgroup.com/documents/DefiningSBCC.pdf>

encourages country teams to think critically about the factors that support or prevent the practice of key malaria behaviors using data that are already available, but to propose data collection activities where information gaps still exist. Communication-based activities will continue to be an important part of addressing these factors, but only when other factors, such as access to goods and services are also addressed.

Key Areas of PMI Support for SBCC

Developing or revising national malaria SBCC strategies

PMI supports the development or revision of national malaria SBCC strategies within the country's broader National Malaria Control Strategy. These strategies are critically important as they should guide donors' and implementing partners' SBCC activities. PMI should work with the NMCP to ensure the national malaria SBCC strategy is clearly linked to malaria control objectives. Furthermore, the national malaria SBCC strategy should reflect global best practices, including those outlined in the [*Roll Back Malaria Strategic Framework for Malaria Social and Behavior Change Communication*](#)¹⁴⁵.

National malaria SBCC strategies should contain the following components:¹⁴⁶

- Situation analysis
- Behavioral analysis
- Audience analysis
- Communication objectives
- Behavioral objectives
- Strategic approaches
- Positioning and strategy outline
- Implementation plan
- Monitoring and evaluation, including indicators

National malaria SBCC strategies should reflect the most recent and currently available data on human behavior and malaria epidemiology, including information collected from national household surveys, like the Demographic and Health Survey (DHS), Malaria Indicator Survey (MIS), and Multiple Indicator Cluster Survey (MICS), as well as other relevant data sources that

¹⁴⁵ breakthroughactionandresearch.org/RBM-Malaria-SBCC-Strategic-Framework

¹⁴⁶ Adapted from the "Designing a social and behavior change communication theory" implementation kit developed by the Health Communication Capacity Collaborative available at <http://sbccimplementationkits.org/courses/designing-a-social-and-behavior-change-communication-strategy/> and the How to Develop a Communication Strategy how-to guide developed by the Health Communication Capacity Collaborative available at <http://www.thehealthcompass.org/how-to-guides/how-develop-communication-strategy>

may include the Malaria Behavior Survey (MBS)¹⁴⁷; health facility surveys; knowledge, attitude, and practice (KAP) surveys; ethnographic research; routine data (such as from the national HMIS or other surveillance systems); or other types of formative research.

The [How to Develop a Communication Strategy](#)¹⁴⁸ guide on the [Health COMpass](#)¹⁴⁹ has additional information on developing a national malaria SBCC strategy. Examples of national malaria SBCC strategies can be found on the [Malaria SBCC Strategies](#)¹⁵⁰ trending topic on the Health COMpass. Technical assistance is also available from USAID central SBCC mechanisms and should be utilized if capacity does not exist in-country to support development or revision of the national malaria SBCC strategy.

Strengthening SBCC capacity

PMI should support capacity strengthening of individuals and organizations to coordinate design, implementation, monitoring, and evaluation of SBCC. Capacity strengthening activities should target NMCP staff (especially from SBCC¹⁵¹ units) and may include Ministry of Health staff (especially from Health Promotion Departments¹⁵²).

At the national and sub-national level, PMI should support the following SBCC capacity strengthening activities:

- Establishment and secretariat support of a malaria SBCC coordinating committee to strengthen the NMCP's ability to coordinate SBCC design, implementation, and evaluation across and within ministries, donors, implementing partners, and private sector partners.
- Technical assistance (e.g., training, mentoring) to the NMCP for selection or development of appropriate indicators for monitoring and analysis and interpretation of existing data to inform design of SBCC strategies and activities.

¹⁴⁷ A tool developed by the Health Communication Capacity Collaborative (HC3) and Breakthrough-Action and in collaboration with the PMI SBCC team to provide data for formative and evaluation research to improve PMI-supported SBCC activities.

¹⁴⁸ <http://www.thehealthcompass.org/how-to-guides/how-develop-communication-strategy>

¹⁴⁹ <http://www.thehealthcompass.org/>

¹⁵⁰ <http://www.thehealthcompass.org/trending-topics/malaria-sbcc-strategies>

¹⁵¹ In some PMI focus countries, the NMCP SBCC unit is called the Advocacy, Communication, and Social Mobilization (ACSM) unit.

¹⁵² In some PMI focus countries, the Ministry of Health, Health Promotion Department is called the Health Education Department.

- Where appropriate, participation of NMCP and Ministry of Health staff in RBM Social and Behavior Change Communication Working Group¹⁵³ (RBM SBCC working) calls and meetings.
- SBCC trainings, workshops, or courses (local or distance, in-person or virtual) to strengthen SBCC capacity. A number of online SBCC trainings have been developed with support from PMI and USAID, including the [Online Training on Evidence-based Malaria Social and Behavior Change Communication](#)¹⁵⁴ and the [SBCC Online Capacity Building Center](#).¹⁵⁵
- Coordination of malaria SBCC activities with other non-health ministerial partners, such as Ministries of Tourism, Ministries of Agriculture, and Ministries of Education, for example, and with private sector partners.

Individuals involved in the design, implementation, monitoring, and evaluation of SBCC activities, might find the resources available on the [Health COMpass](#) including numerous how-to guides useful, such as [How to Develop a Logic Model](#), [How to Conduct a Situation Analysis](#), [How to Do an Audience Analysis](#), and [How to Conduct Qualitative Formative Research](#). Furthermore, the [Springboard for Health Communication Professionals](#)¹⁵⁶ is a virtual platform for exchanging knowledge, experience, and resources about SBCC and promoting collaboration and networking between SBCC professionals and organizations.

Design and implementation of SBCC activities

PMI-supported SBCC activities should support the national malaria SBCC strategy and align with the national malaria strategic plan. Presumably, these objectives include increasing: ITN use, IRS coverage, IPTp coverage, appropriate case management, and SMC coverage (acknowledging that not all strategies are appropriate or applicable in all settings). **Table 1** summarizes the behavior and target population for each of these PMI-supported interventions.

¹⁵³ The RBM SBCC working group was formerly known as the RBM Communication Community of Practice. Additional information about the RBM SBCC working group is available at <http://www.rollbackmalaria.org/architecture/working-groups/ccop> and <https://healthcomspringboard.org/groups/roll-back-malaria-task-force-knowledge-management/>. Information about participation in the RBM SBCC working group is available from the PMI SBCC team.

¹⁵⁴ <http://www.vector-works.org/resources/online-training-on-evidence-based-malaria-social-and-behavior-change-communication-sbcc/>

¹⁵⁵ <https://learning.healthcommcapacity.org/sbcc/>

¹⁵⁶ <https://healthcomspringboard.org/activity/>

Table 1. Key interventions, behavioral objectives, and target population

Community Members		
Intervention	Behavior	Target Population
ITNs	Use an ITN correctly and consistently	All individuals
IRS	Accept IRS	Head of household or designee
MIP (ITNs)	Use an ITN correctly and consistently	Pregnant women
MIP (IPTp)	Attend ANC early and often Take SP during ANC visits	Pregnant women Pregnant women
MIP (Case Management)	Seek prompt and appropriate care for symptoms of malaria	Pregnant women
Case Management	Seek prompt and appropriate care for symptoms of malaria	All individuals and caregivers or designees
SMC	Adhere to SMC regimen throughout campaign	Caregivers or designees

Providers		
Intervention	Behavior	Target Population
ITNs	Adhere to national ITN distribution guidelines	Providers
IRS	Adhere to spray operations guidelines	Spray operators
MIP	Adhere to national MIP guidelines	Providers
Case Management	Adhere to national case management guidelines	Providers

Human behaviors are complex and dependent on a variety of factors ranging from an individual's motivation to act, social norms, access to goods and services, quality of goods and services, and more. Designing effective SBCC activities requires a comprehensive understanding of these factors and the steps needed to practice the behavior. For example, for a pregnant woman to sleep under an ITN, she (and perhaps the household decision-maker) must: 1) acquire enough ITNs to cover every sleeping space; 2) prioritize the pregnant woman if enough ITNs are not available; 3) hang the ITN appropriately; and 4) sleep under the ITN all night, every night.

While the steps needed to practice the behavior may be more-or-less universal, the factors preventing or supporting the behavior are certainly context-specific. Designing SBCC activities requires a thorough understanding of not only the target behaviors and target audiences, but also the steps needed to practice the behaviors and the factors preventing or supporting the behaviors. This step of formative research is essential to ensure SBCC activities are selected and designed appropriately, and may include a variety of data sources, both quantitative (e.g., household surveys, such as the Malaria Behavior Survey) and qualitative (e.g., key informant interviews).

Through this process, it may become clear that the most important factor influencing the behavior is related to access and a communication-based activity is not the most suitable activity. Using a simple example, an SBCC activity to increase demand for IPTp will have limited success if SP stockouts are widespread. Conversely, a situation where SP is available at ANC clinics, but there is a common belief among ANC providers that IPTp is ineffective, indeed calls for a well-designed SBCC activity targeted to service providers.

SBCC activities should be based on a logical framework that identifies: the target behavior; factors preventing or supporting the behavior in the target population (explain why people do or do not engage in the behavior); behavioral and communication objectives to address these factors; specific SBCC activities to be undertaken; and the expected outcomes. Use of behavioral theories can help to inform the development of this framework. Examples of theories include the Health Belief Model, Stages of Change, and Social Learning Theory (a number of commonly used behavior change theories are described in Appendix 1). There is no “correct” theory to use; they can be adapted, modified, or combined based on formative research and can help rationalize and communicate why certain approaches are used.

The Malaria Behavior Survey (MBS) was designed by the Health Communication Capacity Collaborative (HC3) and Breakthrough ACTION in collaboration with the PMI SBCC team as a formative research tool to inform the design of PMI-supported SBCC activities and an evaluation research tool to help determine the behavioral and intermediate outcomes of PMI-supported SBCC activities. The MBS is intended to help PMI and NMCP teams determine the behavioral factors (intermediate outcomes) that support or prohibit the practice of key malaria-related behaviors so that SBCC activities and strategies can be designed to address the identified behavioral factors. Additionally, as an evaluation research tool, the MBS is intended to provide insight into whether the identified behavioral factors are changing.

To ensure that PMI-supported SBCC activities are systematic, theory-informed, evidence-based, and targeted, the PMI team should require implementing partners to:

- Employ an iterative approach to designing, implementing, monitoring, and evaluating SBCC activities. An example of an iterative approach to SBCC includes the [P-Process](#)¹⁵⁷ developed by the Johns Hopkins Center for Communication Programs.
- Analyze existing data or conduct formative behavioral research to understand the barriers and facilitators of malaria-related behaviors, identify appropriate audiences, and identify potential SBCC activities to address barriers or promote facilitators of targeted behaviors.
- Develop a logical framework for the activity design that is based on behavior change theory (see above).

¹⁵⁷ <http://www.thehealthcompass.org/sbcc-tools/p-process>

- Use evidence-based SBCC approaches. The PMI-supported [Malaria Evidence Database](#)¹⁵⁸ highlights and summarizes the impact of malaria SBCC on malaria-related behavioral outcomes.
- Develop a clear set of indicators for monitoring progress of SBCC implementation and evaluating impact. The [Roll Back Malaria SBCC Indicator Reference Guide](#)¹⁵⁹ describes recommended process and outcome indicators for use throughout the project cycle—from design to implementation to monitoring to evaluation.

Accelerator behaviors

For three key malaria-related human behaviors – ITN use, IPTp use, and care-seeking for symptoms of malaria – PMI has supported the development of behavior profiles based on “accelerator behaviors”. The concept of an accelerator behavior, as defined by USAID and as it relates to the USG’s goal of preventing child and maternal deaths, is a behavior that is practiced by a primary actor, such as a caregiver or mother, that directly or indirectly reduces the risk of maternal and child death due to a preventable cause, and has low uptake in a particular context. For malaria, three accelerator behaviors have been identified based on their ability to contribute to the greatest reduction of maternal and newborn deaths and the most rapid achievement of PMI and global malaria goals and objectives: (1) pregnant women and children sleep under an ITN; (2) pregnant women attending ANC visits early and accepting IPTp during these visits; and (3) caregivers seek prompt and appropriate care for symptoms of malaria.

The identification and selection of three malaria-related accelerator behaviors does not preclude PMI country teams from supporting SBCC activities targeting other behaviors, such as those related to IRS, SMC, ITN misuse, ITN care, and ITN repurposing. Behavior profiles could be developed for other malaria-related human behaviors, and the three accelerator behavior profiles can be used as examples in this process. These profiles are best viewed on the [Accelerator Behaviors Website.](#)¹⁶⁰

Provider behavior change and service communication

Facility- and community-based service providers play a critical role in malaria control and prevention as the primary conduit between service delivery points and patients. From an SBCC perspective, providers are both a *target audience* for SBCC activities (e.g., provider behavior change [PBC]) and a *channel for communication* targeted to patients (e.g., service communication).

¹⁵⁸ <https://healthcommcapacity.org/malaria-evidence-database/>

¹⁵⁹ breakthroughactionandresearch.org/RBM-Malaria-SBCC-Indicator-Reference-Guide

¹⁶⁰ <https://acceleratorbehaviors.org/index>

Provider behaviors (**Table 1**) are influenced by a variety of factors, including external motivational factors and internal motivational factors. Typically, efforts to improve provider behaviors focus on addressing the external motivational factors, such as equipment, job aids, resources, direct incentives, workload management, and skills-based knowledge. Often, internal motivational factors that influence provider behaviors, such as personal attitudes and beliefs, social norms, personal and community values, status within the community and within the health system, and recognition, are neglected. PBC activities seek to positively influence provider behavior by addressing these internal motivational factors. Formative research will likely be needed to design SBCC activities that effectively address these factors. A helpful resource that can be used for designing PBC activities is the [*Provider Behavior Change Implementation Kit*](#)¹⁶¹. PBC activities addressing internal motivational factors should complement activities addressing external motivational factors.

Service communication is the use of SBCC activities by providers to influence service-related behaviors among patients across the continuum of care at both facility- and community-based delivery points—before, during and after services. Effective service communication can help improve provider-patient interactions, increase the adoption and maintenance of malaria-related behaviors, and help to create demand for health services. In the before stage, SBCC can help get patients to services by building individual and community support for health issues and related services, influencing norms, and creating demand for services within the community. During service delivery, providers can use SBCC techniques to enhance the patient experience and ensure new behaviors are adopted by improving provider counseling and patient support. After services, SBCC can support follow-up and behavioral maintenance by building and maintaining linkages between communities and service providers. A helpful resource for developing SBCC activities for health services is the [*Service Communication Implementation Kit*](#)¹⁶².

Recommended communication approaches

There are a variety of approaches that can be used to communicate with the target audience that are appropriate for PMI support. Broadly, these approaches include mass media, interpersonal communication, community mobilization, and information and communication technology (ICT).

PMI recommends a transmedia approach to SBCC that uses a mix of communication approaches. **This mix should be informed by formative research (e.g., situation analysis, behavioral analysis, and audience analysis).** A particular communication approach should be developed based on its potential to impact the target behavior, impact factors preventing or supporting the behavior, reach the target audience, and resonate with the target audience. If formative data do

¹⁶¹ <https://sbccimplementationkits.org/provider-behavior-change/>

¹⁶² <http://sbccimplementationkits.org/service-communication/>

not exist, PMI should support the collection and analysis of relevant data to inform channel selection and SBCC activities.

Table 2. Recommended communication approaches

Approach	Description	Channels
Mass Media	<ul style="list-style-type: none"> • Process by which tailored messages are disseminated through diversified media technologies that are intended to reach large audiences; • Powerful tool in reinforcing interpersonal communication, community-based, and ICT activities; • Allows for broad and wide dissemination of information, including to diverse and hard-to-reach audiences, depending on media access; • Generally one-way communication. 	<ul style="list-style-type: none"> • Broadcast media (e.g., radio, television, video, serial dramas, game shows) • Print media (e.g., magazines, newspapers, pamphlets, posters, and pamphlets) • Outdoor media (e.g., billboards)
Interpersonal Communication (IPC)	<ul style="list-style-type: none"> • Process by which two individuals (or a small group) exchange information and ideas through face-to-face interaction; • Effective at converting knowledge to action and targeting behaviors that are more problematic; • Facilitates and encourages appropriate action, especially among marginalized populations, and helps people to discuss their beliefs and feelings about their ability to take appropriate action; • Powerful tool in reinforcing mass media, community-based, and ICT activities; • Generally two-way communication. 	<ul style="list-style-type: none"> • Home visits • Counseling • School demonstrations • Peer education • Outreach • Hotlines • Providers (service communication)
Community Mobilization	<ul style="list-style-type: none"> • Process through which a community's individuals, groups, or organizations plan, carry out, and evaluate activities on a participatory and sustained basis to improve their health and other needs, either on their own initiative or stimulated by others.¹⁶³ 	<ul style="list-style-type: none"> • Community mobilization • Community dialogue • Community drama

¹⁶³ Adapted from [*How to Mobilize Communities for Health and Social Change*](#).

Information and Communication Technology (ICT)	<ul style="list-style-type: none"> • Use a variety of electronic digital communication and information technology, such as web-based and mobile technologies and software applications, that enable users to engage in dialogue and share information; • Electronic digital communication and information technology that is intended to directly improve the effectiveness and efficiency of project interventions.¹⁶⁴ 	<ul style="list-style-type: none"> • Mobile phone apps • SMS • Online platforms • Social media • Interactive Voice Response (IVR)
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The [Malaria SBCC Evidence Database](#)¹⁶⁵, [mHealth Evidence Database](#)¹⁶⁶, and [mHealth Compendium \(Volumes 1-6\)](#)¹⁶⁷ document evidence of the impact of the aforementioned communication approaches.

As other donors – primarily the Global Fund – have historically focused support on mass media, PMI has historically recommended an approximately 70 percent/30 percent split between interpersonal communication and mass media activities. While this recommendation may still be relevant, the appropriate mix should be determined by country context, including epidemiology, situation analysis, behavioral analysis, audience analysis, as well as available budget and priorities of other SBCC stakeholders.

The cost per person reached with IPC is considerably higher than with mass media and thus requires careful consideration of where and how to target. As noted above, mass media is particularly useful at raising awareness of goods, services, and events such as notifying a community about an ITN distribution event or the fact that treatment with ACTs should be free at public facilities. Mass media can also be useful in promoting social norms supportive of practices like ITN use or early ANC attendance. However, for behaviors that have been identified as more difficult to influence, IPC approaches may be needed. These scenarios may include:

- A community where the population may be at increased risk (recent withdrawal of IRS);
- Barriers to behavior uptake are related to factors requiring some level of “coaching” (low sense of self-efficacy to use a product correctly or engage in a behavior);

¹⁶⁴ Adapted from <https://www.thehealthcompass.org/trending-topics/information-and-communication-technology>

¹⁶⁵ <https://healthcommcapacity.org/malaria-evidence-database/>

¹⁶⁶ <https://www.mhealtevidence.org/>

¹⁶⁷ <http://www.africanstrategies4health.org/mhealth-database.html>

- Behaviors for which multiple family members may be part of a decision-making process (prompt care-seeking for fever);
- Behaviors for which engrained cultural practices or beliefs require sensitive communication (ANC attendance).

Because of the higher relative cost per person reached with IPC, countries should ensure that they take advantage of existing “outreach” platforms and opportunities to provide IPC; these may include: supportive supervision visits to CHWs and facility-based service providers, household visit “sweeps” for active case detection, active surveillance in elimination settings, ITN mass campaign enumeration, and routine patient-provider interactions (service communication). Operational research and program evaluation on cost effectiveness of various communication channels is still needed to better inform country-level programming of SBCC activities.

Best practices for malaria SBCC

The recent PMI-supported effort to develop the [*Malaria SBCC Evidence Database*](#)¹⁶⁸ revealed the following best practices for high impact malaria SBCC activities (adopted from the *Malaria Social and Behavior Change Communication Evidence Literature Review*¹⁶⁹):

1. Emphasis and reinforcement of specific health behaviors

While communicating the risk of malaria and providing access to necessary tools are important, providing target populations with specific actionable steps through SBCC activities will lead to improved outcomes. SBCC activities that emphasize specific malaria-related behaviors (particularly behaviors associated with intervention use) are most likely to achieve substantial behavior change, compared to activities only focused on raising risk perception.

2. Use of innovative approaches

The use of ICT approaches, such as SMS, should be considered to address identified factors preventing or supporting malaria-related behaviors. This is especially true for case management behaviors, where there is more evidence. For example, SMS reminders and motivational messages can foster an enabling environment and provide a prompt to action for the implementation of case management practices that are already accepted as the clinical norm by service providers. SMS reminders to community health workers have

¹⁶⁸ <https://healthcommcapacity.org/malaria-evidence-database/>

¹⁶⁹ The Health Communication Capacity Collaborative (HC3). (2017). *Malaria SBCC Evidence Literature Review*. Baltimore, Maryland: Johns Hopkins Center for Communication Programs.

been shown to increase adherence to guidelines, provide motivation for performance, and lead to the creation of habit and improved outcomes.

3. Use of mass media

The evidence strongly supports the use of mass media in addressing identified factors preventing or supporting malaria-related behaviors and promoting malaria-related behaviors. While the majority of the evidence focuses on ITN use, mass media has also been shown to increase the uptake of other malaria-related behaviors.

4. Use of multi-channel approaches

Apart from mass media approaches addressing factors preventing or supporting malaria-related behaviors or promoting malaria-related behaviors, the evidence supports multi-channel approaches. Efforts that combined mass media with other approaches—such as interpersonal communication, community mobilization and engagement, and ICT—were strongly associated with more positive attitudes about ITNs. These positive attitudes were then found to significantly increase the odds of net care practices and increase net use in some settings. The evidence supports a dose-response relationship between the number of sources and messages recalled to the likelihood of adoption/maintenance of malaria-related behaviors. Messages reinforced by various sources results in increased ITN use and care seeking. Evidence suggests that a multi-channel, multi-media approach is needed to achieve high levels of exposure to SBCC activities.

5. Use of integrated multi-media SBCC

Integrated multi-media SBCC activities covering three malaria focal areas –vector controls, malaria in pregnancy, and case management – demonstrated impact on multiple behaviors. Given the overlap of the target audiences and the behaviors, malaria control programs should consider integrated SBCC activities when promoting prevention and treatment behaviors.

6. Use of formative research to improve program design

The evidence suggests that it is important to conduct formative research and address community-specific factors that prevent or support malaria-related behaviors. SBCC activities that resonate with the target audience through their cultural, interpersonal, and seasonal practices are more likely to influence the desired malaria-related behavioral outcome.

7. Use of community change agents, leaders, and community engagement and mobilization efforts

The evidence strongly suggests using community change agents and community leaders/influencers, as well as community mobilization and community engagement

efforts, to address factors preventing or supporting malaria-related behaviors and promote malaria-related behaviors. Community-led efforts resonate better with the target audience and influence behavioral factors and behaviors within the community. These community-led efforts may also indirectly and informally influence malaria-related behavior of friends and family.

Monitoring and evaluating SBCC

There is an increasing focus across PMI to develop more comprehensive and systematic data on the impact of SBCC on uptake of malaria-related behaviors. With this focus comes a greater emphasis on accountability and reporting of SBCC activities, including developing M&E plans, selecting appropriate indicators, and measuring and tracking the selected indicators. PMI-supported SBCC M&E plans should include the following components:

- Behavioral objectives, communication objectives, SBCC activities to address those objectives
- Indicators for each objective, including operational definitions (see below for description of indicators)
- Targets for both the behavioral outcomes and the relevant intermediate outcomes (i.e., behavioral factors)
- Timeline for data collection in relation to activity implementation (i.e., formative, baseline, midpoint, endline)
- Data sources to calculate the indicators, reporting frequency, responsible party(ies)

Behavioral objectives, and the targets used to achieve these objectives, reflect the behavior targeted by the SBCC activity. Communication objectives reflect the behavioral factors that have been identified as influencing uptake of the behavior, sometimes referred to as intermediate outcomes. For example, a *behavioral objective* for an SBCC activity may be to increase ITN use among pregnant women. The *communication objectives* may be to increase the proportion of pregnant women who: feel they are at risk for malaria and that the consequences could be severe; feel that ITNs are a good way to reduce their risk; and feel confident in their ability to use an ITN all night, every night.

RBM SBCC Indicator Reference Guide

The RBM SBCC Working Group has updated the [Roll Back Malaria SBCC Indicator Reference Guide](http://breakthroughactionandresearch.org/RBM-Malaria-SBCC-Indicator-Reference-Guide)¹⁷⁰ with the purpose of encouraging Ministries of Health, donor agencies, and implementing partners to monitor and evaluate the effectiveness of malaria SBCC activities using a more rigorous and standardized approach. Each indicator in the guide includes an

¹⁷⁰ breakthroughactionandresearch.org/RBM-Malaria-SBCC-Indicator-Reference-Guide

explanation of its purpose, definition (including numerator and denominator), measurement, interpretation, strengths, and limitations. The updates in the current version address how to select and prioritize among the indicators, a broader description of potential data sources, and consideration of service provider behaviors.

The indicators in the guide include:

- Recall
- Knowledge
- Risk and efficacy
- Norms
- Attitudes
- Behaviors

While these are not considered required reporting indicators for PMI, PMI partners are encouraged to use the indicators to design, monitor, and evaluate SBCC activities. Change in behavior of the target audience should always be measured, as should reach/exposure of the target audience to the SBCC activity (measured as recall). The indicators for the communication objectives, or intermediate outcomes, will vary depending upon the framework used for the SBCC activity but could include change in knowledge, risk perception, self-efficacy, response efficacy, social norms, and attitudes.

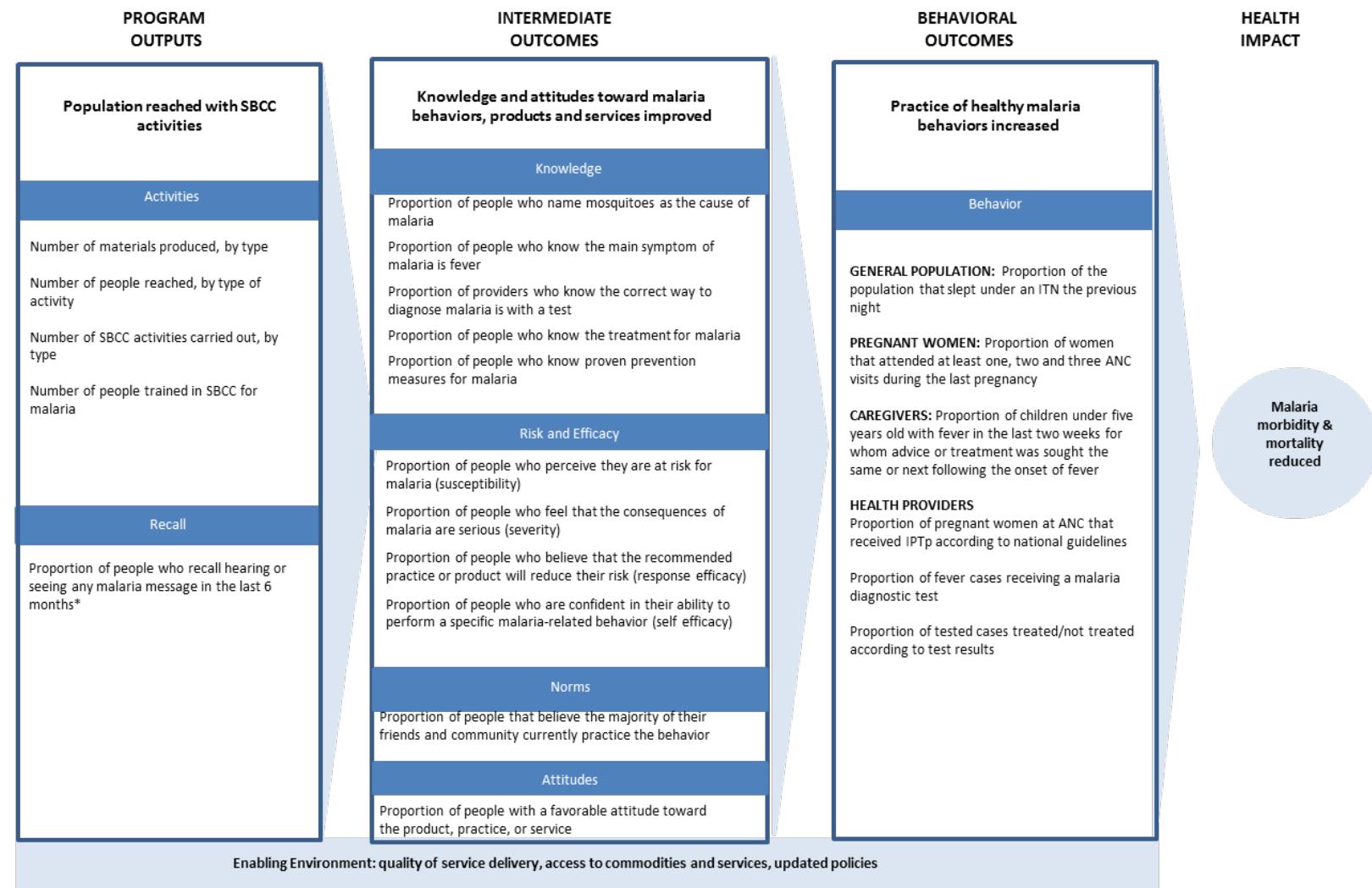
The reference guide uses a practical framework (Figure 1) to illustrate how SBCC activities influence behavior change by showing the logical pathways through which program outputs influence outcomes at multiple levels and can contribute to health impacts. The guide also reflects how the various indicators can be used at all stages of program planning and implementation:

- **Formative research** to design the SBCC intervention
- **Baseline evaluation** to measure conditions before implementation
- **Process monitoring** to track whether activities are being implemented as planned
- **Audience monitoring** to measure intermediate outcomes during implementation (e.g., recall, knowledge, risk, efficacy, norms, attitudes)
- **Endline evaluation** to assess impact on behaviors and intermediate outcomes.

Audience monitoring should be done throughout implementation to assess the extent to which target audiences are reached by the activity, the audience recalls key messages, and may also provide early indications of change in behaviors or intermediate outcomes. This type of monitoring can inform mid-stream adjustments in implementation if there is evidence that the activity is not having the desired effect on the audience. The data collected can also be used to

help make the case (or not) for the activity's overall effectiveness in changing behavior for the endline evaluation. See below for data sources for audience monitoring.

Figure 1. Framework linking SBCC outputs to behavioral outcomes and health impact



Finally, the guide also emphasizes the essential role of health service providers in achieving outcomes of high uptake and coverage with key interventions; this is particularly relevant for MIP and case management interventions. To that end, health service providers are considered a target audience for any and all of these indicators. Factors such as provider knowledge of interventions, self-efficacy to perform a particular task, belief that a product or treatment works, attitudes towards a product or service, and workplace norms are aspects of service provision that warrant careful consideration in SBCC activity planning, design, and M&E.

Data sources

SBCC M&E data may be captured using existing or new data sources including national or sub-national household surveys (e.g., DHS, KAP), health facility surveys, and routine data sources (e.g., HMIS). The core modules for the DHS and MIS already include recall of malaria SBCC activities and the standard behaviors for net use, ANC attendance, IPTp, care-seeking, testing, and treatment with ACTs. However, data from all of these sources have limitations for SBCC M&E that need to be considered when developing M&E plans. For example, national household surveys may not provide the subnational estimates required to measure outcomes of a specific SBCC activity, especially if the activity is targeted to a limited geographic area. It can also be costly and time-consuming to negotiate addition of SBCC malaria questions to such surveys. KAP surveys may offer a more flexible alternative, but there is no standard module for a KAP and thus they require expertise in questionnaire design, sampling, implementation, and analysis.¹⁷¹ Health facility data from surveys or routine data collection systems are necessary for activities targeted to health workers and can provide a wealth of information on various aspects of patient-provider interactions. Data collection methods could include patient observation, patient exit interviews, provider interviews, and register abstraction. Routine data (e.g., HMIS) and commodity inventories are existing health facility data sources that may provide insight on service provider behaviors and commodity availability. Again, there is currently no standardized protocol for health facility-based SBCC data collection and the quality and completeness of these data sources must be considered when interpreting data.

Monitoring implementation of SBCC activities can and should be done through a variety of data sources. Activity reports from implementing partners allow for tracking implementation of key activities (e.g., training, community mobilization). For mass media, media monitoring reports can be commissioned from third-party organizations to ensure broadcasts are aired as planned; broadcast logs from radio and TV stations can also be used. Omnibus surveys are regularly-occurring large surveys conducted for marketing purposes; marketing firms will charge for each question added to the survey. They can be used to track exposure/recall and assess intermediate

¹⁷¹ The Malaria Behavior Survey, a tool developed by the Health Communication Capacity Collaborative (HC3) and Breakthrough-Action and in collaboration with the PMI SBCC team is designed to address this issue.

outcomes. National or regional-level samples can be obtained but sampling strategies are not as robust as DHS and MIS surveys. Mobile phone surveys, media content analysis, and rapid exit surveys (e.g., from an event or health facility visit) are other potential data sources for monitoring. For more detail on the advantages and limitations of all data sources mentioned, please refer to the Data Sources section of the [*Roll Back Malaria SBCC Indicator Reference Guide*](#).¹⁷²

For SBCC formative research, audience monitoring, and outcome evaluation, triangulating several data sources for a more comprehensive understanding of behaviors is recommended. Ideally this will include existing data (e.g., household surveys, HMIS), but building a compelling argument for the results of SBCC activities will typically require planning for data collection designed to capture baseline, midline, and endline data points to adequately evaluate SBCC activities. The timing and budget required for proper M&E should be anticipated by the PMI country team, including pre-intervention baseline data collection.

It may not be possible to attribute changes in behavior, and to an even greater extent, changes in health impact, to a specific SBCC activity; however, descriptive behavioral outcome data, even in the absence of a statistically significant association, can suggest potential associations with SBCC activities and be used to inform programmatic decision-making. This association is strengthened even further if the communication objectives are achieved (e.g., change in risk perception, efficacy, attitudes, norms). 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 activity will influence what kind of conclusions can be drawn from evaluation results. If a partner is able to clearly articulate the rationale for the SBCC approach using a logical framework, and has clearly defined behavioral and communication objectives, this should be used to develop an M&E plan. Based on the M&E plan, if they can demonstrate that the activities were implemented as intended, they reached the target audience, the audience demonstrated a change in the targeted behavioral factors (i.e., intermediate outcomes), and there is some evidence of a measured change in behavior, then a compelling story has been built for the effect of that SBCC activity.

RBM SBCC Working Group reporting guidelines

Reporting for malaria SBCC activities is often missing key information, which limits the ability to identify high-quality activities and to reproduce those activities. To address this gap, the RBM SBCC working group developed a [*Reporting Guide for Malaria Communication Evaluations*](#).¹⁷³

¹⁷² breakthroughactionandresearch.org/RBM-Malaria-SBCC-Indicator-Reference-Guide

¹⁷³ <http://www.healthcommcapacity.org/wp-content/uploads/2014/11/RBM-CCoP-Reporting-Guide-for-Malaria-Communication-Evaluations.pdf>

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.

Operational research for SBCC

As PMI country teams confront SBCC-related OR questions, these questions should be discussed with relevant stakeholders for consideration of how to prioritize and address these questions.

Formative behavioral research to further understand a behavior and factors preventing or supporting a behavior in the absence of existing data is not operational research and is expected.

The PMI Headquarters SBCC team has identified the following operational research priorities at the global level; however, these priorities and questions may also be applicable at the country level. As such, these priorities may be appropriate for both core-funded and MOP-funded SBCC operational research.

1. Evaluate effectiveness of SBCC activities addressing different behavioral factors (e.g., self-efficacy, risk perception, social norms) for key malaria-related behaviors (e.g., patient initiation of services, service provider adherence to guidelines) to inform design of future SBCC activities.
2. Demonstrate a dose-response relationship between a SBCC activity targeting either patients or health care providers and key malaria-related behaviors for malaria in pregnancy and/or case management (e.g., patient initiation of services, service provider adherence to guidelines) to improve quality and cost-effectiveness of SBCC activities.
3. Evaluate the cost-effectiveness of existing and new SBCC approaches and channels (e.g., interpersonal communication, mass media, mobile technology) influencing key malaria-related behaviors.
4. Identify SBCC activities for increasing and maintaining key malaria-related behaviors in elimination settings.

The recent PMI-supported effort to develop the [*Malaria SBCC Evidence Database*](#)¹⁷⁴ revealed the following research gaps that should be taken into considerations when exploring OR opportunities (adopted from the *Malaria Social and Behavior Change Communication Evidence Literature Review*¹⁷⁵):

¹⁷⁴ <https://healthcommcapacity.org/malaria-evidence-database/>

¹⁷⁵ The Health Communication Capacity Collaborative (HC3). (2017). *Malaria SBCC Evidence Literature Review*. Baltimore, Maryland: Johns Hopkins Center for Communication Programs.

1. There is a lack of research identifying the gaps between access to services or commodities for malaria-related behaviors and actual adoption and maintenance of malaria-related behaviors associated with those services or commodities. Formative qualitative research with target audiences in specific contexts could help shed light on the gaps between access and use and inform malaria SBCC activities.
2. There is limited evidence demonstrating the impact of SBCC activities on malaria-related behaviors related to the prevention of malaria in pregnancy, such as IPTp uptake, ANC attendance, and ITN use among pregnant women. A better understanding of the role of SBCC activities on the MIP-related behaviors of pregnant women and households with pregnant women would allow for better tailoring and targeting of SBCC activities.
3. There is a lack of understanding and precise measurement of social norms and beliefs that might have been influenced by SBCC campaigns. The evidence shows that SBCC campaigns focus on social norms and beliefs to promote malaria-related behaviors, but very few follow up to measure whether there was normative change that came out of those SBCC campaigns.
4. Peer-reviewed articles do not adequately describe SBCC activities. A basic description of activity components can be essential for global malaria and SBCC practitioners, policy-makers, and researchers to learn from and apply study findings.

Finally, as with other PMI-supported OR activities, OR concept notes and protocols need to be developed through an interagency collaborative process, as noted in the **OR** chapter.

Additional Considerations for SBCC

SBCC for elimination settings

As more countries begin to shift and accelerate towards malaria elimination nationally and sub-nationally, the focus and implementation of SBCC activities will need to shift to target different populations, behavioral factors (e.g., efficacy, attitudes), utilize new channels, and adjust how behavior change is measured. With transitions to areas with high, moderate to low, very low, and zero transmission, communities will experience fewer and fewer cases of malaria perceived risk of malaria will decrease; however, severity of malaria will increase making imported cases severe. To address these shifts, behavior maintenance will also become more important, particularly with regard to ITN use. Although there is no “one size fits all” approach for specific strategies and channels that should be used for SBCC in elimination settings, key aspects of behavior change should be considered. Please refer to the ‘**SBCC**’ section in the **Elimination** chapter.

Budget

PMI support for SBCC activities should be commensurate with the overall PMI budget, the magnitude of the behavioral challenges, and the SBCC investment by other stakeholders.

Management

As articulated in **PMI Policy**, as with all PMI investments, PMI country teams are expected to manage and monitor SBCC investments:

- In the event that the COR/AOR of a bilateral SBCC mechanism or bilateral mechanism with a SBCC component is not a member of the PMI country team, a member of the PMI country team should serve as an activity manager for the malaria SBCC activities.
- For countries that buy-in to a central SBCC mechanism for malaria SBCC activities or integrated SBCC activities, the PMI country team is expected to select a member of the country team to serve as a Mission-based activity manager for the activity. The Mission-based activity manager will work with the Washington-based activity manager of the project to manage the activity.
- The PMI country team is expected to create linkages between SBCC projects and other projects within the PMI portfolio. For example, SBCC projects working to increase care and treatment seeking should be linked with service delivery projects working to improve the quality of community-based and facility-based malaria case management and supply chain projects working to improve supply of RDTs and ACTs. All PMI-supported implementing partners and their projects are expected to collaborate with and create synergies with PMI-supported SBCC implementing partners and their projects.
- Similarly, PMI is expected to coordinate SBCC activities with the Global Fund principal recipient and other implementing partners and other donors to ensure the implementation of complementary and reinforcing SBCC activities.

PMI Headquarters SBCC Team support

The PMI Headquarters SBCC Team is able to support PMI country teams with design and procurement of SBCC projects (either bilateral SBCC mechanisms, mechanisms with a SBCC component, or scopes of work for a buy-in to a central SBCC mechanism), design or revision of a national malaria SBCC strategy, monitoring and evaluation, and determining appropriate topics for operational research.

To facilitate communication between the PMI SBCC Team and PMI country teams, PMI country teams are requested to identify a SBCC point of contact. The SBCC point of contact will be the PMI SBCC team's primary contact regarding SBCC in-country. The PMI SBCC team will send

periodic updates to the field-based SBCC points of contact and host periodic update and coordination calls with the field-based SBCC points of contact.

Peace Corps

Guidance for collaboration with Peace Corps is available in the '***Peace Corps***' section of the **HSS** chapter. However, as it relates to SBCC activities, Peace Corps and Peace Corps Volunteers are potentially a great resource. It is recommended, however, that PMI ensure that Peace Corps' malaria SBCC activities complement PMI-supported SBCC activities, are evidence-based and theory-informed, and contribute to behavioral and communication objectives outlined in the national malaria SBCC strategy. If possible, Peace Corps and Peace Corps Volunteers should participate in existing or ongoing SBCC activities rather than designing and implementing parallel or duplicative SBCC activities.

SBCC Appendix 1. Additional SBCC Resources

Category	Resource	Description
Overall	Strategic Framework for Malaria SBCC (RBM Partnership)	Technical and advocacy resource for malaria SBCC.
	Springboard for Health Communication Professionals (HC3)	Virtual platform for exchanging knowledge, experience, and resources about SBCC and promoting collaboration and networking between SBCC professionals and organizations.
	Health COMpass (HC3)	Curated repository of SBCC resources, tools, guides, and materials
	Malaria SBCC Evidence Database (HC3)	Searchable database highlighting the results of a systematic review of peer-reviewed and gray literature documenting the impact of SBCC on malaria related behavioral outcomes.
	Accelerator Behaviors Website (Accelerate)	Houses the Global Behavioral Profiles for the three malaria-related accelerator behaviors which illustrate the relationship between the accelerator behavior, steps required to practice the accelerator behavior, factors influencing the practice of the steps or accelerator behavior, and supporting actors and actions. Possible program strategies for addressing the factors influencing the practice of the steps or accelerator behavior or supporting actors and actions are also offered.
Strategy Development and Revision	Repository of National Malaria SBCC Strategies (HC3)	Curated repository of national malaria SBCC strategies.
	How to Develop a Communication Strategy (HC3)	Step-by-step instructions on how to develop a communication strategy—at any level.
Capacity Strengthening	SBCC Online Capacity Building Center (HC3)	
	How-to Guides (HC3)	Short guides that provide step-by-step instructions on how to perform core SBCC tasks, including how to develop a logic model, how to conduct a situation analysis, how to do an audience analysis, and how to conduct qualitative formative research.

Design and Implementation	SBCC Check-In Quality Assurance Tool (HC3)	Easy-to-use tool to assess and assure the quality of SBCC activities.
	Implementation Kits (HC3)	Collection of in-depth guides, implementation kits or k-kits, on specific SBCC topics, including the Provider Behavior Change, Service Communication, Malaria Case Management Monitoring and Evaluation for SBCC, SBCC for Malaria in Pregnancy Strategy Development, and the Promoting Quality Malaria Medicines through SBCC.
Monitoring and Evaluation	SBCC Indicator Reference Guide (RBM Partnership)	Guidance document for malaria SBCC monitoring and evaluation, indicators, and data sources.
	Online Training on Evidence-based Malaria Social and Behavior Change Communication (VectorWorks)	Online training on malaria SBCC theory, formative research, pretesting, monitoring, and evaluation.
Operational Research	Reporting Guide for Malaria Communication Evaluations (RBM Parntership)	Working paper outlining a checklist for reporting on malaria SBCC evaluations.
	PMI Operational Research Priorities (PMI)	List of PMI's operational research priorities.
	PMI Operational Research Projects (PMI)	Searchable database of completed and ongoing PMI-support operational research projects.

SBCC Appendix 2. Common Behavior Change Theories¹⁷⁶

Theory	Basic concepts	When to consider	Expected outcomes
Health Belief Model	Individuals' make health-related decisions based on: <ul style="list-style-type: none"> ○ Belief about their level of risk ○ Perceived benefits associated with changing behavior. 	Promote net use, seasonal prophylaxis & prompt care for fever in low prevalence settings	<ul style="list-style-type: none"> • 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. <ol style="list-style-type: none"> 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 	<ul style="list-style-type: none"> • 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) 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Similar to social cognitive theory • Multiple social and environmental cues drive individuals' choices 	Address multiple audiences with multiple interventions <ul style="list-style-type: none"> ○ 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

¹⁷⁶ 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	<ul style="list-style-type: none"> • Fear inhibits decision-making • Danger management: Individuals adapt to real and perceived risks • Fear management: Individuals invest in managing fear, not risk 	<p>Use with Caution</p> <p>Risk of unintentionally reinforcing existing fears</p> <p>Focus instead on clearly explaining known risks and benefits</p>
Ideation	<ul style="list-style-type: none"> • Multiple factors influence individuals' and groups' behavior • Multiple skills and approaches needed to facilitate behavior change 	<ul style="list-style-type: none"> • Most SBCC activities may benefit from a multi-channel approach. • PMI recommends clearly describing each factor or activity. <p>A coordinated, multi-pronged strategy is developed based on multiple sources of information about the target population.</p>

Surveillance, Monitoring, and Evaluation

New/Key Messages

- Nationally representative 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.
 - 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.
- Health management information systems (HMIS) are a key investment area for PMI. To better document PMI support for HMIS strengthening plans, more information should be provided on the NMCP overall strategy, the level of support (region, district, facilities), and the total number of areas being targeted and covered.
- Nationally representative Health Facility Surveys (HFS) are primarily used for program monitoring and helps monitor readiness of a health facility to provide quality care. As a general rule, HFS should not be repeated more than every 2-3 years, depending on the information required. Note that investigations conducted in health facilities in response to a specific problem would not be considered health facility surveys.
- For more information on the End-Use Verification Tool (EUV), please refer to the **Commodity Procurement and Supply Chain Management** chapter.
- 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.

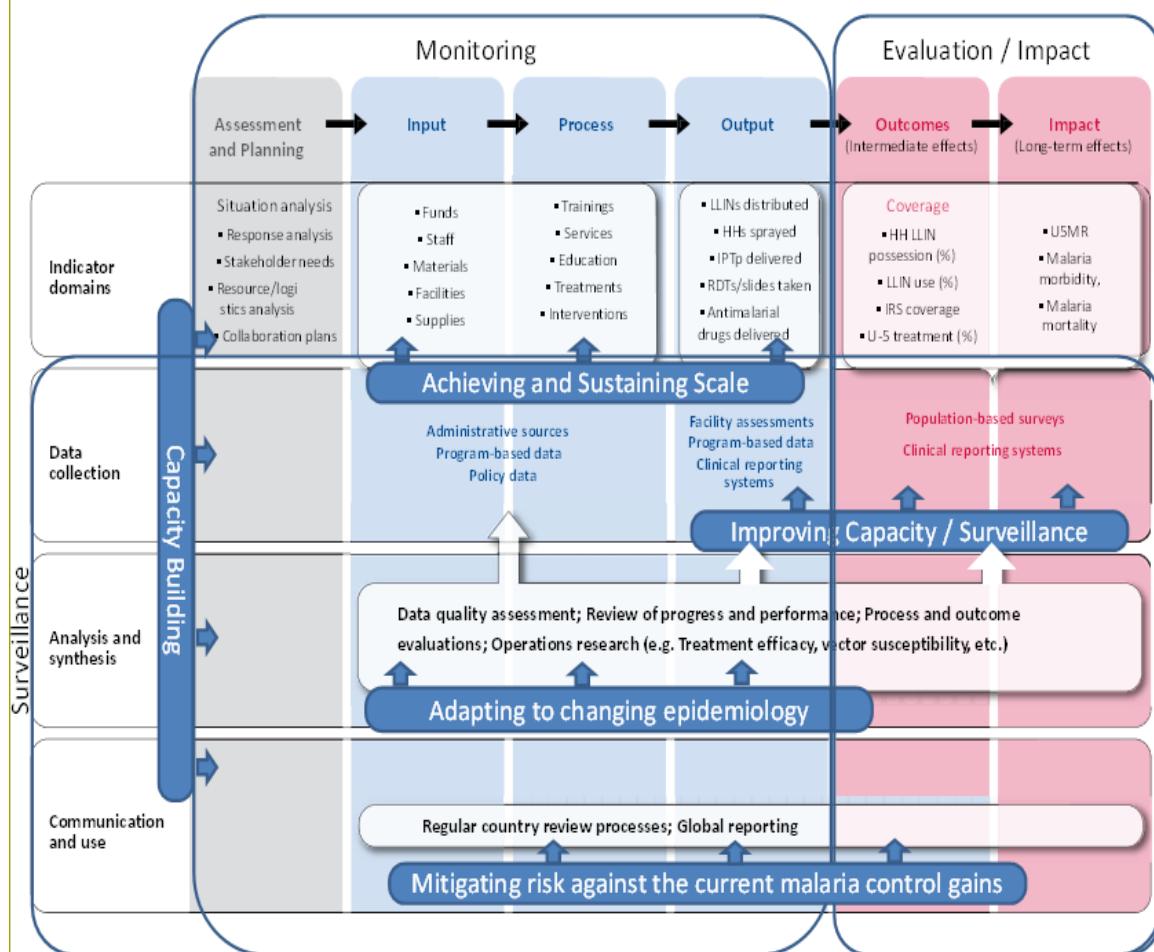
Cost-effective, sustainable solutions

The PMI Headquarters 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 country. For countries nearing 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. As malaria transmission diminishes and fewer deaths are attributable to malaria, use of ACCM will become less effective as a direct indicator for tracking malaria control success (for this reason, ACCM has never been a primary indicator for malaria in the Mekong countries).

Facility-base data collected by the ministries of health and the NMCPs through routine health information systems (RHIS) are a primary data source for hospital-based deaths from malaria. It is important to emphasize that hospital based-deaths grossly underestimate the actual number of malaria deaths because many deaths occur at home, or at facilities not reporting to routine systems. However, trends in mortality can be tracked through longitudinal facility-based data collection systems and, when controlling for factors such as increasing completeness of reporting and increases in health facility use, indicate changes in malaria mortality and case-fatality rates over time.

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

PMI has relied on population-based household surveys to measure malaria morbidity in the form of severe anemia (hemoglobin <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 valid point estimates in medium to low-prevalence areas are making surveys prohibitively expensive for national malaria control programs and donors. Additionally, the surveys do not indicate the density of parasitemia (parasites per microliter of blood), and therefore do not necessarily correlate with incidence of severe illness in moderate/high transmission areas.

To date, weaknesses in most 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, accurate, timely, and visible. Going forward, routine health information will be critical to monitoring changing epidemiology, targeting resources and interventions, and measuring impact. Therefore, PMI encourages more investment in disease surveillance strengthening through routine health information systems.

In most PMI-supported countries, HMIS data (increasingly captured via DHIS-2 platform) is the main data source for suspected and confirmed malaria cases, test positivity rates, hospital admissions, and hospital-based deaths from malaria. PMI recommends a strategy that addresses both increased analysis and overall HMIS system strengthening, such as improved data recording and reporting, and expansion to both private and public facilities.

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 previously defined the pre-elimination phase as a monthly malaria test positivity rate of less than 5% among all febrile patients throughout the year. Thus, countries approaching elimination must have a highly functioning routine health information system that includes reporting of cases diagnosed at community level. Preferred impact indicators in settings moving towards elimination 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 elimination setting can be found in the **Elimination** chapter.

Five Areas of Strategic Focus

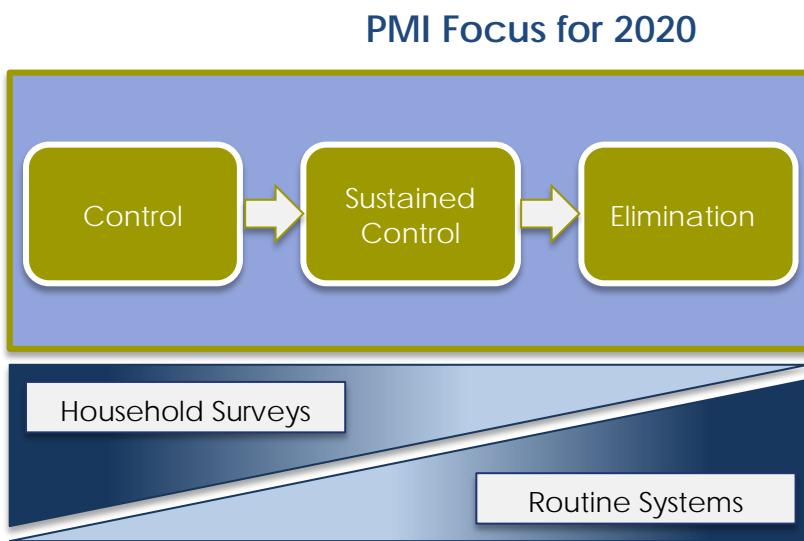
The *PMI 2015-2020 Strategy* has five areas of strategic focus that support PMI's three objectives. Focus areas need to be monitored to assess progress that will ultimately have impact on PMI's objectives. See the *SM&E Framework* (separate document) for more details on how these focus areas align with SM&E objectives.

SM&E for the PMI Strategy, 2015-2020

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 (high, moderate, low, very low, 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 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 more intensive 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.

For reference, the link to the WHO guidance on malaria surveillance for control areas is (<http://www.who.int/malaria/publications/atoz/9789241503341/en/>). For countries moving towards elimination, please contact the PMI Headquarters SM&E Team and Elimination Working Group for guidance. The recently updated WHO Framework for Malaria Elimination also has some useful information on SM&E activities in elimination settings (<http://www.who.int/malaria/publications/atoz/9789241511988/en/>).

Routine health information systems

Routine health information systems (RHIS) will be important for measuring the impact of PMI 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. HMIS typically include a broad set of health indicators (including several malaria indicators) representing all health services provided at the health facility. A few country programs are also using the Integrated Disease Surveillance and Response system (IDSR). IDSR typically 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 (e.g., monthly HMIS reporting versus weekly IDSR reporting), indicator definitions (country dependent), and the number of facilities covered. In general, the HMIS is the preferred system for PMI support; 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-supported countries at this time is that data collected by health facilities (public, private, and community) and reported through the RHIS are not of sufficient quality (e.g., completeness, accuracy, 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.¹⁷⁷ Issues of completeness and accuracy remain, but this should not keep countries from using, information for tracking trends to inform programmatic decision making while still checking data quality and completeness.

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. 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.

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 passive surveillance in higher

¹⁷⁷ 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.

burden areas for the country, selection of high-impact strengthening activities, and a phased approach to implementation across districts and facilities. 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 and the monitoring of case management interventions. 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.

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: recording, reporting, 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. With resources available, this scale-up must be a phased approach. Facility level surveillance support should be part of a larger strategy 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.”¹⁷⁸ However, in the absence of a proven optimal strategy, PMI supports a range of RHIS-strengthening models. The timeframes for supporting RHIS strengthening at each facility will vary and must be guided by local circumstances. Evidence for RHIS strengthening should be presented in the MOP to document progress in performance and geographical coverage. Such evidence could be quantitative (e.g., numbers trained in specific activities or skills, changes in DHIS-2 coverage, numbers of facilities reporting to RHIS, or completeness of reporting to RHIS) or qualitative (e.g., instances of staff from supported facilities designing or leading SM&E training activities, or plans for supported facilities to train or advise other facilities). An essential component of documenting progress is clear enumeration of denominators. For example, activities targeting the district level should include the total number of districts in the country, the number of districts intended to be reached by the PMI-funded intervention and those covered by other government or donor funds. In order to achieve the largest impact, emphasis should be placed on adding or expanding target areas.

To avoid potential confusion with support for sentinel sites or clinical strengthening, PMI requests 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 national levels with an overall long-term goal of nationwide reach of RHIS strengthening efforts.

¹⁷⁸ http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/sentinel/en/

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.

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 **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. 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 no longer support parallel systems. 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.

- **Elimination:** In situations where a country has transitioned into the elimination phase, 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 **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 to assess coverage of interventions and, when needed, estimates of malaria prevalence and ACCM. 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 ongoing 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 and requires a much larger sample size to produce meaningful estimates. 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.
- PMI supports the guidance provided in the RBM MERG Household Survey Indicators for Malaria Control document regarding the use of RDTs (http://www.rollbackmalaria.org/files/files/working-groups/MERG/Reference%20documents/tool_HouseholdSurveyIndicatorsForMalariaControl.pdf). Parasite prevalence should be based on the results of a high quality RDT where *P. falciparum* accounts for nearly all infections (≥ 90 percent) and low-density infections (<200 parasites/ μl) are uncommon. PMI does not support the use of multi-species RDTs in surveys.

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.¹⁷⁹ 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.

¹⁷⁹ 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.

If special surveys are proposed in country MOPs, country teams should provide concise descriptions of the activity that outline 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

Nationally-representative health facility surveys (HFS) are intermittent, comprehensive evaluations of health system function and are primarily used for program monitoring: establishing a baseline and assessing which aspects of the program require intervention or policy change, and then monitoring changes in relevant indicators after the intervention or policy has been implemented. Health facility surveys are useful in situations where routine information systems and household surveys do not provide all of the necessary information on case management practices, system readiness, and training and supervision to meet programmatic needs of the NMCP or PMI. Health facility surveys should not be used as replacements for the HMIS and SM&E efforts should focus on strengthening HMIS; however, when facility readiness/performance data is not available, periodic HFS should be considered. **Investigations conducted in health facilities in response to a specific problem would not be considered health facility surveys. For example, discrepancies between actual case management practices and HMIS reporting are best investigated through smaller-scale investigations than through a nationally-representative HFS.**

Methodology: HFS typically capture cross-sectional data from health facilities on several aspects of the health system including availability of commodities, appropriateness/quality of case management, data reporting, record reviews, diagnostic capacity, health worker training, and other indicators critical to malaria programs. The type of information required, the level of detail, and other factors will determine the appropriate HFS methodology to be used. A HFS may also include assessment of data quality and reporting, although it is not part of some standard protocols.

Scope: Endemic countries should consider nationally representative HFS in cases in which PMI is only working in part of the country or only parts of the country are endemic, sub-national HFS can be considered.

Timing: **As a general rule HFS should not be repeated more than every 2-3 years, depending on the information required.** More frequent HFS may be considered on a case by case basis but there should always be enough time between HFS to allow for interventions or policy changes to produce measurable changes. When possible, HFS should be carried out during the malaria season to obtain the most reliable assessment of malaria service readiness.

Costs: 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 strive to work with other partners to fund HFS.

Integration: Children under five years of age with fever are evaluated in health facilities using integrated case management protocols. When a HFS includes an observation or re-examination module, case management of children should be observed and cases re-examined using an integrated protocol. Commodities, health worker knowledge and materials for IPTp should be included in any HFS. In some situations, commodity or other data for other illnesses seen in facilities may be requested by other programs. As long as costs, timing and complexity of the HFS are not increased, integration of that type may be considered. Co-financing should be sought from other programs requesting data from a PMI-supported HFS.

Outpatient/inpatient: An HFS can include outpatient and/or inpatient assessments. Most HFS that PMI supports are outpatient assessments for which standardized protocols already exist and can be applied with minor adaptation. Inpatient assessments are generally more complex and require additional expertise from trainers, surveyors and supervisors, as well as data processing and interpretation. Inpatient care can vary widely by type/level of inpatient facility making their assessment more complicated. Consult with the SM&E Team when considering inpatient assessments.

Modules: The type of modules used in a HFS will depend on objectives, but may include:

- Health worker and/or supervisor interview
- Health worker and/or laboratory technician observation
- Record review
- Re-examination of sick child
- Facility readiness checklist
 - Infrastructure
 - Diagnostics
 - Medications
 - Reporting forms
- Caretaker exit interview
- Surveyor observations
- Mystery patients

In some situations, an additional module on data quality and reporting may be included.

If you are planning an HFS for the first time, consult with the SM&E Team for additional information.

Examples of health facility surveys

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, and how the results can be interpreted. For PMI purposes, HFS' that produce estimates quickly – within three to six months – should be favored as commodity and case management data become increasingly non-actionable if there are significant delays between the survey and the publication of results.

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
- Caretaker exit interviews
- Health worker observation protocols
- Facility inventory

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

Service availability and readiness assessment

Service availability and readiness assessment (SARA) surveys are 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 generates 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 can also be added. Instruments typically used in a SARA are:

- Staffing matrix
- Inventory of inpatient and observation beds
- Facility infrastructure audit
- Inventory of available clinical services
- Diagnostic capacity assessment
- Inventory of 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

Integrated management of childhood illness HFS' collect 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 of sick child
- Equipment and supply checklist
- Health worker interview (optional)

The tool can be found at:

http://www.who.int/maternal_child_adolescent/documents/9241545860/en/

End-Use verification tool

The EUV is a commodity assessment tool, rather than a health facility survey. Guidance on its use can be found in the **Commodity Procurement and Supply Chain** chapter.

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.

As part of overall malaria control impact evaluations, PMI generally does not support evaluations aimed at establishing/researching a WHO recommended specific intervention's impact on morbidity or mortality (WHO recommended malaria interventions include but are not limited to IRS, ITNs, IPTp, Case Management, and SMC). 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 on 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 include program evaluation components and are generally supported by PMI. Malaria program reviews should be carefully planned and coordinated with all partners (ideally timed to precede a country's new 5-year National Malaria Strategic Plan), 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 (http://www.rollbackmalaria.org/files/files/workinggroups/MERG/Reference%20documents/Framework_for_Evaluating_the_Scale-up_of_National_Malaria_Control_Programs_FINAL.pdf) should be used to ensure consistency and comparability across time and countries. Evaluations of impact should be transparent and participatory. 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 for demographic surveillance sites to monitor births, deaths, and health in geographically-defined populations continuously over time. It is possible, however,

that PMI support 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 Elimination Phases

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

Operational Research

New/Key Messages

- **Study budget:** The OR Committee review covers both technical and budgetary aspects of the concept note. A well-thought out budget is therefore required prior to the approval of the concept note. The expectation is that there will not be a significant difference between the budget proposed in the concept note and the protocol budget. A significant difference is a difference of greater than 10% for the overall study budget as compared to the initial concept note budget.
- A detailed budget using the PMI template included in this guidance is required when submitting the protocol for OR Committee Review.
- **Changes to approved protocols/ongoing studies:** When the technical aspects of an approved protocol are modified (change in research question/objectives, design, methods, etc.), the study amendments and accompanying revised budget must be shared with the OR Committee for approval. Any changes in the technical approach (including objectives, design, study sites, and methodology) and/or the budget during study implementation requires re-submission and re-approval by the OR Committee.
- **Co-funding of OR activities:** When OR activities receive funds from multiple sources, concept notes should clearly explain which study components are being covered by PMI (and their specific costs) and summarize the co-funding from other sources.
- **OR Committee role in the development and implementation of OR studies:** The OR Committee – as an advisory and approval body – is not responsible for handling study implementation or study roll-out challenges. PIs of PMI-funded studies must be fully qualified to implement the work stipulated in the protocol, oversee budget and staff, and comply with all local requirements for research including IRB clearances. OR Committee members will not be involved in study implementation and/or negotiations of implementing partners in their OR Committee capacity. Committee members can suggest technical input on an informal basis in their technical capacity as a member of the PMI team and/or a specific PMI interagency technical team, but such advice should not be considered OR Committee requests or a substitute for OR Committee review and approval of a PMI OR concept note or protocol. If an OR Committee member is involved in study design or implementation, they are recused from Committee deliberations and decisions regarding the study in question.
- **Reclassification of an OR concept or study into an assessment:** Rejected studies must not be converted into assessments unless there is clear statement in the approval form recommending such an action or the study is given a non-research determination by the OR Committee.

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 *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.

Please see **PMI Policy** for a description of the PMI OR leadership and management structures (PMI OR Coordinator, Interagency OR Committee and Management Team) and governance structures for PMI OR decision-making. The guidance included below focuses on objectives and priorities, guiding principles and processes for PMI country teams and PMI headquarters interagency technical teams proposing PMI MOP (country budget) or PMI core-funded (headquarters budget) OR activities.

PMI OR Objectives

As outlined in the *PMI Strategic Guidance for OR (2014)*, to achieve its goal, PMI will support program- and policy-relevant OR that will:

- Improve effectiveness of existing interventions and increase scale-up and quality, including assessing combined interventions (e.g., LLINs and IRS)
- Evaluate ways to mitigate insecticide and drug resistance
- Identify and assess improved and cost-effective approaches to monitoring changes in malaria epidemiology, particularly for documenting impact of malaria control efforts
- Identify and assess approaches to improve the capacity of health systems to optimize delivery and quality of 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 they are frequently implemented by local research groups. These tend to be shorter-term studies (duration of 12-24 months). The amount of country funding proposed for country-specific OR activities vary by country and by year.
- **PMI core funds allocated for OR priorities:** PMI OR studies conceived of and funded centrally with PMI core funding generally address broader issues applicable across the initiative and tend to be larger studies with higher budgets than country-generated OR activities. They may involve two or more PMI-supported 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, the number of interagency core funded concept notes proposed and prioritized for funding, and the incremental funding needs for multi-year studies funded in previous years.

Whether the source of PMI-supported OR studies is core- or country- (MOP) funding, a variety of mechanisms and technical collaboration and oversight by PMI staff are available to carry out PMI funded research. Which mechanism is selected depends on a variety of factors including the research question, country partner context, level of engagement of PMI technical staff, etc. Options include: (1) USAID country bilateral and central implementing partner mechanisms including USAID mechanisms that provide direct funding to local research institutions; (2) research collaboration involving CDC and/or USAID headquarters technical staff and a USAID country bilateral or central implementing partner mechanism with PMI staff directly engaged in protocol development, research implementation oversight, data analysis, etc.; and (3) CDC staff working with a local partner through a CDC mechanism accessed through the CDC IAA.

For option (3) above, because the CDC Interagency Agreement (IAA) includes policy restrictions for USAID appropriated funding to pass to CDC and on to a third party, if the third option is being considered by PMI teams, early discussion is needed to determine whether or not the conditions exist to request an exception and prior approval of an exception request is required before OR study planning moves forward. The relevant IAA language states: “*All transfers of USAID funds under this agreement to third parties, including partner country government entities, are prohibited unless approved in writing by the AOR.*” In particular, exception requests for PMI supported OR through CDC, including with a third party transfer (to a non-government entity), can be considered if there is not a bilateral or global USAID mechanism that can carry out the proposed OR. Direct funding of MOH/NMCP/host country governmental institutions (G2G) can be considered only

through a USAID G2G mechanism and only following the completion of appropriate financial management system audits etc. Funding MOH/NMCP/host country government institutions (G2G) through CDC with USAID appropriated funding (PMI or all other types of funding) is prohibited by USAID agency-level policy restrictions (See **PMI Policy, ‘CDC Interagency Agreement’ section**).

PMI co-funding of OR activities with other donors and organizations also occurs and is highly encouraged. One example is a cost-effectiveness study of vector control interventions in Mozambique, co-funded by UNITAID through IVCC and PMI. 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. Nonetheless, 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 was finalized in early 2016 and is currently available on the PMI website:<https://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/pmiorstrategicguidance.pdf?sfvrsn=14>

Individual countries may have additional priorities to those found on the priority OR listing. Country-specific OR activities are eligible for MOP funding, even if the research priority is not currently found on the most current version of the PMI OR priority list, provided they are consistent with the guidelines for selection of OR activities for PMI funding including addressing key bottlenecks to further progress in the given PMI country.

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 (MOP or core-funded) should be prioritized for funding. These guidelines apply to all PMI-funded OR activities. In general, as previously mentioned, 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. All PMI-funded OR studies should be aligned with one of the PMI OR objectives.
2. For MOP-funded OR activities:
 - a. The OR activity must focus on a country-specific priority that is consistent with the country's immediate needs and national OR strategy.
 - b. Priority should be given to studies that improve the implementation and optimize the efficacy 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.
 - c. 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.
3. For core-funded OR, priority will be given to OR that addresses priority challenges and implementation bottlenecks that would have broadly applicable results for PMI, and that take advantage of PMI's capacity to conduct research across multiple PMI-supported countries.

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 and approved by an interagency OR Committee and monitored and tracked by an interagency OR Management team with overall oversight by the PMI OR Coordinator 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, whether an exception is approved to rely on CDC staff and their research collaboration with a PMI country local partner or through

CDC staff research collaboration with the research partner(s) accessed through a USAID mechanism.

OR Study Development, Review, and Approval Process: MOP-Funded OR

Key considerations

- The OR Committee encourages explicit discussion of key operational challenges and bottlenecks, that may be overcome by undertaking OR studies, during MOP visits and use of these discussions as entry point for strategic selection of OR topics.
- OR should be relevant to country needs, completed in a timely manner, and prepared to broadly disseminate/use results within 2-3 years.
- Dissemination plan outlined at outset ensuring timely sharing of findings for action by NMCP/other implementers and encourage use of results.
- RAs establish a process for tracking adoption and implementation of key OR recommendations and application of results at the country level for annual report and other PMI reporting purposes.

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 (i.e. programmatic and/or implementation bottlenecks), 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 settings. In addition, clear research question(s) should be presented in the MOP or reprogramming request narrative. During the MOP review process or reprogramming request, 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. For a protocol and budget that is already approved and the country team is requesting additional funds through a reprogramming request, the country team must re-submit the revised protocol and budget to the OR Committee for review and receive approval **prior** to submitting the reprogramming request.

Review of MOP-funded concept notes and protocols by the OR Committee are synchronized with the MOP cycle. Concept notes for activities funded with reprogrammed funds will be reviewed in October (**due September 21, 2018**). Concept notes for OR activities given a green-light in draft MOPs will be reviewed in February (**due February 8, 2019**). Ad hoc review of concept notes and

protocols will be possible if a study timeline requires off-cycle review. Deadline reminders are sent out PMI-wide one month in advance.

MOP proposed concept note review

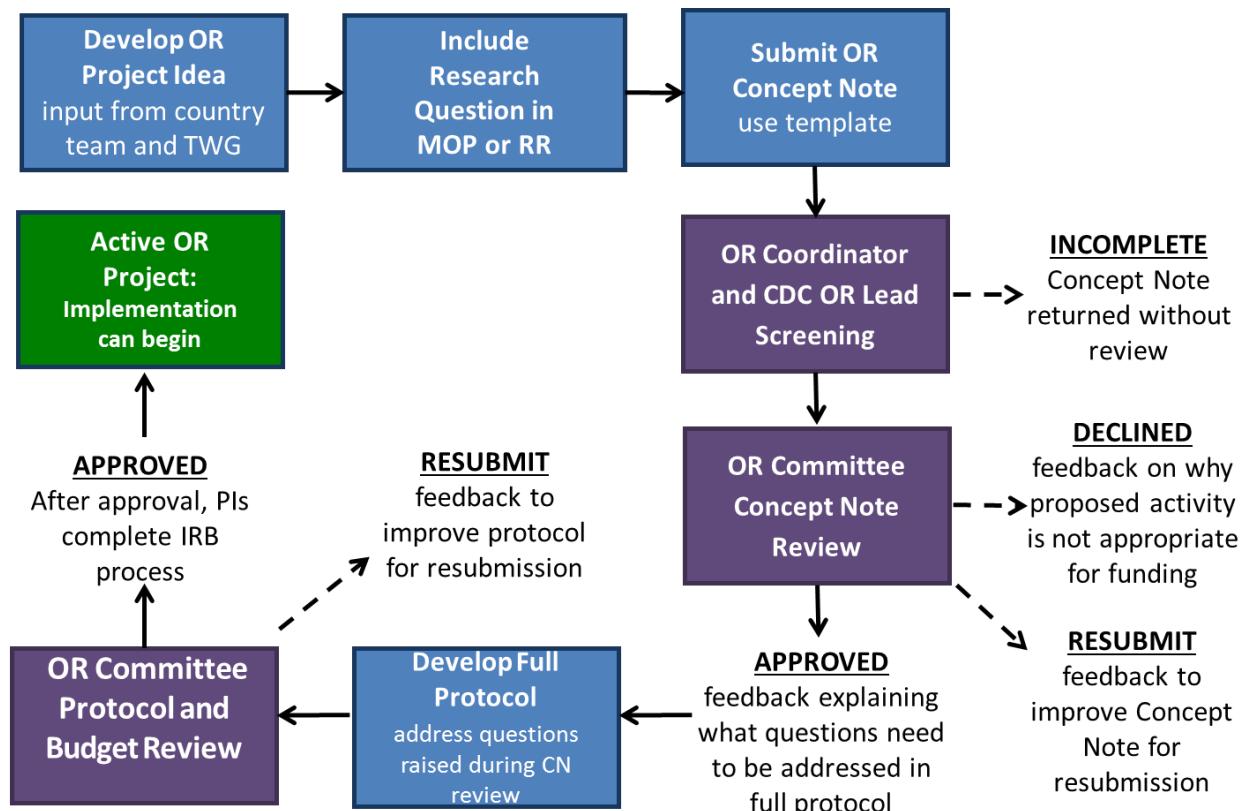
Once a new, proposed OR study is approved in a MOP or reprogramming request, the study team must submit a concept note and budget for review by the interagency OR Committee using the template provided in **OR Appendix 1** (for reprogramming requests for additional funding of approved protocols/ongoing studies due to the study budget has increased, country teams must resubmit the revised protocol and budget to the OR WG for approval prior to submitting the reprogramming request). 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 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 notes reviewed by the OR Committee can have the following three outcomes:

- **Approved:** 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 and budget must be submitted for review by the OR Committee for final approval (**please note, OR Committee review and approval does not substitute or override ethical or institutional reviews**).
- **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 concept note 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. Concept notes can also be declined if they are determined by the PMI OR Committee to be a routine monitoring or evaluation activity. This determination is based on the OR definition outlined in the PMI OR Strategic Guidance and is distinct from an IRB's determination of research vs. non-research status (e.g. there could be a situation when CDC DPDM has made a non-research determination but the PMI OR Committee has deemed the activity OR under PMI's OR definition).

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 changes to the study research question/objectives, design, methods, etc. that have occurred between concept note approval and protocol submission must be explained. Protocol review feedback will be returned to the study POC within three weeks of the protocol submission due date. **Figure 1** depicts the MOP-runded OR review and approval process from inception to implementation:

Figure 1. MOP-Funded OR Project from Idea to Implementation



OR Study Development, Review, and Approval Process: Core-Funded OR

Key considerations

- OR ideas can be brought to relevant technical teams for consideration by any member of the broad PMI interagency headquarters team (CDC Malaria/Entomology Branch and USAID Malaria Division staff). In addition to technical teams identifying questions requiring further research, members of the larger PMI team with specific expertise in an area, such as Resident Advisors or PMI implementing partners, can also flag to their headquarters colleagues an important priority question so that it receives consideration by the appropriate technical team(s).
- Ideas can be put forward at any time during the year or in advance of the annual November 15th fiscal year deadline.
- Dissemination plan outlined at outset ensuring timely sharing of findings for action by PMI/NMCPs/other implementers and encourage use of results.
- PI should establish a process for tracking adoption and implementation of key OR recommendations and application of results across countries as applicable.

Core-funded concept note development

Summary of important aspects of the core-funded OR process:

- The original OR question for research being prioritized falls within the PMI OR list (if not on list, strong justification for proposed question and concurrence of relevant interagency technical team).
- Seek within-agency concurrence for core funded OR ideas before extensive work on the idea to ensure efforts will be in-line with competing priorities
- Relevant interagency technical team(s) engagement/ discussion on the topic and endorsement as a priority area of investigation for PMI in their technical area as the interagency concept note development process occurs.
- All concept Notes requesting core OR funds are reviewed and approved by the OR Committee.

Process and approach

The process and approach for identifying and developing OR proposals for core funding will include the following steps:

1. Originator(s) of OR idea discusses with relevant team of agency experts (not one-on-one

with the PMI Team Leads from each agency) to ensure the research question is indeed consistent with agency priorities and current staffing capacity and infrastructure. This vetting process will help bring the highest priority, highest quality OR ideas to the interagency technical teams.

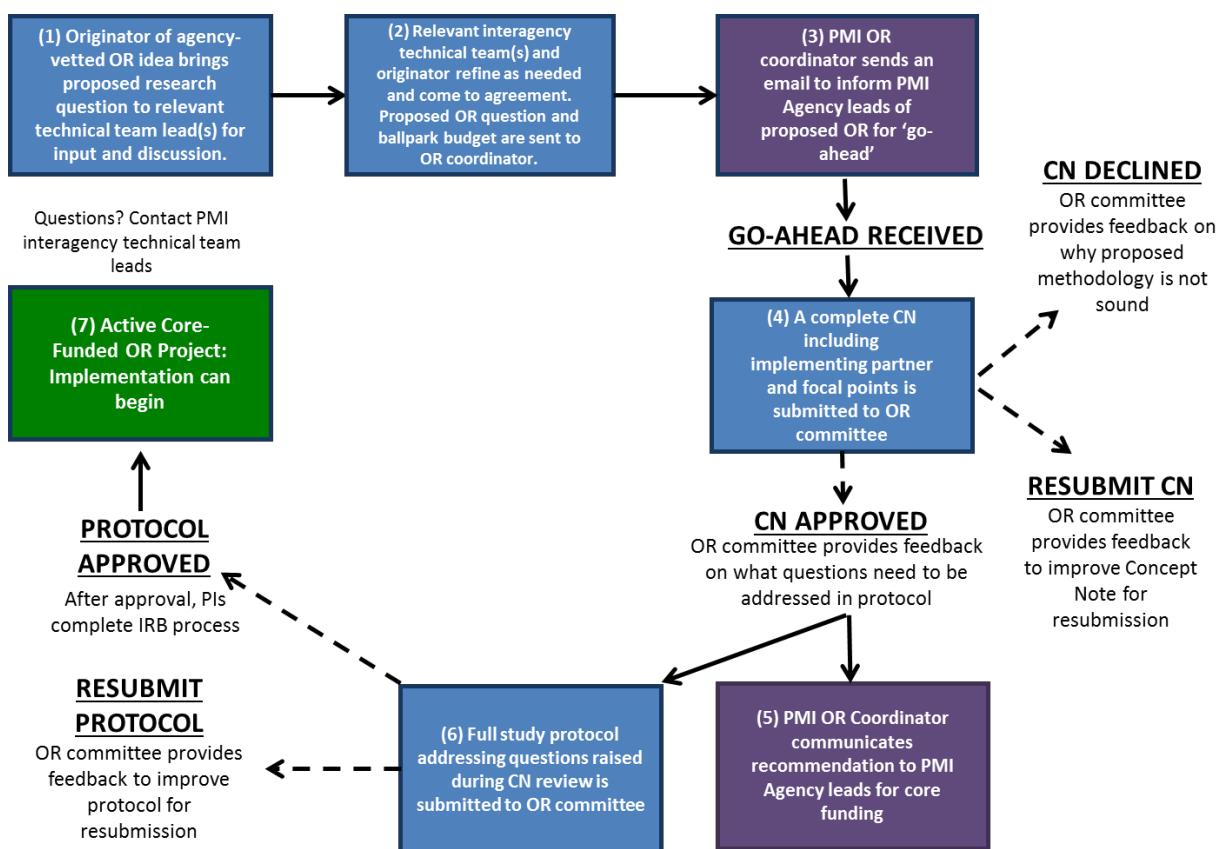
2. Originator of research idea brings proposed research question to relevant interagency technical team leads for input and discussion. PMI OR Coordinator is available to facilitate the initial contact between originator and technical team leads.

Originator may use parts of the concept note template (such as research questions, objectives, and rationale) to present question, or use the ensuing team discussion to shape and develop a fledgling idea further.

3. Relevant interagency technical team(s) and originator refine the idea as needed and come to agreement. Originators are free to reach out to OR Coordinator (Martin Alilio)/OR Management Team (Achuyt Bhattacharai and Meera Venkatesan) for assistance at this or any stage:
 - a. Interagency technical team leads, once approached, will convene a platform for discussing the idea (regularly scheduled team call, ad hoc team call, etc.). If the idea is cross-cutting, all relevant interagency technical teams should be included.
 - b. Once the relevant technical team(s) generally agrees that the idea is feasible, appropriate for core funding, and a priority for PMI, the originator works with technical team members to refine the question and generate a preliminary notional budget, which are sent to the OR Coordinator by the appropriate team lead.
4. OR Coordinator sends an email to inform PMI Agency Leads of proposed OR for determination of ‘go-ahead’. Agency Leads respond with a ‘go-ahead’ within 48 hours.
5. A complete CN, including proposed implementing partner and focal points, is submitted to OR Committee. The OR Committee may:
 - a. Decline a CN with feedback on why proposed methodology is not sound
 - b. Request that a CN be revised and resubmitted
 - c. Approve a CN
6. For approved CNs, the OR Coordinator communicates CN approval recommendation to PMI Agency Leads to confirm core funding requirement.

7. Full study protocol and budget that addresses questions raised by the OR Committee during CN review is submitted to OR Committee. The OR Committee may:
 - a. Request that a protocol be revised and resubmitted
 - b. Approve a protocol
8. Upon approval of the protocol and budget, the OR project is considered active and implementation can begin.

Figure 2: PMI Core-Funded Operational Research Project – Idea to Implementation



Commodities for OR

For OR studies that require commodities (including RDTs, ACTs, LLINs, etc.), it is recommended that orders are placed through the PMI supply chain project so that quality of the commodities can be assured. Once a concept note is approved, the PMI point of contact(s) must inform the Supply Chain Team of the anticipated order and study timeline as soon as possible, to facilitate timely placement of the order and arrival of supplies in country. Contact

can be made directly with the Supply Chain Team or through the OR Coordinator. The study budget in the concept note should include specific lines and estimated costs for commodities that will be purchased through the supply chain project. For core-funded OR commodity needs, the estimated funding for commodities outlined in the study budget will be directed to the centrally-managed malaria commodities procurement project. For MOP-funded OR commodity needs, country teams should specify at least two mechanisms for the OR study – the mechanism implementing the research and the PMI centrally-managed malaria commodities procurement project with the estimated commodity costs directed to the commodity procurement mechanism.

Please note: Concept notes are still required if a country wants to support an OR study being conducted and funded by another donor by providing commodities procured by PMI funds.

Study Budget

- The OR Committee review of concept notes requesting PMI funds covers technical and budgetary aspects of the concept note. A well-thought out budget (using template provided) is therefore required prior to the approval of the concept note. The expectation is that there should not be a significant difference between the budget proposed in the concept note and the protocol budget. A significant difference is defined as a difference greater than 10% between the original concept note budget and final protocol budget. Efforts must be made to develop a detailed budget at the concept note stage since study budgets are part of requirements for OR Committee review and approval. Protocols undergo a thorough review by a subset of OR Committee members and a recommendation for approval or disapproval is then made by the entire OR Committee: protocols are, therefore, approved on the understanding that the budget remains the same as in the concept note.
- The OR Committee provides approval for a study for its technical integrity and budget. Any changes in the technical approach (including research questions/objectives, design, study sites, and methodology) or the budget during the implementation requires re-submission and re-approval by the OR Committee. All protocols, unless clearly indicated by the applicant, are approved on the understanding that the budget remains the same as in the concept note.
- OR Committee approval is required before **additional** funds are requested for ongoing studies through reprogramming or action memos for core funded studies.

Changes to Approved Protocols/Ongoing studies

When the technical or financial aspects of the protocols are modified after the initial protocol is approved: The study protocol amendments and the revised budget will be shared with OR Committee for approval. Protocols for PMI-funded studies must clearly explain what will be accomplished with the approved PMI funds and not include contingencies that encourage collection of data that can be processed if additional funds become available. The OR Committee needs to be notified regarding any protocol changes as soon as possible to avoid study implementation delays. Similarly, any change of the study budget that is greater than 10% need to be approved by the OR Committee.

Co-funding of OR Activities

When OR activities receive funds from multiple sources, concept notes should clearly explain which components of the study are being covered by PMI and the specific cost associated with these components as well as summarize the co-funding from other sources for the study.

OR Committee Role in the Development and Implementation of OR Studies

The OR Committee – as an advisory and approval body – is not responsible for handling study implementation or study roll-out challenges. PIs of PMI-funded studies must be fully qualified to implement the work stipulated in the protocol, oversee budget and staff, and comply with all local requirements for research including IRB clearances. OR Committee members will not be involved in study implementation and/or negotiations of implementing partners in their OR Committee capacity. OR committee members can provide technical input on an informal basis in their technical capacity as a member of the PMI team at large and/or a specific PMI interagency technical team if asked but such advice should not be considered OR Committee guidance or a substitute for OR Committee review and approval of a PMI OR concept note or protocol. If an OR Committee member is involved in study design or implementation, they are recused from Committee deliberations and decisions regarding the study in question.

Reclassification of OR Study into an Assessment

PMI funds should not be used to change a study that has been rejected by the OR Committee into an assessment unless there is clear statement in the approval form recommending such an action or the study is given a non-research determination by the Committee based on research definition outlined in the *PMI Strategy 2015-2020*.

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](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/>)
- Gather for studies that calculate health estimates
(<http://gather-statement.org/gather-statement/>)

Guidelines for Listing PMI and Agency Affiliations for OR Activities

Please refer to **PMI Policy**.

OR Appendix 1: PMI OR Study Concept Note- Submission Template (for MOP or core-funded OR)

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.):

Interagency technical team(s) consulted (Core-funded OR only):

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

<u>Item</u>	<u>Cost (USD)</u>
<u>Personnel</u>	
<u>Supplies</u>	
<i>NOTE: include a separate budget line for items to be procured through the supply chain mechanism</i>	
<u>Equipment</u>	
<u>Training</u>	
<u>Travel</u>	

<u>Result dissemination/outreach</u>	
<u>Overhead</u>	
<u>Other costs</u>	
Total	

OR Appendix 2: PMI OR Semi-Annual Progress Report Template

Title:

Country (if multiple please list):

Research Institution and/or non-USG collaborators (if applicable): 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 2016-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:

OR Appendix 3: PMI OR Priority List

Programmatic Area	Categories	No.	Priority OR Activities
Prevention	ITNs/IRS/Innovative Vector Control	1	Use field trials, modeling and economic assessment to investigate combinations of “continuous” distribution approaches with the goal of identifying optimal combination of strategies for maintaining equitable LLIN coverage as well as efficient methods for scale-up to regional/national levels; possible channels for delivery should include ANC and EPI clinics, commercial sector, social marketing, schools, health days, community-based workers and others
		2	Measure how best to achieve and maintain LLIN ownership and use, particularly in groups with poor access to LLINs and in those areas or among groups (e.g. migrant/mobile populations in GMS, school-age children) with widespread underutilization. Given recent analysis of data from numerous national population-based surveys, the primary focus in most areas should be on addressing inadequate access/ownership
		3	Continue and expand field studies on physical integrity and durability of LLINs and refine the definition of a failed net; identify laboratory tests and other accelerated testing methodology , such as Resistance to Damage scores, that are strongly predictive of field durability
		4	Evaluate combination nets (i.e. insecticide-synergist nets or dual insecticide nets)
		5	Measure the effectiveness and cost-effectiveness of targeting hot spots for IRS (geographically and based on population) with or without optimizing ITN coverage, specifically in lower transmission areas where hot spots can be clearly defined
		6	Evaluate how to sustain gains achieved through IRS when transitioning IRS out of an area (e.g., high LLIN coverage & use, MDA, etc.).
		7	Evaluate whether there is/is not added benefit (effectiveness) to using non-pyrethroid IRS and pyrethroid ITNs in the same area concurrently
		8	Evaluate strategies to reduce transmission from outdoor/early or late biting vectors. Outdoor biting could, but does not have to, include biting those sleeping outdoors. Specifically, test in combination or separately once a sufficient evidence base is demonstrated: a.) attractive targeted sugar baits b.) spatial repellants c.) treated clothing d) treated hammocks e) environmental management f) other new, emerging strategies as appropriate
		9	Evaluate non-pyrethroid insecticide-treated durable wall liners; if proven to be effective identify the operational issues for scale up.
		10	Develop approaches to improve overall entomology sampling methods, including sampling of the outdoor biting population

		11	Test methods of more readily determining the residual insecticide content on nets and walls, including methods for new classes of active ingredients for use with IRS and next generation ITNs
		12	Identify methods and/or tools to facilitate a streamlined and cost-effective distribution system for targeting specific commodities (e.g. insecticide resistant-designated ITNs; newly adopted vector control tools) to different segments of the population.
Insecticide Resistance		13	Conduct field evaluations of new insecticides and other strategies to mitigate or delay the spread of insecticide resistance
		14	Conduct laboratory, experimental hut and field evaluations of potential new insecticides or formats for malaria vector control once evidence base/potential is demonstrated (including eave tubes, etc.)
		15	Determine the effect of insecticide resistance on efficacy of vector control interventions
		16	Determine how best to monitor the effectiveness of insecticides, specifically in relation to resistance intensity and the "older" mosquito population
		17	Investigate the causes of variation in residual efficacy
Prevention, <i>con't</i>	Transmission Reduction	18	Evaluate new interventions or strategies for reducing malaria in areas with persistently high malaria burden despite efforts to scale up proven interventions
		19	Evaluate different approaches for identifying and targeting "hot spots" for vector control and active case detection/treatment in areas with moderate, seasonal or low transmission. Determine whether these hotspots are generated by differences in human-mosquito contact, or treatment or prevention activities
		20	Measure the impact of case management with ACTs on transmission reduction
	Chemoprevention of Malaria in Children and Malaria Vaccine	21	Evaluate the effectiveness of seasonal malaria chemoprevention where recommended by WHO
Case Management		24	Evaluate and improve clinician adherence to diagnostic testing and treatment including pregnancy assessment where applicable; specifically, identify factors associated with clinicians' non-adherence with diagnostic testing and test methods to increase provider adherence at health facility and community level
		25	Evaluate and improve referral for severe disease/danger signs: a.) Assess the ability of clinicians/health workers at outpatient departments, peripheral health facilities, and in the community to identify severe febrile illness, provide appropriate pre-referral management, and facilitate referral; implement strategies to improve as needed b.) Determine outcomes of children with severe febrile illness who do not complete referral, and identify risk factors for better/poorer outcomes

		26	Evaluate and improve provider practices in the private retail sector: a.) Test methods to scale-up quality-assured diagnostic testing and appropriate, high-quality treatment in the retail private and public sector b.) Identify and test innovative methods and a minimum support package for monitoring the quality and accuracy of malaria diagnosis and treatment in the retail private sector
		27	Identify and test methods to improve patient adherence to updated malaria case management procedures (including adherence to diagnostic testing and to recommended treatments)
		28	Identify reasons for and test means to improve delayed or non-care seeking by caretakers of children with fever within 24 hours in countries where DHS/MIS or other data indicate that prompt care seeking is low
		29	Assess the utility and feasibility of applying new tools for QA/QC of malaria diagnostics
Malaria in Pregnancy		30	Determine the population effectiveness of IPTp at varying levels of transmission and SP resistance; can thresholds at which IPTp is not justified be identified?
		31	Test the effectiveness of new strategies for prevention of MIP, including new drugs for IPTp and community delivery of IPTp
		32	Evaluate the impact of SP drug resistance on IPTp efficacy and birth outcomes
		33	Develop and assess methods for improving ANC attendance and ANC service provider practices including provision of IPTp, assess methods to improve integration of MIP interventions into MCH programs
Elimination and Epidemic Malaria	Elimination	34	In areas approaching elimination, determine the best and most cost-effective vector control measures to address residual foci of transmission.
		35	In areas approaching elimination, test the effectiveness and feasibility of new and existing tools to control outdoor malaria transmission. (Tools to be tested would already have existing evidence of efficacy against outdoor biting).
		36	Evaluate the utility and scalability of more sensitive diagnostic tools (e.g. highly-sensitive RDTs, PCR, etc) in an elimination context, including their utility for reactive or proactive case detection.
		37	Evaluate the effectiveness and feasibility of drug-based approaches (e.g. MDA, tMDA) to eliminate malaria, particularly in residual foci where full-scale of control interventions has been achieved.
		38	Test innovative SBCC approaches to effectively promote appropriate malaria prevention and treatment-seeking behaviors in difficult to reach, high-risk populations (e.g. mobile and migrant workers) or to promote continued adherence to those interventions in populations where malaria transmission has significantly decreased or has been interrupted.

	Epidemic Malaria	39	Conduct a pilot evaluation of focused screen and treat and mass screen and treat interventions in response to early epidemic reporting signals in low transmission settings
		40	Determine appropriate/cost effective methods to identify epidemics
Health Systems		41	Evaluate use of continuous surveys to provide information for health system quality improvement (e.g. remedy drug stock outs, improve health worker performance, and measure other indicators related to program impact and effectiveness)
		42	Investigate how best to increase health worker retention, such as through pay for performance schemes
		43	Evaluate cost-effective and sustainable approaches for improving supply chain for drugs, diagnostics, and supplies, such as an SMS for Health program
		44	Conduct economic and cost-effectiveness studies on integrating delivery of malaria control interventions with mass drug administration for neglected tropical diseases
Behavior Change and Communication		45	Evaluate effectiveness of SBCC interventions addressing different behavioral factors (e.g., self-efficacy, risk perception, social norms) for key malaria behaviors (e.g., patient initiation of services, health worker adherence to guidelines) to inform design of future SBCC interventions.
		46	Demonstrate a dose-response relationship between an SBCC intervention targeting either patients or health care providers and key malaria behaviors for malaria in pregnancy and/or case management (e.g. patient initiation of services, health worker adherence to guidelines) to improve quality and cost-effectiveness of SBCC interventions.
		47	Evaluate the cost-effectiveness of existing and new social and behavior change intervention and channels (e.g., interpersonal communication, mass media, mobile technology) for key malaria prevention and case management behaviors.
		48	Explore the most effective communication channels, approaches, and interventions to improve community awareness of falsified or counterfeit antimalarials.
		49	Identify SBCC interventions for increasing and maintaining key malaria prevention and case management behaviors in pre-elimination settings.
Monitoring and Evaluation	Measurement	50	Compare and determine the most effective, sustainable, moderately costed method to monitor malaria burden and trends in different populations and settings and transmission levels (school-based surveys, cross-sectional surveys including serosurveys, sentinel surveillance sites, health facility surveillance , etc.)

	51	Identification of 'thresholds' (or ranges) that would help countries identify the need to 'shift' the focus of their burden measurement: i.e. the threshold when a country moves from monitoring burden through survey-based parasitemia markers, to facility-based surveillance; the threshold to move from facility-based surveillance to community-based or active surveillance methods; the burden threshold (range) for which conducting an impact evaluation using the current plausibility argument no longer fits; the coverage threshold at which impact could be expected (e.g. coverage levels, duration of time at this coverage, etc.)
	52	Evaluate the accuracy of data on malaria service delivery indicators collected in household surveys
Impact of Malaria Control	53	Conduct studies to show the economic impact of malaria control
	54	Conduct observational studies of the impact of malaria prevention interventions on other vector-borne illnesses and neglected tropical diseases

Commodity Procurement and Supply Chain Management

New/Key Messages

- PMI will consider procuring PBO ITNs in specific settings. Please see the **ITN** chapter for more details.
- PMI will consider procuring next generation nets as part of Unitaid's and Global Fund's catalytic initiative or in support of operations research. Please see the **ITN** chapter for more details.
- PMI is requiring greater standardization of the pyrethroid ITNs in terms of size, shape, color accessories, and package artwork.
- PMI will no longer allow sole source procurement of RDTs.
- PMI recommends that countries in sub-Saharan Africa procure RDTs that test for *P. falciparum* only with the exception of Ethiopia and Madagascar, where *P. vivax* is common.
- Orders for AQ+SP for SMC campaigns must be placed at least one year in advance of planned campaign dates to ensure availability of the needed drugs in advance of the campaign.
- The manufacturer of the only WHO-prequalified injectable artesunate product is now availing all three preparations: the 30-, 60- and 120-mg strength presentations, (previously, only the 60- and 120-mg dosage forms were available).
- Direct warehousing and distribution costs should be included as a separate line item in the MOP from both the commodity and the technical assistance activities.
- PMI supports GS1 standardization across the supply chain. PMI is requiring, in a phased approach, that its vendors include GS1 barcodes on products it procures. Country teams should consider supporting country regulatory authorities to require GS1 standards to eventually improve track and trace capabilities.

Commodity Procurement

Introduction

Under the 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. In addition, FY 2019 holds the promise of a number of new malaria control tools including next generation ITNs, tafenoquine, and new G6PD diagnostics. Careful planning for introduction and monitoring of deployment for next generation LLINs is required. Any introduction of tafenoquine and new G6PD diagnostics would be in an OR setting. Please refer to the **Case Management** chapter for further updates on these two new tools.

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: ITNs, ACTs, SP (for IPTp) and AQ+SP (for seasonal malaria chemoprevention), drugs for severe malaria, other malaria pharmaceuticals (e.g., chloroquine, primaquine, and quinine tablets), 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. Additionally, most commodities necessary to implement national surveys (e.g., Malaria Indicator Survey) do not fall within the scope of PMI's malaria commodity procurement partner and alternative arrangements should be made. Please contact the

GHSC-PSM TO2 COR as soon as possible when discussions around the procurement of these malaria-related commodities for national surveys begin. Please also consult the **SM&E** chapter for greater detail around the procurement of those commodities (particularly RDTs and ACTs). As with all procurement, lead times can be lengthy so any research or studies that require commodities should plan sufficiently in advance (see **Commodity Procurement and Supply Chain Appendix 1**).

Insecticide-treated nets

Currently, PMI procures nets with specific approval through the WHOPES. However, with the transition from WHOPES to WHO Prequalification for Vector Control Products, PMI will eventually use WHO PQ listing as the requirement for procurement eligibility. Those products currently approved through WHOPES will convert to WHO PQ with an interim approval. Manufacturers were required to submit a conversion package to WHO PQ by the end of December 2017 to receive interim status. PMI is monitoring the conversion process and once a sufficient number of ITNs have converted to cover PMI requirements, we will require that ITNs we procure have a WHO PQ listing.

Currently, there are 19 WHOPES-approved ITNs. This list includes five PBO ITNs and the Interceptor G2 net, a next generation net that includes chlorfenapyr in addition to a pyrethroid.

The PBO nets have a new WHO policy recommendation (September 2017) that now makes them eligible for PMI procurement. The **ITN** chapter of this guidance outlines PMI's approach to implementing the new policy, including the criteria to meet in order to make them eligible to procure.

The Interceptor G2 ITN does not have a WHO policy recommendation, however, PMI is joining Unitaid and the Global Fund in supporting a catalytic initiative that will establish a co-payment mechanism to bring the cost of next generation nets close to the cost of a standard pyrethroid net and support evidence generation on the effectiveness of the next generation nets. It is anticipated that the initiative will be launched in the third quarter of 2018. Next generation nets, specifically the Interceptor G2, will be eligible for procurement under this initiative and for approved operations research. Further guidance on deployment of next generation nets, including the criteria that must be met, is provided in the **ITN** chapter.

For technical and programmatic reasons, PMI does not procure ITNs 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. It is not yet clear how WHO PQ will manage equivalency. 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/itm_procurement_specifications.pdf?sfvrsn=4.

PMI currently procures over 20 different types of ITNs across dimensions, shape, color, and material. The variation has been driven, in part, by net user preferences. However, a recent PMI-funded analysis demonstrates that while net users do have preferences, these preferences do not impact use.¹⁸⁰ The analysis showed that the biggest factor in use was that a net was provided, not that it met user preferences. With this analysis, the supply chain team worked to identify opportunities to rationalize ITN procurement to achieve best value. The Supply Chain team reviewed the ITN market including conducting an ITN cost of goods analysis, discussed the market and procurement approaches with other global ITN procurers (Global Fund and UNICEF), and conducted a survey of ITN manufacturers.

The landscape analysis highlighted that while ITN prices have dropped significantly over time, there were additional lead time and cost savings that could be gained through greater standardization. Additionally, standardization would lead to greater interchangeability allowing flexibility in moving nets across orders/countries to meet unanticipated demand, and smoothing out production for manufacturers, which also leads to cost and time savings. The need to demonstrate greater efficiencies and value for money is even more important in the current funding environment and with the need to secure the additional resources to deploy more costly, new generation ITNs to combat growing pyrethroid resistance.

The new standards for PMI procured pyrethroid ITNs effective beginning with FY 2018 MOP orders are:

1. Standardize shape to rectangular
2. Standardize ITN height to two heights: 150 cm and 170 cm
3. Standardize ITN color to white (no other colors)
4. Do not include hooks and nails in ITN package
5. Limit packaging artwork to PMI logo, standard language (e.g., not for retail sale) and pictorial instructions

180 Koenker, H. and Yukich, J.O. Effect of user preferences on ITN use: a review of literature and data. Malaria Journal 16:233 (2017) (<http://rdcu.be/tal2>; accessed, August 2017)

If a country needs to deviate from these standard specifications for regulatory reasons, they must justify the additional cost in consultation with the PMI Headquarters Supply Chain and ITN Teams and be granted an exceptional approval from PMI Agency Leads.

PMI requires that all ITNs procured for routine distribution include individual bags. To eliminate waste, campaign ITNs may be procured in bulk packaging as these are usually brought close to the end user and distributed within a matter of hours. However, if a bale were to be opened in a routine system, it could take weeks or months to hand out the nets from that bale at the facility. During that time, these nets are more vulnerable to dirt, rats, or moisture than individually packaged nets. Furthermore, if the ITN is distributed at a central point, like a health center; and then transported some distance to individual homes, there is a risk that the ITN might be damaged before it is hung. For this reason, programs should procure ITNs using individual bags for use in continuous or routine distribution. If a country feels they have a reason to procure ITNs in bulk packaging for a distribution system other than campaign, a justification must be submitted with the order request.

There are ongoing durability studies which may impact procurement policy in the future (see the **ITN** chapter for information on ITN durability).

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 ITN distribution often requires planning for more regularly spaced orders, adequate permanent warehousing options, and more consistent net quantities. **Regardless of the distribution mechanism(s), ITN lead times are approximately ten months, and must be accounted for during planning processes** (see **Commodity Procurement and Supply Chain Appendix 1**).

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, 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 with more than one first-line drug), a prioritization of one of the first-line drugs for PMI procurement is required. With the introduction of SMC in several PMI countries, a number of countries switched to two first line ACTs (adding AL for the lower weight bands). Exceptions to this policy require approval from Agency Leads. 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)¹⁸¹ (such as the US FDA) or the WHO PQ Program.¹⁸² Stringent regulatory authorities employ a robust drug dossier review to consider the safety, efficacy, and quality of pharmaceuticals intended for human use.¹⁸³ Although several SRA-approved ACTs have come to market in the last 10 to 15 years, PMI has expanded its procurement to include WHO PQ ACTs to ensure sufficient supply to meet demand. While the WHO is not a regulatory body, their PQ for artemisinin-based and other products indicated in the treatment of malaria applies a robust dossier and manufacturing site review process, resulting in approved products of known quality, safety, and efficacy.¹⁸⁴

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® (pryronaridine/artesunate).¹⁸⁵ There are also several fixed-dose combination ACT formulations with approval through the WHO PQ. The PQ approval process operates on a 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 PQ and therefore added to the WHO prequalification list¹⁸⁶ 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.

Since 2015, there have been a number of new fixed-dose combination formulations of artemether-lumefantrine approved through the WHO PQ. Specifically, there are now several different co-blister oral presentations: 80 mg artemether/480 mg lumefantrine, 60 mg artemether/360 mg lumefantrine, and 40 mg artemether/240 mg lumefantrine. These new presentations are intended to improve compliance relative to the previous 20 mg/120 mg presentation, which placed a relatively heavy pill burden on the recipient. Unlike the older

¹⁸¹ Currently, the drug regulatory authorities of the European Union, Japan, USA, Canada and Switzerland have implemented International Council for Harmonization of Technical Requirements for 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/membership.html>

¹⁸² <http://apps.who.int/prequal/query/ProductRegistry.aspx>

¹⁸³ 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.

¹⁸⁴ Historically, the WHO PQ approved only ACTs antimalarials (co-blistered products and now co-formulated). Recently, however, non-ACTs used in SMC have been approved through the prequalification program.

¹⁸⁵ PMI has yet to receive a request from any PMI country to procure Pyramax.

¹⁸⁶ <http://apps.who.int/prequal/query/ProductRegistry.aspx>

historical 20/120 tablet presentations, these newer formulations do not allow for weight band substitution. Like any newly procured pharmaceutical, please take into consideration the registration status and the potential need for an importation waiver if the product is not registered.

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.¹⁸⁷ 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 US 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 testing is conducted at qualified laboratories; ISO-17025 compliance and/or a WHO prequalification are acceptable facilities.

Historically, average lead times for ACTs have been about six to eight months from time of receipt of a completed requisition order form (and average lead times for other anti-malarials and essential medicines are about ten to fourteen months). Please see the lead time table in **Commodity Procurement and Supply Chain Appendix 2.**

Sulfadoxine-pyrimethamine

PMI supports the procurement of SP for IPTp to ensure a quality product and to contribute to filling any identified gaps in the country's annual SP quantity needs. To date, there has been no WHO PQ or SRA approved options for SP;¹⁸⁸ as such, PMI has sourced SP from pre-approved wholesalers.¹⁸⁹ However, there is currently one dossier up for review by the WHO PQ for monotherapy SP intended for use in pregnant women as part of IPTp, although it has been under review for over two years. It is unclear when/if it will achieve prequalification.

Historically, SP lead times have been lengthy, around 10-11 months from date of receipt of completed requisition order form to delivery in country. Confounding already long lead times are issues around lack of registered product in the presentations required by PMI-supported

¹⁸⁷ Please see most recent ADS 312 for more information on currently approved wholesalers.

¹⁸⁸ SP is included in two co-blistered presentations currently approved through the WHO PQ. However, neither of those presentations is indicated for use in IPTp.

¹⁸⁹ Please see most recent ADS 312 for more information on currently approved wholesalers.

countries and 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

Since the 2012 WHO policy recommendation regarding SMC, several PMI countries in the Sahel have begun implementing SMC programs. The SMC intervention entails the administration of up to a maximum of four consecutive monthly 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. PMI will be implementing SMC in up to eight countries in 2018 and can procure AQ+SP for use in SMC campaigns. Currently, there is one WHO prequalified vendor for the co-blister presentation of AQ+SP (i.e., packaged in a blister pack together for ease of use). Historically, the limited production capacity has led to challenges in implementing SMC in PMI-supported countries. As of December 2015, there are two dossiers for a dispersible presentation of AQ+SP under review by the WHO PQ. PMI can procure the dispersible formulation through approved wholesalers. Approval through the WHO PQ is expected in early 2018. Of note: there is a dispersible formulation under review with a slightly different strength. For countries implementing SMC, please note that there is a section in the new MOP template including commodity gap tables for AQ+SP.

Given the time-sensitive nature of SMC campaigns (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 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-supported access to sufficient quantities of the globally-limited supply of qualified product.¹⁹⁰ **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.**

Severe malaria medicines

¹⁹⁰ 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. As of December 2017, these two products are still under review by the WHO PQP.

Lead times for all preparations of medicines indicated in the management of severe malaria are lengthy and should be taken into consideration by country teams during quantification and forecasting needs. PMI is able to procure any of the three available WHO prequalified injectable artesunate presentations (30-, 60- and/or 120-mg formulations). There are also three different strength rectal artesunate suppository presentations available (50-, 100- and/or 200-mg formulations). Of these, none are approved through the WHO PQ but there are two 100-mg formulations from two different manufacturers with Expert Review Panel approval by the Global Fund. Approval through the WHO PQ is expected to follow. WHO provided updated guidance on the use of rectal artesunate suppositories, recommending that countries use the 100mg formulation. Currently, PMI is not requiring any presentation over the other but is noting WHO's recommendation. Please see the **Case Management** chapter for additional information.

Injectable artemether and quinine are also available for procurement, although neither has approval though the WHO PQ. Please see the **Case Management** chapter for further information on the appropriate selection of injectables. Auxiliary medicines used in the management of severe malaria are also available for procurement (e.g., glucose/normal saline for intravenous use, paracetamol, etc.). None of the aforementioned products has approval from a stringent regulatory authority, and there may be potential issues around registration, particularly with rectal artesunate preparations. Please work closely with your in-country supply chain implementing partner during supply and demand planning for these and all malaria-related commodities. For additional information, please see **Appendix 3**.

Rapid diagnostic tests

To help countries select RDTs appropriate for use given country-specific epidemiology, WHO, FIND, and CDC have conducted seven 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 1–7 of malaria RDT product testing can be found here:<http://apps.who.int/iris/bitstream/10665/258597/1/9789241512916-eng.pdf?ua=1>.

Building on the results of seven 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 2016): <http://www.who.int/malaria/publications/atoz/rdt-selection-criteria.pdf?ua=1>. In 2018, product testing will be integrated into WHO's diagnostic pre-qualification program. Currently, products from three of PMI's RDT suppliers are pre-qualified. As of December 2017, WHO determined that there are sufficient numbers of the HRP-2 *P. falciparum* RDT prequalified. Therefore, it recommends that only WHO PQ *P. falciparum* RDTs should be procured. There is an insufficient number of WHO PQ RDTs for the combo and pan RDTs, so WHO recommends that procurers continue to use FIND/WHO product testing results for combo and pan tests. PMI is reviewing the list of HRP-2 *P. falciparum* RDTs that have received WHO PQ with the list of *P. falciparum* RDTs that have passed PMI's quality review to determine if we should require WHO PQ or continue with the RDTs that have passed the most recent round of product testing.

Two 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 with the exception of Ethiopia and Madagascar where *P. vivax* is common; see the **Case Management** chapter for a more detailed explanation).
2. The product is on the WHO RDT procurement selection note or has received WHO pre-qualification.

A recent analysis of procurement data has shown that prices for RDTs that are sole-sourced are up to twice the price of the same RDT when there is open competition. An additional analysis undertaken by MalariaCare found that all countries either were using multiple brands of RDTs concurrently or had switched brands. Health workers were able to manage multiple RDT brands or switching brands without significant issues in use. Supervision and job aids supported health workers in managing the change. As such, **PMI will no longer allow sole source selection of RDTs based solely on health worker training concerns beginning with FY 2018 MOP orders.** The Case Management team will help countries work through the implications of this new policy including supporting the development of training and job aids focused on managing different RDTs rather than a single RDT.

WHO has identified malaria parasites with HRP-2 deletions in limited areas of sub-Saharan Africa (see **Case Management** chapter for more details). In settings where HRP-2 deletions are sufficiently prevalent, HRP-2 RDTs may no longer be accurate, and RDTs using non-HRP-2 antigens may be needed. Single-species tests that detect two *P. falciparum* antigens (HRP2 and

pLDH) with two test lines are now available. These tests are difficult to interpret in the case of conflicting results and do not generally provide a diagnostic advantage in detecting symptomatic malaria. **Given the challenges in interpretation and the limited settings experiencing prevalent HRP2 deletions, PMI will not procure two line multi-antigen RDTs for *P. falciparum*.** Some manufacturers also produce a single line RDT that contains antibodies to both HRP-2 and pLDH. It is hoped that this type of test might be a programmatic solution in countries with HRP-2 deleted parasites in limited areas. These tests, though, have not yet been validated against HRP-2 deleted parasites (although WHO is pursuing this validation) and, therefore, cannot at this time be recommended for use in areas where HRP-2 deletions have been identified. Countries that either have evidence of HRP-2 deleted parasites or that suspect that such deleted parasites exist in their countries should contact the PMI Case Management Team for guidance on methods to document the presence of these parasites and for recommendations on alternative RDTs if such deletions are detected. Please also refer to WHO guidance (<http://apps.who.int/iris/bitstream/10665/258972/1/WHO-HTM-GMP-2017.18-eng.pdf>).

RDTs that test for glucose-6-phosphate dehydrogenase (G6PD) deficiency have recently been developed by a couple of manufacturers, but have not yet received a recommendation from WHO. A PMI-supported field test of one brand of this RDT (CareStart®) demonstrated that they can detect major G6PD deficiencies, but can miss some minor deficiencies. There are several more sensitive G6PD tests under development, most of which require a device (i.e., not an RDT) and are estimated to be available in 2019. As G6PD testing is not required prior to administration of low-dose primaquine for radical cure of *P. falciparum*, such testing is only indicated prior to radical cure treatment for *P. vivax*. Therefore, requests for procurement of G6PD tests will be considered on a case by case basis only from PMI countries with ongoing *P. vivax* transmission. If relevant in your country programs, please contact the PMI Headquarters Supply Chain and Case Management Teams to discuss the planned indications and deployment of these G6PD RDTs.

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 the **Entomological Monitoring and Insecticide Resistance** chapter.

Lot 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, RDTs, and ITNs. All pharmaceuticals approved by non-SRAs, including those approved through the WHO PQ, must be tested prior or concurrent to shipment (depending on how they were approved and on the procurement history with PMI and historical volumes procured) in accordance with PMI standard operating procedures and work instructions (detailed documents developed by the QA partner for PMI, SGS). For all pharmaceuticals, there is a quality testing strategy, with WHO-prequalified and wholesaler-sourced products requiring 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. Additionally, while routine testing of SRA-approved products is not necessary, PMI's QA strategy now includes an annual sampling of retain samples for all SRA-approved products, based on volumes procured, for compendial testing.

Like pharmaceuticals, all RDT lots are subject to quality control testing through WHO-supported laboratories to ensure appropriate test performance and long-term stability. In 2018, it is likely that arrangements for lot testing of RDTs will transition. Once the new arrangements are finalized, updated guidance will be circulated.

ITNs undergo a physical inspection at the manufacturing site to identify any defects prior to release for shipping. Additional mechanical and chemical testing based on WHOPES standards is undertaken on samples concurrent to shipping. PMI has worked with the Global Fund and UNICEF to harmonize pre-shipment inspection and testing protocols for ITNs.

All test reports (of pharmaceutical, RDT, and ITN quality) are kept on file electronically with PMI's quality assurance partner and with the PMI Headquarters Supply Chain Team. These may be obtained upon request by PMI country teams and regional advisors.

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, ITNs, 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 stock outs have been a recurrent

problem for country programs and may continue with potential decreases in donor contributions. PMI has observed that transition to a new Global Fund grant has posed supply risk in the past. If a PMI focus country will be transitioning to a new grant, the country team may consider some contingency planning for potential delays in Global Fund initial orders.

As in previous years, several PMI-supported 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 flexibility in commodity funding.¹⁹¹ 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. Because of the relatively short shelf life of most ACTs (24 months), the stockpile stock can often fall under countries' importation shelf life requirements of 75 to 80 percent remaining shelf-life. As the stockpile stock is typically drawn on when countries are facing stock shortages and the amounts provided are typically only 1 to 2 months of stock, countries can accept lower shelf life product without risk of expiry. For example, if a country is experiencing a stock out and is provided with a 2 month supply stockpile stock with 50% shelf life (12 months remaining shelf life), this stock will be used before it expires in a year. As such, country teams are encouraged to work with NMCPs and drug regulatory authorities to seek waivers for the importation of lower shelf-life product in these situations.

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,

¹⁹¹ 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 only used rarely for the procurement of LLINs.

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 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 indicate that 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. Countries should identify options to mitigate the risk of theft, including regular inspection of storage facilities, review of inventory records, and comparison of logistics and case management data to identify significant discrepancies between reported cases and consumption. Countries should also work to strengthen the national regulatory authority.

With regards to expiry, PMI and its 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 US-donated commodities falls under waste/fraud/abuse statutes.

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. Global Health Supply Chain – Procurement and Supply Chain Management (GHSC-PSM)
Malaria Task Order (TO2) – The GHSC-PSM IDIQ and Malaria task order were awarded to

Chemonics in April 2015. The malaria task order supports USAID's implementation of malaria programs through the procurement, management and delivery of high quality, safe, and effective malaria commodities; the provision of on-the-ground logistics, supply chain, and related systems strengthening technical assistance and implementation capacity; provides technical leadership to strengthen the global supply, demand, financing, and introduction of existing and future malaria commodities. PMI focus countries are required to use PMI's central mechanism for all non-IRS commodity procurement needs. 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, ITNs, SP, etc. To further visibility and realistic budgeting, the in-country direct warehousing and distribution costs should be included as a separate line item in the MOP from both the procurement and the technical assistance activities.

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., ITNs for a joint campaign where UNICEF is already procuring a portion of ITNs 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 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.

Global Standards through GS1 Implementation

PMI, in coordination with other USAID health supply chain divisions, is preparing the USAID global supply chain system to implement global standards using GS1. While these standards are being implemented globally in markets like Argentina, Turkey, the United States, and the European Union, adoption has been low in developing and emerging markets to date.

Current global health supply chains are a collaborative effort between multiple donors including USAID, Global Fund, UNICEF, etc. What often starts as a network of disparate global supply chains managed by different donors and procurement agencies, often converge when products reach a country's central warehouse. These supply chains rely on trading partners to share data. However, the current approach to managing and sharing supply chain information undermines the value and use of global health supply chain data. Implementing GS1 ensures visibility through the supply chain in the areas of product and location identification, data capture, and master, transactional, and event data exchange. On a global level, this increases PMI's ability to maintain updated product data from suppliers. In addition, other donors such as Global Fund are looking at implementing GS1 into their supply chain, enabling smoother data exchange for the future when looking towards coordinated supply planning. GHSC-PSM is also working with suppliers for their products and packaging to be GS1 compliant, which includes a GS1 barcode for automated identification and data capture to decrease time and mistakes, therefore lowering overall costs, when shipping and receiving products in warehouses both at the global and in-country levels and ultimately at facilities if country systems have adopted these standards. It also increases exchangeability of products between countries.

PMI also supports technical assistance for implementation of global standards in country to improve visibility including identification of counterfeit products and eventually moving towards a full track and trace system. As at the global level, this is a multi-year endeavor. It depends largely on the maturity of the supply chain system and commitment of country stakeholders in

driving use and adoption. Given the relatively new position of global standards as a component of systems strengthening, it is recommended that country programs consider a Learn – Assess – Plan – Pilot – Scale approach to develop a plan that looks towards building an enabling environment for future implementation.

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, and thereby allowing improved 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 relatively limited products and typically with shorter shelf lives, complex dosing requirements, and varied demand due to the seasonality and dynamic epidemiology of malaria.¹⁹² 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, PRH, MCH, etc.) and where other health elements are relying on government systems, PMI investments must be coordinated with other USG health supply chain investments. Additionally, Global Fund recently established a supply chain department whose strategy seeks to more actively address country level supply chain constraints. In 2017, the Global Fund began conducting supply chain assessments with the eventual goal of completing assessments in 20 countries. Country teams should be aware of

¹⁹² Guidelines for Managing the Malaria Supply Chain. <https://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/guidelines-for-managing-the-malaria-supply-chain.pdf>

Global Fund's supply chain plans for PMI countries and identify what impact they may have on PMI supply chain investment.

Logistics Management Information Systems

A logistics management information system (LMIS) is the foundation of a supply chain management system. Improving data visibility along the entire supply chain is critical to improving overall supply chain performance, forecasting accuracy, optimizing inventory levels, and improving supply chain accountability. Strengthening LMIS and warehouse management systems is the second highest USAID supply chain investment only following commodity procurement in terms of cost. Country teams should prioritize strengthening LMIS in their supply chain funding.

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, multiple stakeholders are involved in these efforts and PMI should coordinate support and participate in discussions with these other stakeholders. Electronic LMIS (eLMIS) systems have been established in some PMI-supported countries. The time and budget required to implement an eLMIS is dependent on the existence and level of functionality of a paper based LMIS already established in country. Multiple LMIS software options are available to countries interested in an eLMIS but the business processes, including clearly defined roles and procedures, should drive the choice of technology. PMI country teams should participate in discussions on whether to transition to an eLMIS to ensure all key issues are taken into

consideration.¹⁹³ For example, leadership support from the MOH or other local group, internet access, IT support, computer access, etc. should be taken into account when transitioning to an eLMIS system.

Based on the maturity of a country's LMIS, PMI's investment should evolve. For example, countries with weak or no systems efforts should focus on establishing a basic system of recording and reporting logistics data, and then build in automation (eLMIS) as far down the supply chain as feasible. With a system in place the focus may shift to, improving reporting rates through supervision, and using data visualization (e.g., dashboards) to improve supply chain decision-making.

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 and is registered by the National Drug Regulatory Authority (in the absence of current registration, a waiver will be needed, and if approved, is a lengthy process that could delay arrival and distribution of commodities). Other issues to consider relate to logistics. What are the storage requirements of a product at the central, health facility and community level? Is there sufficient capacity within the country to distribute and manage the products? Do they require cold chain during storage and distribution? What is the shelf-life of the product? Have the requisite health care workers been properly trained in the management of the commodity? 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 appropriately 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. This is usually done in two steps. First forecasting total need and then developing a supply plan that builds in existing inventory, current orders, and available funding from all sources. The supply plan determines the quantity and frequency of orders/shipments. Countries may use a variety of tools, including the RBM

¹⁹³ eLMIS Selection Guide :Electronically Managing Supply Chain Information. <https://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/elmis-selection-guide-electronically-managing-supply-chain-information.pdf>

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 supports use of 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 of the supply plan to adjust for changes in consumption and when shipments arrive. **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-supported countries, this remains an area for ongoing priority attention. In general, countries should conduct annual commodity forecasts, ideally with quarterly updates of the supply plans. These forecasting exercises are also part of the Global Fund concept note preparation. 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 Unit¹⁹⁴ that is charged with this responsibility, in addition to general coordination of malaria supply chain management. Once quantification and forecasts have been developed, periodic (quarterly) reviews of supply plans should be conducted to ensure timely adjustments are made based on actual deliveries, consumption patterns, and planned procurements.

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 past years' MOP reviews, an interagency team worked to develop a gap analysis tool 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.

¹⁹⁴ Logistics Management Units: What, Why, and How of the Central Coordination of Supply Chain Management. <https://www.pmi.gov/docs/default-source/default-document-library/tools-curricula/logistics-management-units-what-why-and-how-of-the-central-coordination-of-supply-chain-management.pdf>

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 Distribution Practices standards, for all products at all levels of the system. Policies will be in place to prevent expiries (e.g., first-to-expire, first-out or procedures for what to do with short-dated stock, etc.) 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. Fees for storage and distribution range from between 5 and 15 percent based on services provided (e.g., some central medical stores only deliver to the provincial or district level while others clear, store and deliver to the health facility level). Payment of these fees requires pre-approval by the U.S. Global Malaria Coordinator. Please contact PMI HQ for more information on obtaining prior approval for the payment of service fees for warehousing and distribution. Where transparency and accountability is in place, PMI uses government owned or managed warehouses and distribution systems (e.g., central medical stores). In these cases, PMI will provide technical assistance to ensure supply chain management systems maintain or improve their performance, efficiency and accountability.

Where accountability and transparency are not in place or where storage and distribution systems do not meet Good Distribution Practices 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.

A number of countries are moving away from directly operating warehousing and distribution for the public health supply chain and instead are outsourcing these services to private logistics providers. In such situations, the technical assistance focus should shift from building direct warehousing and distribution capacity to strengthening contract management of third party logistics providers and oversight of the supply chain.

Funding for direct warehousing and distribution services, either paid to parastatals or implemented by a supply chain partner, should be included in a separate line from commodity or pharmaceutical management technical assistance costs.

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 supply chain and logistics cycle, through to the end user. PMI country teams should work with NMCPs 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 and RDT 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.

An important component of the quality assurance continuum is post-marketing surveillance (PMS), which can provide general information not only on the relative quality of medicines circulating in the market, but also help pinpoint weaknesses with the supply chain. When considering whether this is an appropriate use of PMI funds, country teams should take into account the scope/scale of interest, sampling methodology, private vs public market, and as importantly, intended use of data after collection and the longer term strategy for implementing a PMS activity. As a one-off activity, data collected will have little use, unless used to highlight an acute known or suspected problem (e.g., collaboration with USAID's OIG, for example). Moreover, there are a limited number of partners whose scope of work can accommodate these activities.

It is also important to distinguish PMS from pharmacovigilance, an activity not supported with PMI funds. Pharmacovigilance is a complex series of processes generally used to establish causal relationships between a previously unknown adverse drug reaction (or any drug-related problem)

and a specific drug once the drug is circulating among the general population.¹⁹⁵ And while a critical part of both a mature drug regulatory system and meaningful public health program, even nascent pharmacovigilance activities require substantial financial and human capital; it should not be confused with basic post-marketing surveillance activities. To establish and maintain a functional pharmacovigilance system requires significant support over an extended period of time.

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, injectable artesunate, 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 focus countries are required to provide data for the PPMRm, and PMI country teams should routinely review their countries' PPMRms to flag low stocks. The PPMRm can be accessed at www.ppmrm.org.
- **End-Use Verification (EUV) Survey:** 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-supported countries two 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. In countries

¹⁹⁵WHO defines pharmacovigilance as “The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.”

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. Countries are encouraged to reach out to the PMI HQ EUV team and their supply chain technical assistance partner to discuss the best sampling approach, while also keeping in mind costs. Any decisions to stop the EUV and use another tool must receive HQ approval.

- **Task Order Malaria (TOM) Table:** PMI monitors the status of its commodity orders through the Task Order Malaria (TOM) table produced weekly by PMI's central procurement mechanism. The TOM table provides information on each active order (i.e., orders remain on the TOM table until two weeks after delivery), including order quantities, agreed delivery dates, and expected delivery dates by country. PMI country teams are encouraged to review orders on a regular basis and reach out to its supply chain backstop with any questions.

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 2: Average Lead Time Table

Product Category	Product	RO Validation	Sourcing Activity	Approval and PO Release	Average Production Time	QA	Mode of Transport	Average Delivery Time	Total Lead Time (RO Creation to Delivery)	
ACTs	AL	1	5	1	10	8	Air	8	33 weeks	8 months
	ASAQ	1	5	1	10	8	Air	8	33 weeks	8 months
Severe Malaria Pharma	Artesunate Suppositories	1	5	1	13	8	Air	8	36 weeks	8 months
	Artesunate Inj	1	0	2	16	10	Air	8	37 weeks	8 months
	Artemether Inj	1	5	1	16	10	Air	8	41 weeks	9 months
	Quinine Inj	1	5	1	16	10	Air	8	41 weeks	9 months
Other Malaria Pharma	Quinine Tab	1	5	1	12	8	Air	8	35 weeks	8 months
	SP	1	5	1	16	8	Air	8	39 weeks	9 months
	SPAQ	1	5	1	16	8	Air	8	39 weeks	9 months
	Other Malaria Pharma ¹	1	5	1	16	8	Air	8	39 weeks	9 months
LLIN	-	1	4	1	20	8	Ocean	11	45 weeks	10 months
Lab Supplies	-	1	3	2	10	0	Air	8	24 weeks	6 months
Essential Medicines²		1	5	2	12	5	Air	8	33 weeks	8 months
RDT	-	1	5	1	6	5	Air	8	26 weeks	6 months

1) This includes products such as chloroquine and primaquine

2) QA requirement and lead-time on Essential Medicines will vary greatly based on manufacturer and product

Commodity Procurement and Supply Chain Management

Appendix 3: Assumptions for Quantification of Parenteral Severe Malaria Drugs

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 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 (4) vials of parenteral 60-mg artesunate for an average man weighing 170 pounds, or about 77 kilos (where 1 kg = 2.2 pounds) as an **initial loading dose**. As the WHO treatment recommendation calls for a **total of three (3) parental doses over 24 hours**, the dosing schedule in this example would therefore be four vials initially, followed by the second dose of four vials 12 hours later, followed by the third and final dose 24 hours after the initial dose, again of four vials. That would be a total of 4 vials x 3 doses = 12 vials total to treat one average sized man using the 60-mg preparation.¹⁹⁶

For rectal artesunate dosing, WHO treatment guidelines, third edition, recommend a 10 mg/kg pre-referral dosage. Per the October 2017 WHO information note, if using a 100 mg suppository, this would be one suppository for children 2 months up to 3 years and two suppositories for children 3 years up to 5 years. Available preparations include 50-, 100- and 200-mg capsule suppositories. As a reminder, rectal artesunate is indicated in children less than six years old; use in older children and adults directly contradicts WHO treatment guidelines. Again, country teams will have to make estimates based on available population data. Calculations for pre-referral

¹⁹⁶ Injectable artesunate has two administration routes: intravenous (as a bolus) or intramuscular. Also of note: although there are three WHO-prequalified strengths of injectable artesunate, only the 60- and 120-mg dosage formulations are available for public sector procurement. The 30-mg dosage formulation is only offered for private sector procurement by the WHO-approved manufacturer, Guilin.

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 requisition order forms in advance of procuring parenteral severe malaria commodities, the PMI Headquarters Supply Chain Team (which includes a clinical pharmacist) can be available for consultation to help prepare accurate requests (based on available data).

Elimination

New/Key Messages

- In 2017, WHO published an updated *Framework for Malaria Elimination*¹⁹⁷, revising its recommended terminology and strategy placing all endemic countries on a continuum of transmission. This framework no longer uses the term pre-elimination previously defined as test-positivity rate less than 5% (of all febrile patients tested) throughout the year. As the PMI Strategy 2015-2020 includes an objective on pre-elimination, PMI is maintaining this term solely for tracking progress towards this objective thru 2012. Going forward, PMI will align its terminology with that recommended by WHO in this framework.
- Although many PMI countries have areas of very low transmission, efforts to move towards elimination will not be successful if the necessary financing, health systems, and human capacities are not in place to implement and track elimination activities.
- In countries where malaria burden varies significantly, and thus sub-national elimination is being pursued, **priority for PMI funding should be given to supporting interventions to further reduce mortality and morbidity in high burden areas.** However, in such settings, limited support for elimination activities can be considered by PMI country teams, but should be balanced against the need to scale up core control interventions to achieve PMI's primary objectives to reduce morbidity and mortality.
- As countries approach elimination, the purpose of entomological monitoring shifts to focal investigations in areas of residual transmission and interventions tailored to particular environmental characteristics and site selection for entomologic monitoring becomes more dynamic and driven by epidemiological data.
- Timely, complete, and accurate recording and reporting of passively-detected, confirmed malaria cases diagnosed in both the public and private sectors is the foundation for tracking progress and identifying cases and foci for additional, intensified response measures in elimination settings.
- The role of new tools and approaches, such as focal or mass drug administration and highly-sensitive diagnostic tests, remains unclear and, therefore, they are not recommended for routine implementation. PMI is conducting operational research to identify their appropriate application and feasibility, where appropriate.¹⁹⁸
- Countries that have strategies for elimination (e.g., Burma, Cambodia, Ethiopia, Madagascar, Senegal, Thailand/Regional, Zambia, Zanzibar, Zimbabwe) should ensure that elimination goals, objectives and targets, and the geographic focus of those efforts are included in the Strategy Section of their FY 2019 MOPs. The Pre-Elimination Chapter previously included in the FY 2018 MOP will not be in the FY 2019 MOP.

¹⁹⁷ <http://www.who.int/malaria/publications/atoz/9789241511988/en/>

¹⁹⁸ More information on mass drug administration can be found in the **Vaccines and Other Preventive Approaches** chapter of the technical guidance.

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 national and regional malaria elimination, and the longer-term vision of eradication. Over the past century, more than 100 countries, including the United States, have eliminated malaria from within its borders. Most recently, several countries in WHO’s Eastern Mediterranean and American Regions, and the entire European Region have interrupted local transmission and have been or are being certified by WHO as having eliminated malaria. Although elimination is being achieved globally, most PMI countries in sub-Saharan Africa continue to focus on control and further reduction of malaria mortality. Within the context of this scale-up, a sub-set of PMI-supported countries have made tremendous progress in reducing malaria mortality and morbidity and are now building the systems required to move towards elimination.

In 2015, three noteworthy global policy documents were released—the WHO’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 countries to set goals for malaria elimination and for global 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*. Pre-elimination phase, as previously described by WHO, includes areas where universal coverage of preventive and case management interventions has resulted in reduced malaria transmission to a level where monthly test-positivity rate remains less than 5% (of all febrile patients tested) are confirmed to carry malaria parasites each month throughout the year and health information systems are in place to track that progress.

In 2017, WHO released its updated *Framework for Malaria Elimination* that includes updated recommendations on terminology and classification of the stages as countries transition towards elimination. Among those changes, the term pre-elimination is no longer recommended for use. To align with this recommendation, PMI will only continue to use the term pre-elimination to monitor against the objective in its current Strategy. For other contexts, PMI headquarters and country teams are encouraged to align its terminology and tracking of country progress with WHO’s updated guidance.

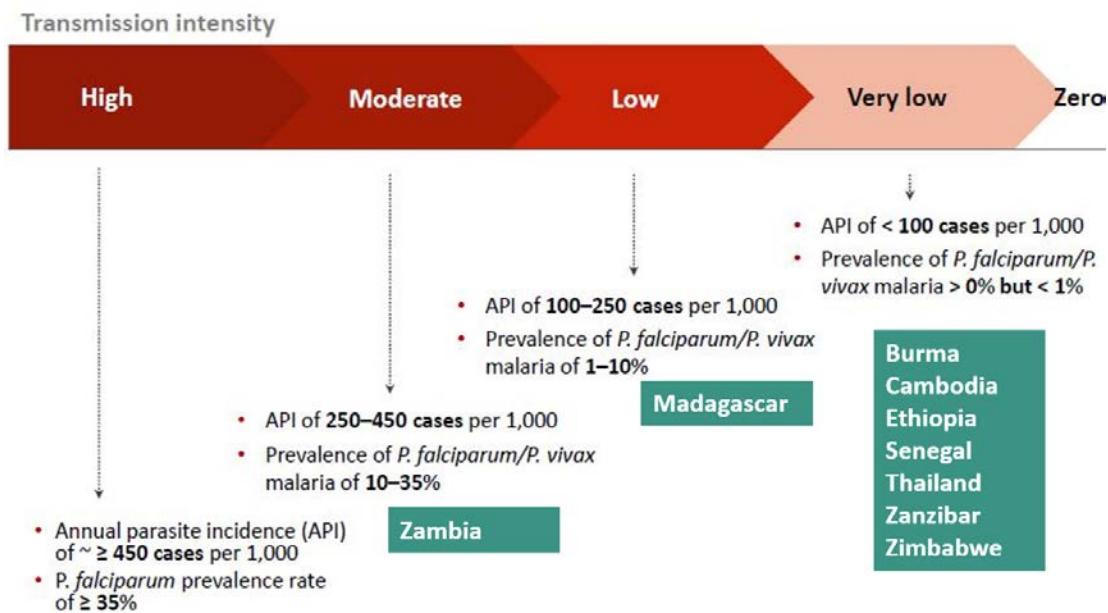
Malaria elimination builds on the foundation laid by intensive malaria control, with universal coverage of efficacious interventions for vector control among populations at risk and case management. As malaria-affected countries fully scale up core control interventions, it is likely

that some areas will witness significant reductions in malaria burden while burden remains high in others. Therefore, malaria control and elimination activities must increasingly be tailored and focalized based on malaria risk stratification to address the specific needs of areas with differing epidemiologic profiles. This can only be accomplished if countries have the capacity to collect, analyze, and interpret real-time, high-quality health management information system (HMIS)/malaria surveillance information.

The WHO *Global Technical Strategy for Malaria 2016-2030* and the *WHO Framework for Malaria Elimination* 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, parasites, and vectors), environmental factors, and 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.

WHO's new *Framework for Malaria Elimination* revises the previous stages on the path towards elimination into three phases, the transmission reduction phase with indicative transmission categories of high, moderate, low, and very low (which includes the previously-defined broad continuum from malaria control to pre-elimination), the elimination phase, and the prevention of reintroduction phase (**Figure 1**). This reorientation emphasizes that all countries, regardless of where they lie on that continuum should have a long-term vision of malaria elimination.

Figure 1. Indicative Categories of Transmission Intensity and Categorization of Relevant PMI Countries/Areas



Source: WHO *Framework for Malaria Elimination*, 2017

Several PMI countries have now set national or sub-national goals of malaria elimination, scaled up control measures, and are improving their routine malaria information systems (see **Table 1**).

Table 1. Progress in Reaching Elimination in PMI-supported Countries/Areas

Policy		Routine Data*				Survey Data	
Country/Area	Pre-/Elimination Strategy	Test Positivity		Case Confirmation Rate	HF Reporting Rate	Malaria Prevalence	ITN/IRS Coverage
		API	Rate				
Thailand	Y	<1	<5	100	100	<1	51
Cambodia	Y	1-10	5-50	100	100	<1	90
Zanzibar	Y	1-10	<5	100	88	<1	75
Burma	Y	1-10	5-50	100	100	<1	19
Madagascar	N	10-100	5-50	82	91	7	80
Zimbabwe	Y	10-100	5-50	100	100	<1	62
Senegal	Y	10-100	5-50	98	99	<1	83
Ethiopia	Y	10-100	5-50	86	92	<1	71
Zambia	Y	>100	>50	82	87	19	77

*Limited to the public sector

Source: WHO *World Malaria Report* 2016 and FY 2018 MOPs

Color coding: Green- target achieved, Yellow- progress toward target, but target not achieved, Red- significant progress needed

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 and associated indicators will be important to consider for countries to monitor progress towards elimination:

Technical Feasibility:

- Evidence-based data on the achievement of successful malaria control
 - *Relevant survey indicators: ITN/IRS coverage, treatment seeking within 24 hours of fever onset, and malaria prevalence*
- 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, treatment, and reporting of all malaria cases
 - *Relevant routine indicators: number of cases and deaths, Annual Parasite Incidence (API), test positivity rate, case confirmation rate*
- 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
 - *Relevant routine indicators: completeness and timeliness of HMIS and malaria information system*
- Enabling environment with strong political commitment and collaboration amongst relevant ministries, and with engagement of key private sector stakeholders

Financial Feasibility:

- Strong political commitment evidenced by a dedicated, sustained funding (both domestic and external) to achieve and maintain malaria elimination

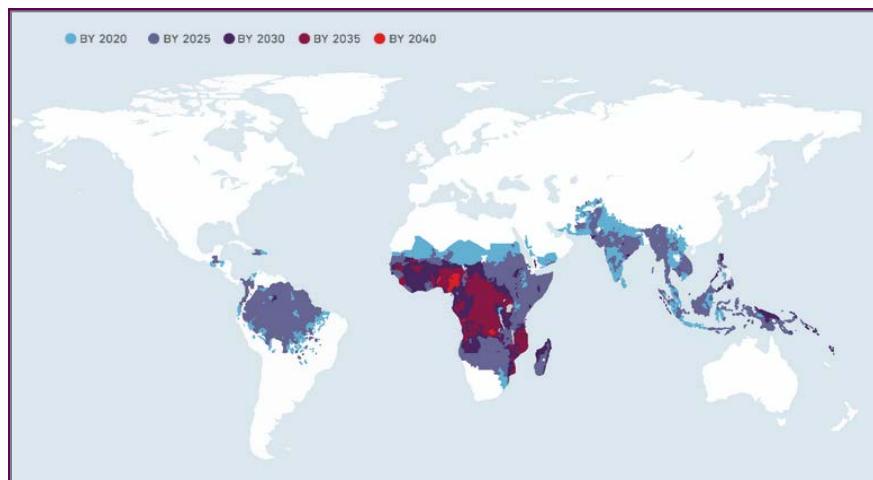
PMI and other partners have developed new tools including Ethiopia's Malaria Elimination Baseline Assessment Tool that are intended to systematically assess the system and human capacity readiness at national and sub-national levels to move towards elimination. An evaluation of the technical and operational situation using such tools is an essential first step in planning and implementing elimination activities. The findings of assessments using these tools will provide programs with necessary information on what areas require further strengthening, which will enable better prioritization of PMI and country resources. Anyone interested in learning more about these tools and its potential adaptation and use in other countries can contact the PMI Elimination Working Group.

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 for PMI funding should be given to supporting interventions to further reduce mortality and morbidity in high burden areas.** These control efforts focused on high transmission areas will be crucial in limiting the exportation of source cases to 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. In order to aspire for a malaria-free world, all PMI-supported 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 systems, 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

High-Risk Populations Within Elimination Settings

As malaria burden decreases in a country, spatial heterogeneity, as well as new demographic risk factors, will become increasingly relevant. Often, it is not uncommon that certain groups may continue to carry a higher burden of malaria despite reductions in the general population.

Examples of such emerging high risk groups include indigenous people in Central and South America, ethnic minority groups and forest workers in the Greater Mekong Subregion, and migrant agricultural workers in Ethiopia. These groups share some common characteristics, including geographic isolation from or reduced access to mass media and public health structures and preventive tools, lower wealth status and literacy, poorer housing, and increased movement for economic pursuits. In some instances, particularly in farm and forest workers, their work requires them to move from lower to high risk areas and to carry out activities, including working outdoors during peak mosquito biting times, which increases their risk of infection.

Reaching these populations can be particularly challenging, as they may only stay in one location for a few weeks or months or may be conducting unsanctioned work, which leads them to avoid contact with any government authorities or facilities. These groups also tend to have lower literacy or may speak a different language, and are likely unaware of the availability of health services in their temporary locations, unless the farm or plantation provides those services. In some settings, traditional control measures, like standard LLINs and IRS, may not be appropriate for their living and work situations.

Migrant and mobile populations may also be inadvertently excluded from net distribution or household surveys, as they do not appear on the local census which is used as a basis for population estimates in both situations.

Innovative approaches must be developed and tested to both identify and reach these high-risk populations. Examples of approaches that have been piloted in PMI focus countries include:

- Providing LLINs to farm/plantation owners to distribute to their workers
- Setting up farm or plantation clinics or training mobile malaria workers
- Training taxi drivers to provide malaria messages and referral to services to migrant populations
- Using innovative sampling (e.g., snowball, respondent-driven, and time-location sampling) to conduct surveys of mobile/migrant populations
- Developing SBCC materials in languages appropriate to the targeted population, including dual language materials for use in cross-border settings
- Establishing border health posts

- Employing novel surveillance approaches to capture testing and treatment data so that these high-risk groups are accounted for in monitoring and evaluation efforts

Entomological Monitoring and Vector Control

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. Thus, where one samples is less important than sampling consistently and rigorously. In contrast, marked heterogeneity in malaria transmission within regions and even neighboring foci 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.

Under the new WHO framework for elimination, a focus is “a defined and circumscribed area situated in a currently or formerly malarious area that contains the epidemiological and ecological factors necessary for malaria transmission.” Foci are classified as active, residual non-active or cleared. Active foci are those where local transmission has not been interrupted. Foci with recent local transmission are considered residual non-active foci while those where local transmission has not been observed for at least three years are considered cleared. The entomological monitoring and vector control strategies should be tailored to the status of each individual focus. Vector control should be maintained in both active and residual non-active foci. For cleared foci, the receptivity and vulnerability of the area should be assessed along with the capacity for the health system to respond to malaria outbreaks before vector control is ceased. The strategy for entomological monitoring should also be adjusted according to the classification of foci.

Site selection for entomological monitoring

In elimination settings, decisions as to where entomological monitoring should be carried out should be based on malaria burden data, whether passively collected case data or prevalence survey data. Entomological monitoring should concentrate on active 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. In residual non-active foci or cleared foci where transmission has been interrupted, continued entomologic monitoring is likely to be of little value. Nonetheless, limited longitudinal fixed site monitoring may be useful to maintain vector monitoring capacity and to train field staff. The PMI Headquarters Vector Monitoring and Control Team will help advise for specific

elimination settings. For further information on the needed components of entomological monitoring, refer to the **Entomologic Monitoring and Insecticide Resistance** chapter.

Entomological investigations may be implemented in active foci that have persistent transmission despite high coverage of vector control interventions. These active foci should be targeted for entomological investigation based upon aggregate API reported through the routine health system. Time-limited entomological investigations may also be warranted in residual non-active or cleared foci in response to outbreaks. These entomological surveys should be done in conjunction with epidemiological investigations to assess intervention coverage and human behaviors that may result in increased risk of malaria. If no clear risk factors are identified during the initial assessment, a more detailed entomologic assessment may be necessary, as the increase in cases 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 common vector control interventions broadly scaled up in control areas – LLINs and IRS – should be targeted to areas where transmission is ongoing in elimination settings. It should be noted that even if a mosquito population shows tendencies to bite or rest outdoors, that indoor interventions can still have a significant impact on the population as a whole since indoor and outdoor biting populations are not distinct (i.e., within a mosquito's lifespan it is likely to try to feed/rest for at least a short time indoors where it could come in contact with an insecticide treated net or surface). Although no clear criteria exist for stopping LLIN distribution, WHO recommends that vector control intervention coverage should be maintained at least until transmission has been fully interrupted and, if feasible, beyond that point, to minimize the risk of reintroduction. In the case of Ethiopia, for example, districts with an annual parasite incidence of <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 malaria case surveillance systems are in place to monitor the situation closely.

As malaria transmission declines, recalcitrant foci of transmission or hotspots may emerge. Investigation of such foci should:

- 1) Determine coverage of standard interventions – whether LLINs or IRS plus case management – followed by prompt corrective action should coverage be low
- 2) If coverage is high and transmission is ongoing, then epidemiological and entomological investigations should be conducted to determine the source of residual transmission which is defined as persistence of transmission after good coverage has been achieved

with high-quality vector control interventions to which local vectors are fully susceptible.¹⁹⁹

- 3) Entomological investigations should include:
 - a. Vector discrimination
 - b. Insecticide resistance monitoring
 - c. Monitoring of the durability and effectiveness of LLINs

If residual transmission appears to be associated with certain occupations (e.g., forestry, mining, or agriculture), investigations should focus on identifying high risk behaviors in these workers and tools that might be effective in reducing work-related transmission. For instance, insecticide treated hammock nets are procured by PMI in Cambodia for such populations. In some cases, it may also be necessary to assess the resistance profile of the predominant vector, should this be feasible.

If LLINs and IRS have been fully implemented in targeted foci and transmission continues, interventions that may not be appropriate in a control context, where broad scale coverage is needed, may be needed in elimination settings to tackle residual transmission; these may include interventions targeting larvae as the rubric of ‘fixed, few, and findable’ may be less relevant in a severely circumscribed focus when the object is malaria elimination.

Because residual transmission may be occurring away from houses or outdoors, operations research to determine the acceptability, feasibility, and effectiveness of novel interventions to address residual transmission (e.g., insecticide treated clothing, repellents, or other vector control approaches) may be needed. **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.**

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 very low transmission settings, MIP is associated with spontaneous abortion, stillbirth, prematurity, and low birth weight. For these reasons, all PMI-supported countries,

¹⁹⁹ WHO Malaria Terminology. WHO Global Malaria Programme.

regardless of transmission levels, should continue to address prevention and control of malaria in pregnant women and ensure effective case management.

Prevention

ITN

Countries proceeding towards 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 PMI-supported countries, transmission has been substantially reduced due to effective prevention and control measures. Some PMI-supported 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. **The 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. Appropriate management of vivax malaria during pregnancy needs to include, when feasible, strategies to prevent relapses without the use of primaquine.

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.

Care must be taken when deploying strategies, such as mass drug administration²⁰⁰, to avoid inappropriate treatment of pregnant women, particularly during the first trimester of pregnancy. This may pose a challenge since it requires the identification of women in early pregnancy who may not yet appear to be pregnant or may not disclose this information. Screening, including offering pregnancy tests and/or conducting an interview to ask about pregnancy status directly, may not be an optimal approach as many women may not wish to reveal their pregnancy status. Given that approximately 20% of the population is comprised of women of reproductive age who may be pregnant, the number of women who need to be screened for pregnancy is substantial across countries. In addition to privacy issues, costs of screening may be another barrier. Recent MDA pilots have excluded infants and pregnant women from receiving the intervention. It is also important to note that primaquine is contraindicated in pregnancy and lactating women, as the drug can be excreted in breast milk. PMI-supported countries considering some of the newer approaches to control of malaria in pregnancy should consult with the relevant PMI Headquarters teams (Elimination, Case Management, and MIP) in the planning phases of such activities.

Case Management

As transmission decreases, it becomes essential to enhance case management to find all suspected malaria cases, confirm with a diagnostic test treat all cases according to national treatment policies, conduct an investigation to collect case information and determine likely location of infection (i.e., local vs. imported), and report both testing results and case information.

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 for *P. falciparum* and *P. vivax* in concentrations at or above 200 parasites per microliter, which is sufficiently sensitive for identifying parasitemia in patients with clinical symptoms. Highly sensitive RDTs (hsRDTs) are now available and may be useful for certain indications in

²⁰⁰ Please see Other Preventive Approaches for more detailed description of Mass Drug Administration.

elimination settings. The hsRDT developed by SD Bioline has a limit of detection of parasite density that is about 10–20 times lower than conventional RDTs. WHO does not recommend the use of hsRDTs for clinical diagnosis and indicates that further research is needed to determine the role of more highly-sensitive tests for case finding activities. Such hsRDTs may have a role, for example, in the context of reactive case detection (see '*Surveillance Approaches*' section). PMI is supporting operational research on hsRDTs for reactive case detection in Burma and Cambodia, as well as in the setting of the IPTp study in Malawi. Results from these and other studies will assist in determining whether and in what contexts these new tools may be useful. Neither WHO nor PMI recommend the use of highly-sensitive RDTs for surveillance nor diagnosis of clinical malaria cases in any setting, and will not support procurement of these tests as a replacement for currently available RDTs.

In 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, 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 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. 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. PMI should prioritize support to ensure these skills are retained in these settings.

All PMI-supported countries, and particularly those moving towards 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 slide banks are included in the updated 2016 WHO Malaria Microscopy Quality Assurance Manual.²⁰¹

The highest priority must be placed on ensuring an uninterrupted supply of essential diagnostic and treatment commodities in 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. District-level buffer stocks in Cambodia have successfully prevented most stockouts in PMI targeted districts. PMI should consider prioritizing support to help ensure these uninterrupted supplies, and understand that occasional expiration of small amounts of unused commodities is often unavoidable, particularly if the country is to be prepared for unexpected focal increases in malaria cases.

The need for rapid diagnosis, treatment, and response to malaria cases also necessitates quick and easy access to care for affected populations. In 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 as in the E8 countries, health services provided in high risk settings (such as plantations in Cambodia or mining camps) also have been used to facilitate access to care.

Treatment

Curative drug treatment of uncomplicated and severe malaria cases does not differ in elimination settings from areas of higher transmission. When moving towards elimination, additional efforts are recommended to ensure treatment adherence and clearance of infection. Use of directly observed therapy (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 and as an alternative to therapeutic efficacy monitoring in low transmission settings).

²⁰¹ http://apps.who.int/iris/bitstream/10665/204266/1/9789241549394_eng.pdf

Single, low-dose primaquine for *P. falciparum*

In 2015, WHO updated its guidelines to recommend the administration of a single gametocytocidal dose of primaquine to be given in addition to an ACT for falciparum malaria **in low transmission areas.**²⁰²

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. PMI supported a study to assess the safety of single low dose primaquine in G6PD deficient patients in Cambodia; and other partners have conducted similar studies in some African settings, including Mali, Kenya, Swaziland, Zanzibar, Zimbabwe, and Senegal. Preliminary findings from the Cambodia study suggest that single low dose primaquine was well-tolerated and did not result in significant decline in hemoglobin concentrations by day 7 in 9 G6PD deficient patients, although the number of G6PD-deficient patients was small. Preliminary results of administering single dose primaquine during MDA in the Mekong and dosing of G6PD deficient adult males without malaria in Mali with doses up to 0.5mg/kg and

²⁰² 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

G6PD deficient children ages 5-17 years with 0.4mg/kg have not noted any clinically significant hemolysis.

Studies show that primaquine kills gametocytes and is the only drug to kill mature falciparum 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 and/or in a setting with confirmed artemisinin resistance.²⁰³

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 elimination areas. This would include case finding around an index case (reactive case detection) or community surveys (active case detection).

In 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 for falciparum, as guided by the national malaria treatment policy.

Treatment of non-falciparum infections

Countries outside of tropical Africa on the path to eliminating malaria will often have proportionately higher levels of non-falciparum infections, particularly *P. vivax*. Appropriate treatment begins with accurate diagnosis. Treatment of liver-stage infections in *P. vivax* is necessary for preventing relapses. Before radical cure with primaquine is administered, the G6PD status of the patient should be tested. When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine should adhere to national treatment guidelines that should be based on a local assessment of the risks and benefits of adding primaquine. Treatment guidelines for *P. vivax* can be found in detail in Annex 2 of WHO's 2017 "A Framework for Malaria Elimination" and its 2015 "Guidelines for the Treatment of Malaria."

²⁰³ Although the recommendations did not define low transmission, the recent WHO Elimination Framework defines very low transmission as areas having an annual parasite incidence of ≤ 100 and a prevalence of *P. falciparum/P. vivax* of $\leq 1\%$. It is also reasonable to use a health facility test positivity rate of $<5\%$ as a threshold.

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 chapters 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. Other survey methodologies (e.g., respondent-driven sampling to estimate malaria intervention coverage, as well as malaria burden) in populations lacking a sampling frame (e.g., mobile and migrant populations) have been adapted from methods used for monitoring persons with HIV. These methods, though, have been difficult to conduct and appear to be less applicable in the malaria setting where social networks are less well-defined and established.

Although population surveys may still be needed in an 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 elimination, the national household surveys will become less sensitive given the same sample size of these surveys is insufficient to monitor 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. **Countries transitioning to elimination should increasingly use longitudinal health facility and community-based surveillance data, if of sufficient quality, to monitor seasonal and annual trends in malaria burden, as described in the surveillance section below.**

National-level surveys (e.g., DHS) are 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 elimination, the proportion of child mortality attributable to malaria

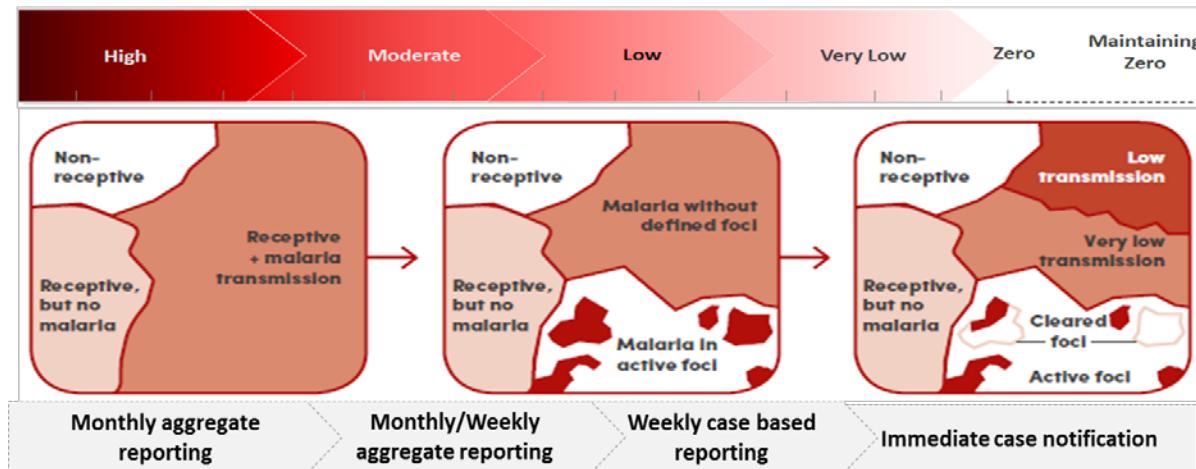
declines and ACCM is no longer an accurate indicator to measure malaria elimination progress. Countries will still need to collect ACCM as a basic demographic indicator and to measure progress in maternal and child health beyond malaria. However, PMI should bear less of the financial and logistic burden of organizing the DHS surveys in elimination settings.

As a country or region approaches 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 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.

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-term process and is addressed in detail in the **SM&E** chapter. Countries in elimination are expected to have a well-functioning routine surveillance system that collects timely, aggregate data which is a pre-requisite for any country aiming to achieve this phase. For countries in 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 foci investigation and response that will be needed during the elimination phase. The increasing spatial heterogeneities as transmission decreases necessitates a shift from reporting aggregate data by month over large geographic areas (e.g., district) to reporting near real-time, individual case data over small areas (foci) (Figure 3).

Figure 3. Increasing spatial heterogeneity and frequency of malaria surveillance reporting as transmission decreases



Surveillance system requirements for elimination

- Implementation of a national system to collect facility and community-based data on confirmed malaria cases in order to reliably measure malaria incidence in all regions of the country:** Countries (or regions) approaching elimination will require a surveillance system capable of recording and 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, including public, private, non-governmental organizations, military, etc.
- Ability to identify, investigate, and control malaria transmission foci:** In the 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. The investigation of the index case and subsequent response measures (reactive case detection) could include testing and treatment of family members and close neighbors. Geolocation is beneficial to identify areas of ongoing transmission and allow cross-referencing of control activities in the area to target additional efforts.
- Building disease surveillance capacity:** Building disease surveillance capacity should be supported in all PMI focus countries. In elimination settings, the capacity of local health authorities to rapidly identify, investigate, and respond to outbreaks is critical. In such settings, PMI will support the training and supervision of health workers and surveillance and environmental/entomological officers to detect and report cases, investigate foci, and respond with appropriate control measures.

Disease surveillance tools

National disease surveillance systems

In many PMI countries, multiple surveillance systems exist which collect malaria data at varying frequencies. In collaboration with the NMCP and MOH authorities, PMI teams should prioritize specific areas for programmatic support. In elimination countries or regions, the focus of PMI support to surveillance systems should be on developing the critical surveillance capacity necessary to achieve timely, aggregate, comprehensive data. 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):** Health Management Information Systems (HMIS) typically report aggregate health-facility level data on a monthly basis. These data do not have the resolution or timeliness needed for targeted elimination efforts (e.g., case listing or detection of transmission foci). In some instances, case-based surveillance tools can be integrated into HMIS via an electronic platform such as DHIS-2. In general, countries nearing elimination should have well-functioning routine aggregate data systems and will focus investments on developing timely, case-based data systems for elimination certification.

Integrated epidemiologic surveillance systems, such as IDSR, provide timely 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:** Some countries have stand-alone malaria surveillance systems with more frequent reporting (e.g., weekly) than routine HMIS systems. While PMI does not generally support national parallel surveillance systems for malaria, in some instances these systems may be necessary for targeted elimination areas. Any considerations of support for parallel systems should be discussed with the PMI Headquarters SM&E and Elimination Teams 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, timely access to malaria data collected through HMIS or IDSR. In countries moving towards but that have not yet reached the elimination phase, weekly IDSR reporting is

likely an adequate platform and the MOH must coordinate appropriate data access for the NMCPs. However, some countries approaching the elimination phase may require a malaria-specific, supplementary surveillance system that builds on the HMIS/IDSR platform and reports directly to national or sub-national malaria control authorities with greater frequency. These 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. Systems and modules to support individual case reporting and tracking are being rapidly developed, including RTI's Coconut Surveillance platform used in Zanzibar and the DHIS-2 TRACKER being piloted in Zimbabwe and Burma.

Hardware/software

There are no specific requirements regarding hardware and software for an effective pre-elimination surveillance system. However, the ability to rapidly share 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. 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.

A landscaping of currently available mobile technologies and a roadmap for mobile solutions for malaria elimination surveillance systems was commissioned by the Bill and Melinda Gates Foundation and is available at <http://vitalwave.com/case-study/mobile-solutions-for-malaria-elimination-surveillance-systems/>.

Surveillance approaches

The following are approaches to surveillance that can be supported through PMI funding where appropriate:

- **Passive surveillance:** Passive surveillance systems rely on data on individuals presenting for care within the health system. These data are aggregated and reported on a periodic basis (usually monthly). In elimination settings, the system ideally should include all cases in a geographic area including public, private sector, and community level data. Passive surveillance does not generally capture cases and deaths that occur outside of a health care setting, and thus might not provide a complete picture of malaria burden. 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 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 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 the elimination phase, when cases are few and health system capacity and resources allow. Active surveillance can be used in the 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.
 - Transit programs to screen high-risk individuals for malaria when entering the country or low- prevalence areas within a country.

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 conventional 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 strategy to reduce and interrupt transmission. See **Other Preventive Approaches** chapter ('**MSaT**' 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 Elimination Working Group and will generally be required to first be piloted as an OR study, assuming other evidence of effectiveness is unavailable, so that its effectiveness can be assessed.

- **Reactive case detection:** 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"²⁰⁴ 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 personal, household, and environmental information that helps determine whether the case was likely to be locally-transmitted or imported. Further 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 of additional confirmed cases.

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, whether testing is performed on asymptomatic persons or only symptomatic, 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 transmission is occurring, the likelihood of finding additional cases is highest in the index household and decreases rapidly beyond 200m from the index household. 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.

²⁰⁴ 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

Social and Behavior Change Communication (SBCC)

In areas with high, moderate, low, and very low transmission alike, use and uptake of malaria interventions rely heavily on community awareness, demand, and acceptance of essential commodities and services. As such, SBCC can play an integral role in malaria elimination. With transitions to malaria elimination, communities will experience fewer and fewer cases of malaria resulting in a decrease in perceived risk; however, the severity of malaria cases might increase. To address these shifts across transmission settings, behavior maintenance will also become more important particularly with regard to ITN use. Although there is no “one size fits all” approach for specific strategies and channels that should be used for SBCC in elimination settings, key aspects of behavior change should be considered (please refer to the SBCC Guidance for a description of communication approaches supported by PMI across all transmission settings).

Vector control

Two of PMI’s main interventions – insecticide-treated mosquito nets (ITNs) and indoor residual spraying (IRS) – are aimed at controlling mosquito populations and are especially important in sub-Saharan Africa where nocturnal indoor-biting and resting behaviors are common. While these interventions are highly effective, the gains may be quickly reversed if net use or IRS acceptance falls. As such, the transient adoption of a behavior is not enough, particularly in an elimination setting; consistent use of ITNs and acceptance of IRS must be maintained at high levels.

While behavior maintenance for ITN use and acceptance of IRS is important in areas transitioning to low, very low and zero transmission, additional considerations should be made. For example, establishing or reinforcing net use in fixed or sedentary communities may function differently than in smaller, mobile, migrant and vulnerable populations. In these settings, monitoring shifts in human attitudes, perceptions and behaviors will be important. To better understand behavioral influences and barriers in these settings, formative assessments using new surveys and sampling techniques may also be required.

Case management

A key component of SBCC for malaria case management is increasing treatment seeking behaviors especially through the public sector. In all transmission settings, SBCC for case management at the community level should focus on establishing trust in the malaria test result and raising awareness of the broad spectrum of fever causes. It is equally important that SBCC targeted at service providers focus on increased awareness of the broad spectrum of fever causes, emphasize adherence to national case management guidelines (for diagnosis and treatment) and improved communication for patients who do not receive treatment for malaria when presented with a negative RDT.

Malaria in pregnancy

At the community level, SBCC should encourage consistent ITN use, ANC attendance, prompt testing and treatment seeking for fever, and promote the uptake of IPTp, when appropriate. Activities that target service providers should continue to encourage provider adherence to national guidelines for IPTp dosing (timing and frequency) and malaria case management.

Surveillance, monitoring, and evaluation

As countries shift to lower transmission and improve SM&E activities to capture robust data, special considerations to collect behavioral data on a routine basis should be made. For example, as active case detection is employed in low, very low and zero transmission areas, behavioral components could be incorporated into investigations to further understand and measure the uptake of the relevant behaviors as well as related behavioral factors. Refer to the Malaria Social and Behavior Change Communication Indicator Reference Guide, Second Edition, for indicators that can be adapted for elimination settings.

While household surveys may still be used to measure behaviors of fixed populations (geographically and demographically), additional considerations for SBCC SM&E activities include shifting to examining mobility as a system (e.g., monitoring human movement) and determining what effect the direction of that movement will have on malaria transmission. The Greater Mekong Sub-Region has implemented SBCC interventions targeted towards mobile populations that have included net lending programs and interpersonal communication with travelers along known travel routes. Countries with mobile populations may wish to build off the lessons learned from experiences in the Greater Mekong Sub-Region. Please see your Headquarters country support team for access to this learning.