Background Paper

Screen and treat strategies for malaria elimination: a review of evidence

Prepared for the
Bill & Melinda Gates
Foundation

July 2018

UCSF Institute for Global Health Sciences
Global Health Group

Background Paper

Screen and treat strategies for malaria elimination: a review of evidence

Prepared for the
Bill & Melinda Gates Foundation

July 2018

UCSF Institute for Global Health Sciences
Global Health Group

UCSF Global Health Group
550 16th Street, 3rd Floor, Box 1224
San Francisco, CA 94158

Recommended Citation
The Global Health Group (2018). *Screen and treat strategies for malaria elimination: a review of evidence*. San Francisco: Institute for Global Health Sciences, University of California, San Francisco. Produced in the United States of America.

Cover Photo
Nurse performing malaria screening and treatment in Namibia as part of a trial to evaluate reactive focal interventions including reactive case detection. Photo by Nana Kofi Acquah, courtesy of Novartis Foundation.

Contributors and Acknowledgements
This background paper is a rapid synthesis of current evidence prepared for and funded by the Bill & Melinda Gates Foundation, intended to inform the development and implementation of policies and strategies related to screen and treat approaches for malaria elimination.

The paper was authored by Gretchen Newby, Kelly Harvard, Roly Gosling, Chris Cotter, Michelle Roh, Adam Bennett, and Ingrid Chen of the Global Health Group at the University of California, San Francisco (UCSF), Jimee Hwang (Centers for Disease Control and Prevention/President's Malaria Initiative and UCSF Global Health Group), Nakul Chitnis (Swiss Tropical and Public Health Institute), and Michelle Hsiang (University of Texas Southwestern and UCSF Global Health Group).

The following individuals reviewed the report and provided important assistance and feedback: Andrea Bosman, Jane Cunningham, and attendees of a Technical Consultation on research requirements to support policy recommendations on highly sensitive malaria diagnostic tests, Global Malaria Program, World Health Organization, Geneva, Switzerland, June 4-5, 2018.

The authors acknowledge with thanks Kate Brown Lee who formatted this report.

The authors are responsible for any errors or omissions.

Contents

Acronyms

ACD	Active Case Detection
AL	Artemether-Lumefantrine
APMEN	Asia Pacific Malaria Elimination Network
APROG	Antiparasite Rollout Group
ASAQ	Artesunate-Amodiaquine
CHW	Community Health Worker
CRCT	Cluster-Randomized Controlled Trial
DALY	Disability Adjusted Life-Year
DP	Dihydroartemisinin-Piperaquine
DPR Korea	Democratic People's Republic of Korea
E8	Elimination 8
fMDA	Focal Mass Drug Administration
FSAT	Focal Screen and Treat
FTAT	Focal Test and Treat
IDP	Internally Displaced Persons
IRR	Incidence Rate Ratio
LAMP	Loop-mediated Isothermal Amplification
Lao PDR	Lao People's Democratic Republic
M&E	Monitoring and Evaluation
MDA	Mass Drug Administration
MSAT	Mass Screen and Treat
MTAT	Mass Test and Treat
OR	Odds Ratio
PCD	Passive Case Detection
PCR	Polymerase Chain Reaction
POC	Point of Care
POR	Prevention of Reintroduction
PQ	Primaquine
RACD	Reactive Case Detection
RDT	Rapid Diagnostic Test
SAT	Screen and Treat
SOP	Standard Operating Procedure
WHO	World Health Organization

Introduction

Passive case detection (PCD) is the foundation of malaria surveillance and the primary mechanism for case identification in both control and elimination programs.[1] However, PCD requires that patients seek care—either from community health workers (CHWs) or at local health facilities equipped with the necessary diagnostic and treatment options—and rates of treatment-seeking behavior for fever in endemic countries are highly variable.[2,3] Accessibility is a significant challenge for malaria patients in remote areas, and for vulnerable, underserved populations such as migrants and refugees. In very low transmission settings, the few remaining cases may be missed due to low index of suspicion by health workers who opt not to test for malaria. In addition, a large proportion of malaria infections are minimally symptomatic or asymptomatic; thus, most of these cases will not come to the attention of health facilities.[1,4,5] This phenomenon becomes increasingly challenging in elimination settings in which rapidly identifying and treating individual infections is key to interrupting transmission.[6,7]

To supplement routine case management and overcome the limitations of PCD, particularly in lower transmission settings, a variety of malaria infection screen and treat (SAT) methods may be deployed by control and elimination programs. Broadly, two SAT approaches are used: active case detection (ACD) and reactive case detection (RACD). ACD may be directed at high risk areas or populations identified through PCD, referred to as "proactive" case detection, but it is not implemented specifically in response to a recent individual case. RACD is conducted in a targeted, reactive fashion after recent identification of an individual case, usually detected through PCD. ACD can be applied at mass or focal scales, while RACD is applied at focal scales (Box 1).[8]

SAT approaches allow programs to gather detailed epidemiological data on local malaria transmission and intervention coverage which can be used to guide the selection and targeting of additional interventions. In theory, SAT approaches may also directly contribute to the reduction and interruption of malaria transmission in that they allow for identification and prompt treatment of individual cases and foci which otherwise would have been missed by PCD. However, there is very minimal evidence regarding the utility or effectiveness of SAT in reducing transmission.[9] A major limitation is that many malaria programs rely on traditional diagnostics (microscopy and rapid diagnostic tests [RDTs]) that are unlikely to detect parasite densities less than approximately 100 parasites/µl. Infections with densities lower than this threshold can be transmitted to mosquitoes, but the contribution of this low-density parasite reservoir to onward transmission has not been fully characterized.[6,10,11] Additional challenges of SAT include heavy resource and logistical requirements and poor or inconsistent implementation by malaria programs due to a lack of high-level guidance and policy on best practices.[4,12,13]

Box 1: Terminology[8]

Passive case detection: detection of malaria cases among patients who, on their own initiative, visit health services for diagnosis and treatment, usually for a febrile illness.

Screen and Treat: all people in a geographical area are screened, regardless of whether they have symptoms of malaria; positive cases are subsequently treated.

- **Active case detection:** Detection by health workers of malaria cases at community and household levels, sometimes in population groups that are considered at high risk (this may be referred to as proactive case detection). Active case detection can consist of screening for fever followed by parasitological examination of all febrile patients or as parasitological examination of the target population without prior screening for fever. This can be done at mass scale or focal scale.

- **Reactive case detection:** Active case detection undertaken in response to a confirmed case or cluster of cases, in which a population potentially linked to such cases is screened and tested. This is done at focal scale.

In 2015, the World Health Organization (WHO) convened an evidence review group to evaluate the use of drug-based interventions for malaria elimination, specifically SAT and mass drug administration (MDA). Bypassing the challenges associated with malaria diagnosis, MDA involves the administration of antimalarial treatment to every member of a defined population or every person living in a defined geographical area (except those for whom the medicine is contraindicated) at approximately the same time and often at repeated intervals. The aim of MDA is to clear the parasite reservoir in humans and provide periods of chemoprophylaxis against blood stage infection, resulting in a decrease in malaria transmission.[8] The group's conclusions on MDA relied heavily upon two systematic reviews,[14,15] while those on SAT derived from a handful of representative studies; the outcome was that the WHO's Malaria Policy Advisory Committee does not recommend the use of SAT at mass or focal scales using current diagnostic tests as an intervention to reduce transmission.[9,16] However, the 2017 WHO Malaria Elimination Framework details the roles and usefulness

of ACD and RACD as surveillance tools, noting that both are important components of an elimination strategy,[1] and most malaria elimination programs are regularly implementing one or both of these SAT approaches.

In light of this lack of coherent messaging regarding the use of SAT for malaria elimination and growing evidence available from both published literature and malaria program experience, the objective of this paper was to conduct a systematic review to assess utility and effectiveness of SAT for surveillance and transmission reduction. The paper also includes evidence and experience on SAT conducted in combination with MDA and/or expanded access to community-level PCD. We use the term SAT to include proactive and reactive case detection strategies that require use of a diagnostic test (sometimes referred to as Test and Treat) and those that do not require the use of a diagnostic test and are based on presence of fever or epidemiological attributes and risk factors. We include peer-reviewed literature as well as grey literature and unpublished experiences from national programs in our analysis. We provide recommendations on decision-making considerations and identify priority evidence gaps for future research needs to guide the use of SAT for malaria elimination.

Methods

We conducted a comprehensive literature review and an assessment of programmatic experience with SAT implementation.

Literature search

A search on PubMed and Google Scholar of literature published between January 1900 and April 2018 was carried out using the following search terms, selected based on previous research[17] on active case detection: malaria AND reactive case detection, OR active case detection, OR proactive case detection, OR mass screen and treat, OR MSAT, OR mass test and treat, OR MTAT, OR focal screen and treat, OR FSAT, OR focal test and treat, OR FTAT, OR case investigation, OR reactive case investigation, OR case follow up, OR contact tracing, OR test treat and track, OR elimination case finding, OR elimination blood survey, OR elimination surveillance. Search results were assessed using the following exclusion criteria:

1. Studies on diseases other than malaria
2. Studies on the immunology, entomology, ecology, or genetics of malaria
3. Cross-sectional surveys designed to establish prevalence or characterize transmission patterns in a population
4. SAT studies that target only pregnant women, infants, or school children
5. SAT studies that do not provide information on the treatment component
6. SAT studies that provide neither quantitative details nor information on operational/ programmatic considerations
7. Non-English language studies

Analysis of published literature

The studies included in the analysis were categorized by study design, year of publication, eco-epidemiological setting (including region and country, transmission intensity, *Plasmodium* species), and SAT approach, specifically target population size (mass versus focal), proactive versus reactive, and diagnostic testing method used. If transmission intensity or *Plasmodium* species were not reported, this information was collected from contemporaneous studies or WHO reports. Studies were classified as mass if the operational unit was a village or larger; studies that targeted sub-village populations were classified as focal. Transmission intensity categories were based on WHO guidelines.[1] Some manuscripts included more than one transmission setting or location and were therefore considered to be separate studies for the purpose of the analysis.

Intervention studies were further examined to assess their effectiveness in decreasing transmission. No intervention studies directly assessing impact of RACD on transmission were found; thus, RACD studies were analyzed based on yield, in terms of 1) test positivity rate among individuals screened, and 2) percent increase in detection of infections by PCD+RACD compared to PCD alone ([(number of PCD-detected cases triggering RACD + number of RACD-identified infections)*100] / number of PCD-detected cases triggering RACD). Means weighted by the sample size of each study were compared across transmission intensity settings and diagnostic methods used (standard point of care [POC] diagnostics - RDT and microscopy - versus molecular methods, including polymerase chain reaction [PCR] and loop-mediated isothermal amplification [LAMP]). T-test p-values were used to assess the null hypothesis that the difference in weighted means = 0.

Key themes and findings from other observational and descriptive studies, including modeling studies, were also described and compared. Findings from papers documenting programmatic experience with SAT were summarized alongside findings from a review of unpublished literature (see below).

Programmatic assessment

A landscaping of published and unpublished evidence on programmatic experience with SAT was carried out. Published evidence was identified using the search terms and exclusion criteria described above. Unpublished evidence was gathered using the existing infrastructure of two large regional networks, Asia Pacific Malaria Elimination Network (APMEN)[18] and Elimination 8 (E8)[19] in southern Africa, as well as the Antiparasite Rollout Group (APROG),[20] a multi-stakeholder expert committee aiming to harmonize and advance research, policy, and implementation of drug-based antiparasite strategies such as SAT and MDA. Details on programmatic SAT activities captured in grey literature, program documentation, survey responses, and meeting presentations and discussions were collated and analyzed.

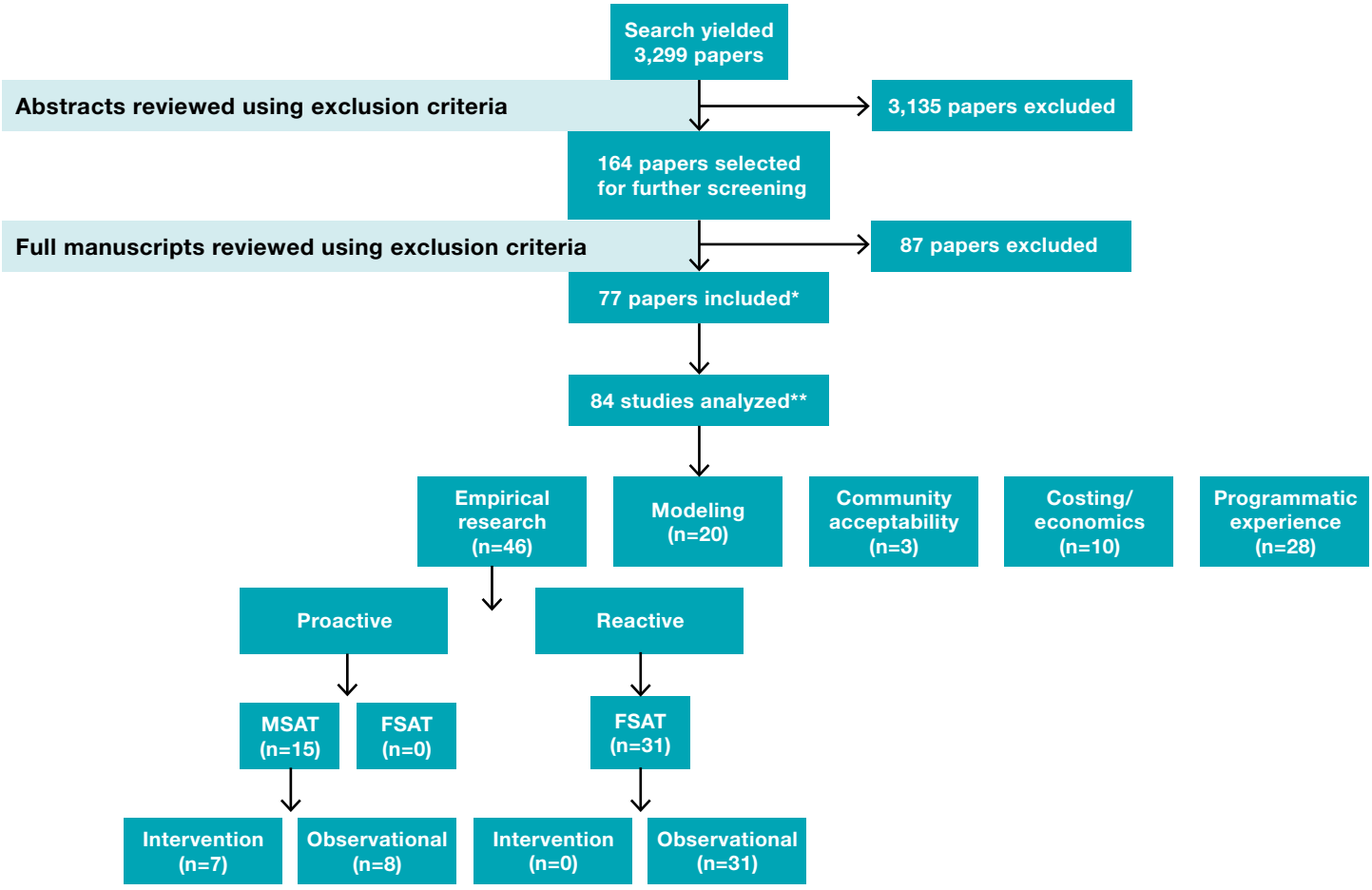
First, previous surveys conducted among APMEN member countries on various aspects of surveillance and active case detection activities were reviewed

and any SAT approaches being implemented were summarized.[21,22] Since these surveys were carried out in 2012 and 2014, respectively, a review of recent national malaria strategic plans and other program materials was done in order to ensure that the documented SAT activities were up to date. For E8 countries, the assessment began with a review of national malaria strategic plans and other program materials. Because strategic plans do not always reflect actual activities, a short survey was developed and disseminated to APMEN and E8 member countries aimed at determining which SAT approaches are currently being implemented and how, and the programs' rationale for their activity choices (see Appendix A for survey questions). Finally, presentations and attendee discussion notes from two APROG meetings held in 2017 were summarized. While SAT activities are also widely implemented in the Americas, the absence of a convening network with focused coordination of surveillance activities precluded easy access to and inclusion of programmatic data. Thus, evidence from the Americas was limited to published literature.[23–27]

Results

The literature search yielded 3,299 papers. Based on the title and/or content of the abstracts, 164 of the papers did not clearly meet the exclusion criteria and were selected for closer screening of the full manuscripts (see Appendix B for the 164 references). Of these, 77 papers did not meet any exclusion criteria and were included in the analysis. Six of the 77 papers presented results from more than one transmission setting,[28] location,[12,29,30] or SAT approach[31,32] and these were analyzed individually; thus, there were 84 total studies included in the analysis. These were then divided into five broad study designs: empirical research studies, modeling studies, qualitative studies of community acceptability, costing/economic studies, and studies documenting programmatic experience and perspectives (Figure 1 and Appendix C). Several studies fit into more than one category. All 84 studies were published in 2005 or later. Seventy-six percent (n=64) were published in the last five years. Fifty-five percent (n=46) were published in the last three years, after the 2015 WHO recommendation against the use of SAT for transmission interruption. In terms of geography, studies from the Americas had the lowest representation (n=5, or 6%). Thirty-six percent (n=30) were from Asia Pacific. The majority (n=49, or 58%) were from sub-Saharan Africa, of which 45% (n=22, or 26% of total) were from Zambia.

Figure 1: Literature search results



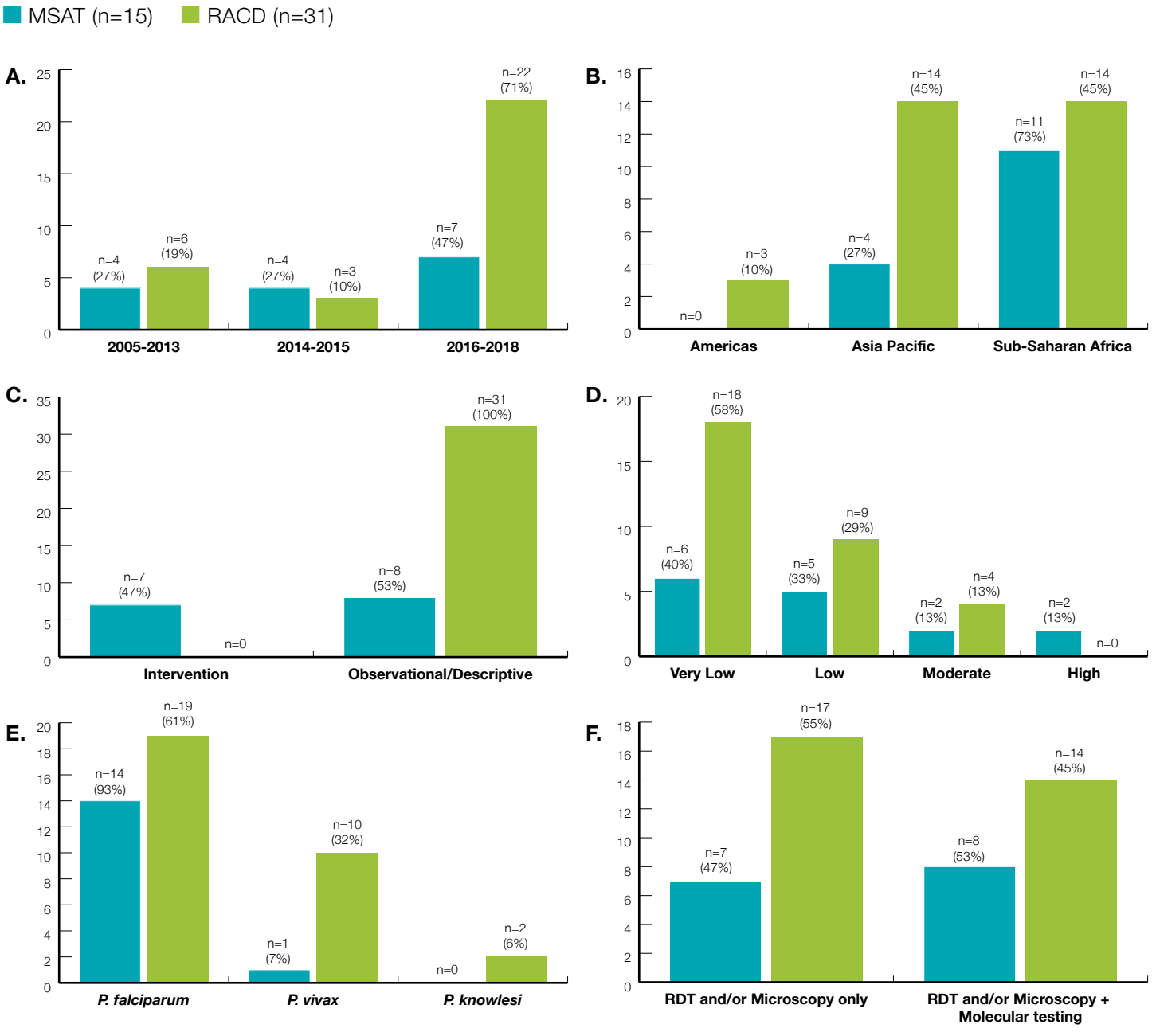
* Six of the 77 papers presented results from more than one transmission setting, location, or SAT approach and these results were analyzed individually; thus, the total number of studies analyzed was 84

** Several of the 84 studies fit into more than one category

Empirical research studies

Of the 46 empirical research studies, breakdown by SAT approach, year, region, study type, transmission setting, species, and diagnostic test used are shown in Figure 2. Considering SAT approach, 15 were focused on proactive mass screen and treat (MSAT) and 31 on focal RACD. Using the definition of focal screen and treat (FSAT) targeting a sub-village level or smaller, there were no proactive FSAT studies identified. Two papers presented results from both proactive MSAT and focal RACD interventions, thus they are counted twice.[31,32] Two of the MSAT studies included a focal MDA (fMDA) component, which is also referred to as mass testing and focal drug administration by WHO.[8] Most of the studies (n=29, or 63%) were published in the last three years. Two-thirds of all studies and three-fourths of studies from the last three

Figure 2: Features of empirical research studies – **A)** Year published, **B)** Geographic region, **C)** Study type, **D)** Transmission setting, **E)** Parasite species, **F)** Diagnostic test used



years were on RACD. By geography, the Americas were least represented (n=3, with one study each from Brazil, Colombia, and Peru). Eighteen took place in six countries in Asia Pacific (Cambodia, China, India, Indonesia, Thailand, Vanuatu), and the majority (n=25) took place in sub-Saharan Africa, including ten studies from Zambia.

The studies were stratified based on transmission intensity categories defined in the WHO Elimination Framework,[1] and the majority took place in low or very low transmission settings (Figure 2D). One study compared the impact of interventions in both low and high transmission settings and is counted twice.[28] There was considerable variability in transmission dynamics and ecologies across studies. Settings ranged from rural to peri-urban to urban, sea level to mountainous highland, and open plains to dense tropical rainforest. Transmission was perennial or highly seasonal with either one or two annual peaks.

Due to heavy representation of sub-Saharan Africa, *Plasmodium falciparum* was the dominant parasite species in the majority of the studies; *P. vivax* was the dominant parasite in studies from the Americas and Asia Pacific (Figure 2E). In terms of diagnostic test used (Figure 2F), most studies used RDT only (n=21, or 46%), versus microscopy only (n=3, or 7%). While molecular methods were primarily used for research purposes (n= 22, or 48% of all studies, mainly on RACD), PCR/LAMP results were also used to inform treatment in three MSAT studies[32–34] and four RACD studies.[32,35–37] Studies from sub-Saharan Africa mainly used RDT while studies from the Americas and Asia Pacific were more likely to use microscopy, with or without the addition of a molecular test.

The quality of evidence in terms of study design was strongest for MSAT, for which there were seven intervention studies that measured impact on malaria transmission (Figure 1). The remaining studies were observational or descriptive evaluations of yield and/or technical and operational approaches utilized. Outcomes were generally measured as incidence or prevalence of infections. Several studies aimed to identify demographic and epidemiologic risk factors for infection detection. Technical and operational aspects evaluated included response time, target population size, radius size, diagnostic test, and use of monitoring and evaluation tools.

Proactive MSAT

Empirical research studies on proactive MSAT are shown in Table 1. The studies mainly took place in low and very low transmission settings, with two taking place in high and two in moderate transmission settings. The seven intervention studies evaluated MSAT alone or in combination with fMDA.

Table 1: Proactive MSAT empirical research studies

Transmission Setting (annual incidence; prevalence)	MSAT study type	
	Intervention studies	Observational/ descriptive studies
High (450+ per 1000; >35%)	^Eisele et al 2016 Zambia[28]* Tiono et al 2013 Burkina Faso[40]	None
Moderate (250-450 per 1000; 10-35%)	Larsen et al 2015(b) Zambia[42]	Sutcliffe et al 2012 Zambia[43]
Low (100-250 per 1000; 1-10%)	Sutanto et al 2018 Indonesia[39] Bousema et al 2016 Kenya[38]* ^Eisele et al 2016 Zambia[28]*	Scott et al 2016 Ethiopia[46] Stresman et al 2015 Kenya[45]
Very Low (<100 per 1000; <1%)	Cook et al 2015(b) Zanzibar[41]	Rossi et al 2018(b) Cambodia[32] Donald et al 2016 Vanuatu[31] Cook et al 2015(a) Zanzibar[33] Hoyer et al 2012 Cambodia[34] Lee et al 2010 São Tomé and Príncipe[44]

^ Eisele et al 2016 compared interventions in two different transmission settings, thus it appears twice
* MSAT + fMDA studies

MSAT intervention studies

Details of the MSAT intervention studies are shown in Table 2. All were cluster randomized controlled trials (CRCT) except for one cluster non-randomized controlled trial. Four intervention studies were of MSAT only. Three were of MSAT used in combination with fMDA, in which a sentinel population was screened with RDTs and drugs were administered to the entire household or compound if there was at least one RDT-positive present.[28,38] All but one study took place in a *P. falciparum*-predominant sub-Saharan African setting and used RDT to screen for infection. The one study from southeast Asia took place in a *P. vivax*- and *P. falciparum*-predominant endemic setting and used microscopy.[39] All interventions were initiated before the rainy season. There was otherwise considerable heterogeneity in terms of the operational approach (e.g. number of rounds, choice of drug, sentinel population among MSAT+fMDA studies) and coverage. There was also considerable heterogeneity in the outcome measures, in terms of population assessed (e.g. children only versus all ages) and diagnostic method used. The assessment periods ranged from weeks to one year, and none assessed impact in the subsequent transmission season.

Of the four MSAT-only intervention studies, three showed no statistically significant impact. The first took place in Burkina Faso, a high, seasonal transmission setting. Despite three rounds of village-level MSAT with a high target population coverage of 96%, there was no effect on prevalence of infection or malaria incidence the following year compared to control villages.[40] In Zanzibar, where transmission is very low, seasonal, and focal, two rounds of village-level MSAT did not have an effect on monthly malaria incidence.[41] Average coverage of the target population in Zanzibar across both rounds was just under 50% which may have contributed to the outcome. In a low transmission, *P. vivax*- and *P. falciparum*-predominant setting in Indonesia, neither two nor three rounds of MSAT using microscopy reduced transmission, despite reasonably high coverage of almost 90%.[39] All three studies emphasized the limitations of RDT or microscopy in detecting low-density parasitemia. In Zanzibar, PCR analysis showed that only 4% of positive carriers were detected by RDTs and subsequently treated; further, the RDTs used were *P. falciparum*-specific, yet PCR revealed the presence of *P. vivax*, *P. malariae*, and *P. ovale* infections.[41] Similarly, in Indonesia, microscopy only identified one quarter of PCR-positive carriers and was more efficient in diagnosing *P. falciparum* versus *P. vivax*.[39]

The one MSAT study that showed impact on transmission was from Southern Province, Zambia.[42] After three rounds of MSAT in approximately 85,000 individuals with estimated population coverage of 88%, there was a decrease in the odds of RDT-detectable infection among children less than 5 years of age (OR 0.47, 95% CI 0.24-0.90). However, the prevalence assessment was measured using RDT only, and the impact on incidence (IRR 0.83, 95% CI 0.68-1.01) was modest and not significant. The overall lower-than-expected impact was attributed to the limitations of RDTs to detect low-density infections.[42]

The other intervention studies measured impact of MSAT+fMDA.[28,38] A CRCT in Southern Province, Zambia evaluated the short-term (5 months) impact of two rounds of MSAT+fMDA in high and low transmission settings on prevalence in children and incidence in all ages. Except for the prevalence assessment in the low transmission area, the measures of effect for MSAT+fMDA versus control were less than one, suggesting effectiveness, but findings were not statistically significant. In the third intervention arm of MDA-only (no screening), there was a statistically significant impact in the higher transmission setting for prevalence and incidence of RDT-detectable infection, but not incidence of symptomatic cases. In the lower transmission setting, MDA resulted in a statistically significant lower incidence of symptomatic cases but not prevalence or incidence of infection.[28] In Kenya, the impact of one round of MSAT+fMDA on PCR-detectable prevalence among all age groups was evaluated in a low transmission, highland fringe setting.[38] Despite high coverage, there was a modest effect in the intervention areas after 4 weeks but no effect by 16 weeks, and no effect at any time point in the evaluation zone beyond the intervention areas but within 500 meters. Coverage of targeted households was 96% compared to just under 60% in the Zambia study.[28] As with the MSAT-only studies, authors partly attributed the poor performance of MSAT+fMDA to the inability of RDTs to detect low-density infections.[28,38]

MSAT observational studies

Of the eight MSAT observational studies, there was one study from moderate (Zambia) and two studies from low (Ethiopia, Kenya) transmission settings. The rest were from very low transmission settings in Africa (São Tomé and Príncipe, Zanzibar) and Asia Pacific (Cambodia, Vanuatu) (Table 1). These studies were pilots or reports of program experience with MSAT and aimed to assess **1)** impact on transmission, **2)** yield and operational feasibility of different diagnostic approaches, and/or **3)** overall operational feasibility of specific approaches (e.g. targeting of high risk groups).

Table 2: MSAT Intervention

Study	Country	Setting	SAT method	Study design	No. MSAT intervention clusters	Intervention population size	Test	SAT rounds	Drug regimen	Coverage	Outcome				
											Prevalence		Cumulative Incidence		
											Follow up period (months)	Infection, OR, 95% CI†	Follow up period (months)	Symptomatic cases, IRR, 95% CI†	Infection, IRR, 95% CI*
Tiono et al 2013[40]	Burkina Faso	High	MSAT	CRCT	9	5–10K	RDT	3	AL	96%	12	0.92, p=0.3, by PCR	12	1.06, p=0.3 ¥	-
Larsen et al 2015(b)[42]	Zambia	Mod	MSAT	CRCT	8	85K	RDT	3	AL	88%	12	**0.47, 0.24–0.90, by RDT§**	12	0.83, 0.68–1.01	-
Sutanto et al 2018[39]	Indonesia	Low	MSAT	CRCT (3 arms: 2 or 3 rounds vs. control)	5 and 6 for 2 and 3 rounds, respectively	<5K	slide**	2 or 3	DP+PQ	87% and 89% for 2 and 3 rounds, respectively	-	-	5	-	2 rounds 1.04, 0.36–2.98, and 1.44, 0.34–6.15, 3 rounds 0.99, 0.62–1.59, and 1.23, 0.34–4.46, by slide and PCR, respectively
Cook et al 2015(b)[41]	Zanzibar	Very Low	MSAT	Non-randomized cluster controlled trial	5	5–10K	RDT**	2	ASAQ	53%/43% in rounds 1/2	-	-	6	no difference at any point (p=0.7)	-
Eisele et al #2016[28]	Zambia	High	MSAT+ fMDA	CRCT (3rd arm with MDA only)	10	30–50K	RDT	2	DP to household when ≥1 positive (3rd arm DP without screening)	63%/54% in rounds 1/2 (88/72% for MDA)	12	MSAT+fMDA 0.57, 0.13–2.50 (**MDA 0.13, 0.02–0.92**) by RDT§	5	MSAT+ fMDA 0.97, 0.73–1.29 (MDA 0.85, 0.63–1.15)	MSAT+ fMDA 0.75, 0.31–1.78 (**MDA 0.41, 0.18–0.98**) by RDT
Eisele et al #2016[28]	as above	Low	MSAT+ fMDA	as above	as above	as above	as above	as above	as above	63%/54% in rounds 1/2 (88/72% for MDA)	12	MSAT+fMDA 1.28, 0.36–4.6 (MDA 0.86, 0.25–3.04) by RDT§	5	MSAT+ fMDA 0.80, .60–1.08 (**MDA 0.50, 0.35–0.72**)	MSAT+ fMDA 0.77, 0.22–2.71 (MDA 0.30, .06–1.49) by RDT
Bousema et al 2016[38]	Kenya	Low	MSAT+ fMDA	CRCT	5	<5K	RDT**	1	AL to compound when ≥1 positive in febrile individuals or children	94%	4	difference 1.0, -8.3–10.4, p=0.8, by PCR	-	-	-

Statistically significant outcomes shown in **bold**.

CRCT	cluster randomized controlled trial
MSAT	mass screen and treat
fMDA	focal mass drug administration
K	thousand
RDT	rapid diagnostic test
OR	odds ratio
IRR	incidence rate ratio
AL	artemether-lumefantrine
DP	dihydroartemisinin-piperaquine
PQ	primaquine
ASAQ	artesunate-amodiaquine
POC	point of care

* assessed in children
** molecular testing also performed in assessments of parasite prevalence
† all ages unless otherwise indicated
¥ cases with parasite density >5000 p/μL in child <5 years of age per year
§ children <5 years of age
# one paper with two transmission settings

Two studies aimed to measure impact of MSAT on transmission reduction: a quasi-experimental study from Zambia[43] and an ecological study from Príncipe[44] The Zambia study took place in a moderate transmission setting among ~1,500 individuals from randomly selected households. One versus 5 rounds of MSAT over one year was compared, as was one versus 10 rounds over two years. Parasite prevalence by RDT was significantly lower in areas that received multiple MSAT rounds, and effects were greater in the area with lower baseline prevalence (a six- versus two-fold reduction was observed when baseline prevalence was 4% versus 24%). However, there was only one cluster per arm, prevalence was not measured concurrently in the comparison arms, and effects may have been overestimated due to the fact that households were repeatedly surveyed and their malaria prevention behaviors (including bed net usage and care-seeking) may have been influenced by study participation.[43] On Príncipe island, three rounds of annual, island-wide MSAT targeting about 6,000 individuals were carried out by the malaria program as part of a package of pre-elimination interventions that also included vector control, intermittent preventative therapy for pregnant women, and strong case management.[44] The dramatic decline in incidence from 16 per 100 population after other interventions were already in place to 0.7 per 100 population with the addition of MSAT suggested that MSAT was a critical component, but ecological effects could not be ruled out.

Five studies from low and very low transmission settings evaluated the yield or operational feasibility of different diagnostic approaches. In the Kenya highlands, the use of RDT to inform household-level treatment was evaluated to gauge the efficiency of a future MSAT+fMDA approach. RDT-positive households included 77% of PCR-positive individuals but the subsequent MSAT+fMDA trial, as described above, did not show notable impact.[45] In the other four studies from Cambodia,[32,34] Vanuatu,[31] and Zanzibar,[33] the use of molecular methods yielded positivity rates from under 1% to 3.8% and increased detection of infections by two- to five-fold compared to RDT. Three of these studies used molecular testing results in real-time to guide treatment.[32–34] In Cambodia, MSAT using PCR was evaluated, but the turnaround time between sample collection and treatment was high at 8 days. It was noted that a mobile lab would help overcome some of the delays and logistical challenges inherent in PCR-based diagnosis.[34] A more recent study from Cambodia also noted long turnaround times for PCR and called for more sensitive POC diagnostics.[32] However, in Zanzibar, LAMP (a molecular test that can be conducted with a 3-hour turnaround time) was deemed neither field-friendly nor operationally feasible as a programmatic tool due to cost and complexity of the methods.[33]

Overall operational feasibility was assessed in a program experience report from a low transmission region in Ethiopia.[46] One round of MSAT was implemented in approximately 30,000 individuals residing in six villages. RDT positivity rate was 1.4% on average, and no clear risk factors for infection were identified. The staff and training needs for this pilot were believed to exceed existing programmatic capacity.[46] A previously-described study in Cambodia evaluated MSAT delivery methods: to address the challenge of reaching mobile populations and migrant workers, proactive case detection was conducted in villages in conjunction with pre-intervention social mobilization and promotion. Attendance by at-risk and mobile populations was consistently high across three rounds of proactive MSAT.[32]

RACD

The RACD studies were evenly split between sub-Saharan Africa and Asia Pacific, plus three studies from the Americas (Figure 2 and Table 3). Six of the sub-Saharan Africa studies took place in Zambia. The majority of the RACD studies were carried out in very low transmission settings in countries in the pre-elimination or elimination phase. Two studies from China took place in provinces in a prevention of reintroduction (POR) phase.[30,47] There were no intervention studies designed to measure impact of RACD on transmission. *P. falciparum* was the predominant/targeted parasite species in two-thirds of the studies, and *P. vivax* in one-third. The median duration of the studies was 12 months. Median number of RACD events was 113, and median number of individuals screened in each study was 1,621. The numbers screened per event were not consistently reported, but the average number of individuals screened per RACD event was calculated and the median number across studies was 17. All studies were observational with a cross-sectional study design, of which seven also included a case-control design whereby standard RACD was compared to RACD conducted in control household(s).[24,48–53] The main goals of these studies were to evaluate **1)** household-level clustering, **2)** operational considerations, and/or **3)** yield of different diagnostic approaches. Some studies provided a descriptive assessment of the value of RACD activities to the program; these are included in the Programmatic experiences section.[29,54–58]

Household-level clustering

The rationale for RACD is based on the assumption that local transmission potential is higher around the residence of an index case, leading to the clustering of infections. To test this hypothesis, studies implemented a case-control or cross-sectional study design. Some studies compared the

Table 3: Details of RACD empirical research studies

Study	Country	Setting	Parasite species	Study period (months)	Sample sizes		
					No. screened	RACD events	Avg No. screened per RACD event
Branch et al 2005[23]	Peru	Moderate	Pv > Pf	4	573	-	-
Hamze et al 2016[48]	Democratic Republic of Congo	Moderate	Pf	2	68	19	4
Larsen et al 2015(a)[29]	Zambia (Lusaka)	Moderate	Pf	12	3,955	144	27
Larsen et al 2015(a)[29]	Zambia (S. Province)	Moderate	Pf	12	143,295	1,848	78
Aidoo et al 2018[51]	Kenya	Low	Pf	12	720*	50	14
Larsen et al 2017[55]	Zambia	Low	Pf	24	14,409	854	17
Molina Gomez et al 2017[26]	Colombia	Low	Pv > Pf	N/R***	288	16	18
Pinchoff et al 2015[62]	Zambia	Low	Pf	12	1,621	426	4
Rogawski et al 2012[37]	Thailand	Low	Pv > Pf	0.5	187	1	187
Rulisa et al 2013[49]	Rwanda	Low	Pf[99]	6	N/R***	115	-
Stresman et al 2010[50]	Zambia	Low	Pf	3	186	23	8
van Eijk et al 2016[12]	India (Chennai)	Low	Pv	12	868	18	48
van Eijk et al 2016[12]	India (Nadiad)	Low	Pv > Pf	12	131	20	7
Chihanga et al 2016[54]	Botswana	Very low	Pf	26	3,237	277	12
Cotter et al 2017[30]	Thailand	Very low	Pv > Pf[99]	12	18,505	271	68
Cotter et al 2017[30]	Indonesia	Very low	Pk > Pv > Pf[35]	4	931	57	16
Deutsch-Feldman et al 2018[59]	Zambia	Very low	Pf	15	3,016	145	21
Donald et al 2016[31]	Vanuatu	Very low	Pf > Pv	12	173	5	35
Feng et al 2018[57]	China	Very low	Pv > Pf	48	5,144	150	34
Fontoura et al 2016[24]	Brazil	Very low	Pv	6	5,866*	41	143
Herdiana et al 2016[35]	Indonesia	Very low	Pk > Pv > Pf	19	1,495	36	42
Hustedt et al 2016[53]	Cambodia	Very low	Pv > Pf	10	1,898*	270	7
Littrell et al 2013[60]	Senegal	Very low	Pf	3	5,520	110	50
Rossi et al 2018(a)[36]	Cambodia	Very low	Pf > Pv	19	785	194	4
Rossi et al 2018(b)[32]	Cambodia	Very low	Pf > Pv	4	273	30	9
Smith et al 2017[52]	Namibia	Very low	Pf	19	1,856	116	16
Sturrock et al 2013[61]	Swaziland	Very low	Pf	31	3671	250	15
Tejedor-Garavito et al 2017[58]	Swaziland	Very low	Pf	22	9,859	N/R***	-
Wang et al 2017[56]	China	Very low	Pv	36	3,662	182	20
Cotter et al 2017[30]	China	Prevention of reintroduction	Pf	12	N/R***	19	-
Zhang et al 2018[47]	China	Prevention of reintroduction	Pf > Po > Pv > Pm	48	3,461	N/R***	-

* Denominators for molecular testing different (Aidoo et al n=571, Fontoura et al n=5807, Hustedt et al n=1596)
** Total positivity rate 0.3% but RDT/Slide and PCR-specific rates not reported
*** Not reported

Study	Target population beyond index HH	POC testing			Molecular testing		
		method	% positive	% increase in cases (vs PCD alone)	method	% positive	% increase in cases (vs PCD alone)
Branch et al 2005[23]	100m	Slide	32.5	-	-	-	-
Hamze et al 2016[48]	-	RDT	7.4	26.3	-	-	-
Larsen et al 2015(a)[29]	8 adjacent HH	RDT	1.9	45.8	-	-	-
Larsen et al 2015(a)[29]	140m	RDT	15.5	1201.4	-	-	-
Aidoo et al 2018[51]	5 HH within 100m	Slide	10.0	144.0	PCR	25.2	288.0
Larsen et al 2017[55]	140m	RDT	8.3	140.5	-	-	-
Molina Gomez et al 2017[26]	4 closest HH	Slide	3.8	68.8	PCR	14.2	256.3
Pinchoff et al 2015[62]	-	RDT	45.0	172.5	-	-	-
Rogawski et al 2012[37]	1km, high risk groups	Slide	0.5	100.0	pooled PCR	2.1	400.0
Rulisa et al 2013[49]	N/R***	RDT	-	-	-	-	-
Stresman et al 2010[50]	-	RDT, Slide	2.7	21.7	PCR	7.0	56.5
van Eijk et al 2016[12]	200m	Slide	0.5	22.2	PCR	0.5	22.2
van Eijk et al 2016[12]	1 km	Slide	0.0	0.0	PCR	0.0	0.0
Chihanga et al 2016[54]	100m	RDT	1.1	13.4	-	-	-
Cotter et al 2017[30]	1-2km	Slide	0.1	9.6	-	-	-
Cotter et al 2017[30]	500m	Slide	0.3	5.3	-	-	-
Deutsch-Feldman et al 2018[59]	140m and 250m	RDT	1.1	22.8	PCR	2.4	50.3
Donald et al 2016[31]	500m	RDT	0.0	0.0	PCR	0.1	20.0
Feng et al 2018[57]	300m	RDT	0.1	4.0	-	-	
Fontoura et al 2016[24]	5 HH within 3km	Slide	1.8	263.4	PCR	5.0	714.6
Herdiana et al 2016[35]	500m	Slide	0.2	8.3	LAMP, PCR	0.4	16.7
Hustedt et al 2016[53]	5-10 HH	RDT	0.5	3.3	PCR	1.1	6.3
Littrell et al 2013[60]	100-150m, 300-500m	RDT	0.4	20.9	-	-	-
Rossi et al 2018(a)[36]	co-workers/co-travelers	RDT	0.9	3.6	PCR	3.9	16.0
Rossi et al 2018(b)[32]	co-workers/co-travelers	RDT	0.0	0.0	PCR	1.1	10.0
Smith et al 2017[52]	4 HH	RDT	1.0	15.5	LAMP	2.3	36.2
Sturrock et al 2013[61]	1km	RDT	2.0	29.6	-	-	-
Tejedor-Garavito et al 2017[58]	1km, then 500m	RDT	1.1	-	-	-	-
Wang et al 2017[56]	N/R***	RDT	0.3	5.5	-	-	-
Cotter et al 2017[30]	1km	RDT	-	0.0	-	-	-
Zhang et al 2018[47]	febrile co-travelers only	RDT, Slide	**	-	PCR	**	-

Pf *Plasmodium falciparum*
Pv *Plasmodium vivax*
Pk *Plasmodium knowlesi*
Po *Plasmodium ovale*
Pm *Plasmodium malariae*

HH household
RDT rapid diagnostic test
PCR polymerase chain reaction
LAMP loop-mediated isothermal amplification
PCD passive case detection

* Denominators for molecular testing different (Aidoo et al n=571, Fontoura et al n=5807, Hustedt et al n=1596)
** Total positivity rate 0.3% but RDT/Slide and PCR-specific rates not reported
*** Not reported

yield of household clustering in RACD to another high-risk control, and others used genotyping to assess clustering.

Seven studies implemented a case-control design to evaluate household clustering around index cases. In four studies,[24,50–52] yield of RACD within index case households was compared to yield in randomly selected control households; two of these restricted control households to within a minimum distance from case households.[24,51] In two other case-control studies,[48,49] yield of RACD within index case households was compared to yield in the households of fever patients who tested negative for malaria. In the final case-control study, yield by standard RACD was compared to proactive case detection in areas with high or low incidence in the prior year.[53] The case-control studies were conducted in moderate (n=1), low (n=3), and very low (n=3) transmission settings. Except for two studies from *P. vivax*-predominant, very low transmission settings in Brazil and Cambodia,[24,53] all studies were from *P. falciparum*-predominant settings in sub-Saharan Africa.

RACD triggered by confirmed index cases was more likely to identify additional infections compared to controls in all of the African case-control studies except for one from a moderate transmission, internally displaced persons (IDP) camp setting where there was no difference.[48] Reported odds ratios for infection in case versus control households in the African studies ranged from 1.3 to 6.1 and were generally higher in low and very low transmission settings. In the two African studies that compared risk in households neighboring index cases versus control households, one from a low transmission setting found similar risk in index households.[51] The other, from a very low transmission setting, found a 5.0 times higher adjusted odds for infection among neighboring households.[52] In the case-control study from a *P. vivax*-predominant setting in Brazil, there was 3.4 and 1.6 higher adjusted odds of infection in index and neighboring households, respectively, compared to control households.[24] Of note, this study used aggressive RACD with four total testing visits over a 180-day period. Finally, the case-control study from a *P. vivax*-predominant setting in Cambodia showed a higher odds of infection detection in both the high and low incidence control households compared to index case and neighboring households.[53] These results suggest that proactive case detection may be more efficient than household-based RACD in settings where exposure to malaria occurs away from the community. However, testing of case and control households was not conducted contemporaneously.[53]

Several other RACD studies utilized a cross-sectional study design to evaluate household clustering by comparing test-positivity rates in households with closer proximity to index cases versus households farther away. Although RACD coverage was not uniform and often not reported, all confirmed such clustering.[23,35,55,58–61] Only one study, from Zambia, showed no difference in risk of infection in index versus neighboring households, but households beyond 250 meters were not sampled, precluding assessment of decreasing risk with distance from the index case.[59] Of note, only two of the cross-sectional studies were from non-African settings. One, a *P. knowlesi*-predominant setting in Indonesia, did show evidence of household clustering, but due to the small sample size, the analysis did not adjust for other risk factors such as forest exposure.[35] In the other, a *P. vivax*- and *P. falciparum*-endemic setting in the Peruvian Amazon, significant spatial clustering was observed for both species within households of index cases and those immediately adjacent.[23]

To confirm local transmission as a driver of clustering, three studies used genotyping to examine relatedness between index cases and additional infections found through RACD. Single-nucleotide polymorphism genotyping analysis in a study from Cambodia showed relatedness of *P. falciparum* infections among co-exposed individuals.[36] In a Colombian study, *P. falciparum* and *P. vivax* microsatellite genotyping was used; none of the genotypes found in primary cases matched those found in secondary cases, though some genotypes were shared among the secondary cases.[26] In a *P. vivax*-predominant setting in Brazil, two thirds of all infections were genetically unrelated to each other within an apparent malaria cluster, but most clusters had at least one identical or similar genotype shared by two or more parasite samples.[24]

Operational Considerations

Almost half of the RACD studies evaluated different operational components of RACD, including aspects of the triggering case, response time, radius size or target population, number of rounds, coverage, diagnostic method, antimalarial drug, and how certain epidemiological risk factors were associated with increased yield. While some studies explored these questions through case-control or cross-sectional study designs, most presented their evaluations descriptively. Monitoring of RACD in terms of completeness and data quality were also common themes.

Triggering index case

The triggering case was usually referred to as the index, or sometimes sentinel case. Index case considerations included: **1)** detection method (passive and/or active), **2)** case origin (local versus imported), and **3)** species. In all studies, symptomatic laboratory-confirmed (RDT or microscopy) cases passively detected and reported at health facilities triggered RACD. In three studies, RACD was triggered by cases found in active (or proactive) case

detection.[23,26,32] Only one of these studies compared yield of RACD between the two different types of triggering index cases; the sample size was small (n=8 RACD events for each type of index case) but, interestingly, yield for RACD triggered by a passively versus actively detected index case was higher by microscopy (4.6% versus 2.7%) but lower by PCR (8% versus 24%).[26] Except for four studies from southern Africa, most studies did not specify whether case origin was considered in the decision to implement RACD. In Zambia, RACD was limited to locally-acquired cases.[29,59] In Swaziland, locally-acquired cases always triggered RACD; imported cases also triggered RACD if there was potential for local transmission near the residence, but no analysis was reported on whether local versus imported cases were more likely to result in the identification of positive secondary cases.[58,61] In terms of species, most studies did not specify any requirements for the index case. However, in three studies from mixed *P. falciparum/P. vivax*-endemic settings, RACD was only initiated for *P. falciparum* index cases.[23,32,36] In Cambodia, the rationale for targeting *P. falciparum* only was a national goal to eliminate drug-resistant *P. falciparum*;[32,36] in Peru, the rationale was not stated.[23]

Timing and frequency

Because the goal of RACD is to obtain timely surveillance information or prevent ongoing transmission, it is generally performed as soon as possible. Fourteen studies reported RACD response time; median was within 7 days of the index case diagnosis. Of two studies[52,61] that analyzed the association between infection and response time, only one found that secondary cases were more likely to be detected with RDT when RACD was conducted within 7 days of index case detection.[61] With regards to frequency of RACD, almost all studies reported one round. Some studies reported on the number of return visits necessary to maximize coverage of the target population and/or capture secondary cases that may not have been detectable during the first visit (median three visits).[23,24,50–52,60] In one study from Brazil, the target population was sequentially targeted in four testing rounds over 180 days in order to catch secondary cases as well as *P. vivax* relapses, which in that area usually occurred within 180 days.[24] Infections were detected in each round and it was estimated that such aggressive RACD was still missing almost 80% of the infections in the population.

Target population based on radius or risk factors

Nearly all studies included index case households among their target populations; only one[47] implemented RACD solely among co-travelers to prevent reintroduction of malaria (Table 3). All but four studies[48–50,62] targeted populations beyond the index household, with the upper limit reported as maximum meters (median 500, range 100 to 3000) or number of households (median 5, range 4 to 10). In the decision regarding whether and how far to screen beyond the index case household, maximum flight range for *Anopheles* mosquitoes as well as local or published data regarding clustering of infections were considered.[24,29,35,59,61] However, determination of screening radii also reflected operational considerations, including: population density (e.g. urban versus rural setting),[12,29,60] ecological conditions facilitating local transmission (e.g. transmission season, rainfall, proximity to water sources, vector densities),[26,49,61,62] and general feasibility given resource and time constraints.[12,55–57,61]

Individual-level clinical or demographic factors were also considered in protocols or analyses regarding the optimal target population. In addition to co-travelers, co-exposed or occupational contacts (e.g. forest workers) were also included in RACD due to their increased risk.[32,36,37] One of these studies compared test positivity rates of this approach to standard RACD of households and found no difference.[32] Current or recent fever was found to be a risk factor for infection detection in RACD,[35,48,53,55] but a general finding was that a significant proportion of infections were asymptomatic. Nonetheless, and presumably due to operational constraints, three studies restricted screening to subjects with fever, including two Chinese studies[47,56] and the study of RACD in an IDP camp.[48] Other risk factors associated with infection detection in RACD include past history of malaria,[24,53] male gender,[32,35,47,52,58,60] and lack of vector control (e.g. indoor residual spray coverage or bed net use).[49,50,52,53,61] However, no studies directly targeted these characteristics for screening.

Taken together, findings of associations between individual level risk factors for infection detection suggested that these individuals could be prioritized for RACD.[60] Given that most of the resources associated with RACD are put toward the field visit and not screening of individuals (see Costing and Programmatic sections), we also reviewed the studies to see if any examined index case and household-level risk factors that would inform whether an RACD event or household screening could be avoided. However, outside of ecological factors and household-level indoor residual spray coverage, no studies assessed whether such factors were associated with increased detection of infections

Diagnostic method

Standard microscopy and/or RDT was used in all RACD studies. None of the studies using microscopy reported turnaround time for microscopy results, nor commented on feasibility of using microscopy for RACD. No studies

reported any operational challenges with the use of RDT. For the four studies that used molecular testing to inform treatment, real-time multiplex PCR was conducted locally by a research institute[32,36,37] with a >12 day turnaround time or LAMP was conducted within a local health department[35] with turnaround time <7 days (personal communication).

Antimalarial drug

When reported, most studies used the local first line antimalarial drug to treat malaria infection detected in RACD. Only two studies reported using single low-dose primaquine to treat RACD-detected *P. falciparum* infections.[32,36]

Monitoring of routine RACD implementation

In recognition of the absence of standardized metrics to evaluate RACD performance, a monitoring and evaluation (M&E) tool was piloted in three countries – China, Indonesia, and Thailand – that routinely use RACD. Piloting the tool revealed important operational gaps and challenges in each country, allowing the programs to strengthen procedures and improve decision-making and accountability. Study authors recommended that the essential indicators utilized in the M&E tool be widely adopted in order to standardize routine monitoring and evaluation of RACD (Box 2).[30] A few other studies of program implementation of RACD reported challenges with high coverage of target populations.[54,55,61] No other studies of program implementation reported on data quality of RACD.

Box 2: RACD indicators[30]

Malaria cases reported to the database from health facilities
Malaria cases reported to the database within a specified amount of time
Malaria cases reported to the database that were investigated
Malaria cases reported to the database that were investigated within a specified amount of time
RACD events that occurred (out of total RACD events that should occur)
RACD events that occurred within a specified amount of time
Total population screened during RACD events*
Positive malaria cases identified through RACD

* Ideally, total population available to be screened will be recorded to determine screening coverage achieved

Yield of RACD using different diagnostic approaches

The most common measure used to report the yield or benefit of RACD was test positivity rate among individuals screened using standard POC diagnostics. Some studies also used more sensitive molecular methods, including LAMP, nested PCR, real-time multiplex PCR, quantitative PCR, and, in one study,[37] pooled PCR. Molecular testing results were reported mainly for research or surveillance purposes, as turnaround time and logistics precluded their use to inform treatment in most studies. While not directly reported by most studies, we calculated the percent increase in detection of cases using RDT/microscopy-based RACD compared to PCD alone, and the added yield of using PCR/LAMP-based RACD (Table 3 and Figure 3).

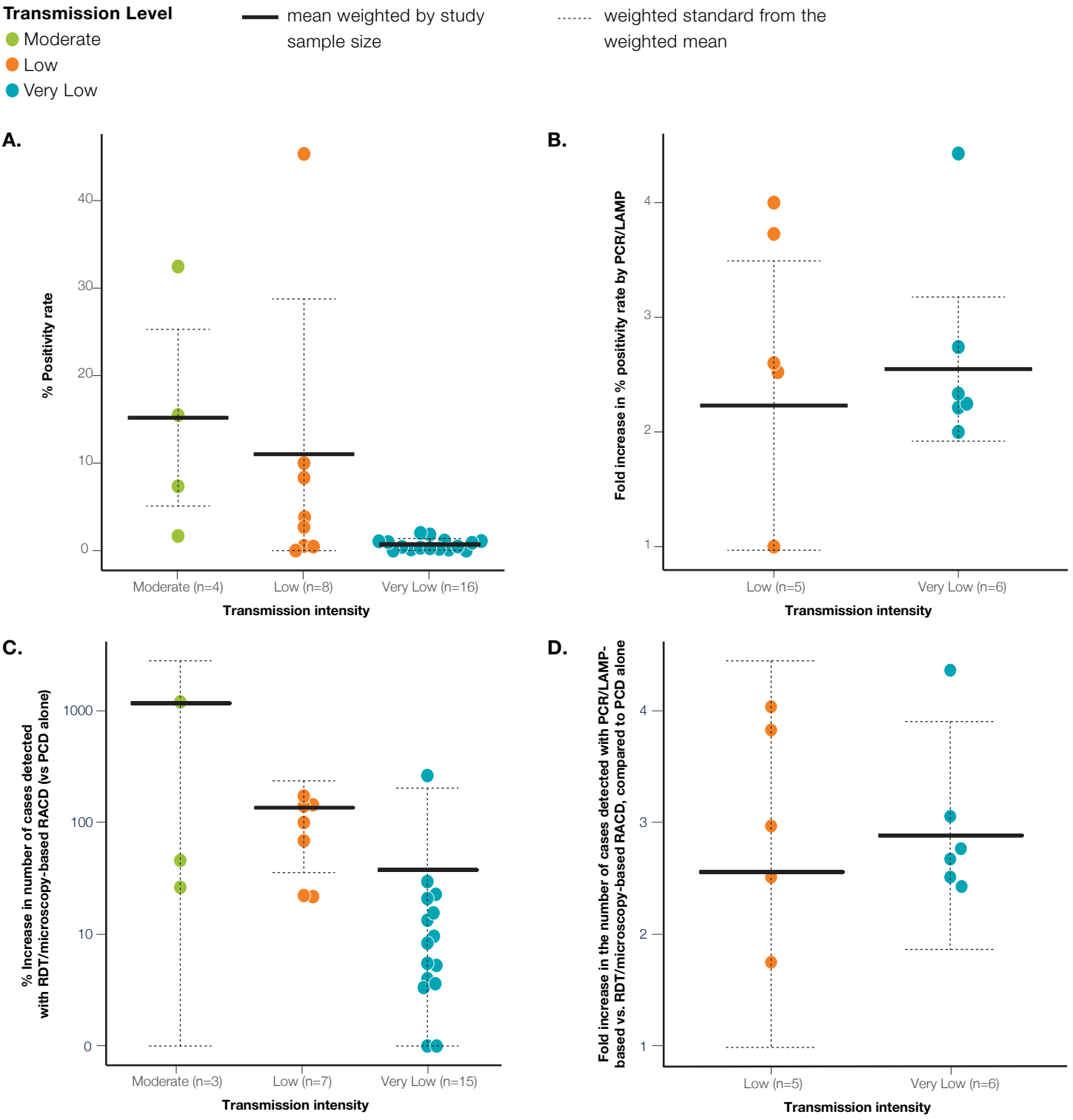
Test positivity rate among individuals screened

In 28 of the 31 studies, test positivity rates for RACD using standard POC diagnostics were reported. Test positivity rates correlated with transmission intensity: weighted means were 15.2%, 11.0%, and 0.7% in moderate, low, and very low transmission settings, respectively (Figure 3A). Removing the outliers (upper outliers present in moderate[23] and low[62] transmission settings), the mean remained similar for moderate transmission settings (15.1%) but decreased to 7.7% for low transmission settings. More sensitive molecular testing was used in 14 studies, all of which were from low or very low transmission settings. In eleven studies with non-zero values for test positivity by both methods, use of molecular methods increased detection of infections by 2.2 fold in low transmission settings and 2.5 fold in very low transmission settings (Figure 3B).

Increased detection of cases using RACD compared to PCD alone

In 27 of the 31 studies, the number of index cases triggering RACD was reported, enabling a calculation of percent increase in the number of cases detected by RACD compared to PCD alone. As with test positivity rate among individuals screened, this value correlated with transmission intensity: weighted means were 1169%, 136%, and 38% for moderate, low, and very low transmission settings, respectively (Figure 3C). However, removing the upper outlier for moderate[29] and very low[24] transmission settings, the weighted means were 45% and 12%, respectively. Using molecular methods in RACD, the fold increase in the number of cases detected with RACD compared to PCD alone was similar to the fold increase in test positivity rate among individuals screened in RACD: 2.1- and 2.5-fold in low and very low transmission settings, respectively (Figure 3D).

Figure 3. Yield of RACD for infection detection, by transmission intensity setting.
A. Percent positivity rate among individual screened, using RDT or microscopy, **B.** Fold increase in % positivity rate using PCR/LAMP as compared to RDT/microscopy, **C.** Percent increase in the number of cases detected by RDT/microscopy-based RACD versus PCD alone, **D.** Fold increase in percent increase in the number of cases detected by PCR/LAMP-based versus RDT/microscopy-based RACD, compared to PCD alone.



Estimates on the proportion of the population parasite reservoir reached by RACD

In 27 of the 31 studies, the number of index cases triggering RACD was reported, enabling a calculation of percent increase in the number of cases detected by RACD compared to PCD alone. As with test positivity rate among individuals screened, this value correlated with transmission intensity: weighted means were 1169%, 136%, and 38% for moderate, low, and very low transmission settings, respectively (Figure 3C). However, removing the outliers (upper outlier present in moderate[29] and very low[24] transmission settings), the weighted means decreased to 45% and 12%, respectively. Of note, there were limited data for moderate transmission settings (only two data points after removing the outlier). Using molecular methods in RACD, the fold increase in the number of cases detected with RACD compared to PCD alone was similar to the fold increase in test positivity rate among individuals screened in RACD: 2.1- and 2.5-fold in low and very low transmission settings, respectively (Figure 3D).

Other surveillance outcomes

Although RACD is considered a method to identify hotspots or active foci,[12,52,57,61] no studies reported on these measures. RACD is also recommended as a surveillance tool that can inform targeting of interventions.[63] However, no studies reported on the use of RACD to inform intervention targeting.

Other surrogate outcomes of transmission

Of the aforementioned case-control studies, one measured gameotocytemia and found no differences in control versus case households.[50] One study measured vector density and found no difference between index case and neighboring households compared to controls.[51]

Modeling studies

Since 2010, 20 mathematical and simulation models have been developed to estimate the impact and efficiency of various SAT strategies. The vast majority (n=17, or 85%) have been developed for Africa, either for multiple sites,[64–68] or focusing on particular countries, primarily Zambia (n=7, or 41%),[13,69–74] South Africa (n=3, or 18%),[75–77] and Tanzania (mainland and Zanzibar; n=2, or 12%).[78,79] Only three modeling studies focused on non-African geographies, including two in Asia Pacific (Myanmar and Lao People's Democratic Republic [Lao PDR])[80,81] and one in the Americas (Peru).[27] Most modeling studies (n=10, or 50%) compared the impact of SAT interventions across a range of transmission settings. Of the remaining ten studies, five were in very low transmission settings (25%), two in low (10%), two in moderate (10%), and one in high (5%). Ten studies modeled MSAT (50%), four modeled FSAT (20%), and five modeled RACD (25%); one study modeled both MSAT and RACD (5%).

Several studies examined the impact of MSAT by varying timing, frequency, drug, and diagnostic sensitivity. A study in a low transmission setting in Peru found that three monthly rounds of MSAT at 100% coverage during the dry season could significantly reduce *P. falciparum* transmission to elimination levels if sustained over ten years. Using molecular methods for infection detection, time to elimination was reduced to four years; lower coverage using either diagnostic approach extended the necessary length of time.[27] Similarly, in an African setting with marked seasonal transmission, three monthly dry season MSATs had more impact than a single MSAT; the effects were most pronounced but shortest-lived in high transmission areas unless repeated. Increasing coverage and diagnostic sensitivity and combining MSAT with vector control increased the impact in all transmission levels.[67] Another model found that regular MSATs using highly sensitive diagnostics (detecting 2 parasites/µl) could lead to elimination in lower transmission settings but would not be effective in high transmission settings; however, a more sensitive diagnostic could reduce the number of MSAT interventions needed to achieve elimination.[68] In Zambia, coverage achieved during MSAT was more important for determining impact than drug choice.[69,74]

The impact of MSAT in combination with other interventions was modeled in three studies. Adding MSAT to high coverage of ITNs can speed up reduction of transmission and reach elimination levels in lower transmission settings in Africa; in moderate transmission settings, adding MSAT to high coverage of ITNs plus IRS is also effective.[66] Similar results were seen in a model that examined the impact of adding MSAT to ITNs and strong case management in moderate and high transmission settings in Africa.[65] From a cost-effectiveness perspective, MSAT is most efficient at reducing transmission when added to moderate coverage of ITNs in moderate and high transmission settings, but it is not cost-effective on its own or in lower transmission settings.[64]

Three studies modeled the impact of MSAT compared to MDA and determined that MDA has more impact on reducing transmission than MSAT due to limited infection detection of standard diagnostics.[70,78,79] In settings where cases are known to cluster, MSAT followed by fMDA is more effective than MSAT alone.[70,78] However, serology-based MSAT may be an effective strategy for achieving elimination in lower transmission settings if coverage is high.[70]

The four FSAT studies modeled the impact of proactive case detection among visitors and returning residents at border entry points. Three took place in South Africa at the border with Mozambique and the fourth in Lao PDR; all four modeled *P. falciparum* transmission.[81] Three of the studies modeled proactive FSAT as part of a comprehensive package of interventions that included vector control and MDA, and determined that FSAT on its own could reduce the infectious reservoir but was not sufficient to achieve elimination; however, it was deemed an essential component of the full intervention package.[75,76,81] The other study examined the role of coverage and diagnostic sensitivity on the impact of proactive FSAT at border entry points on transmission.[77] Regardless of coverage achieved or sensitivity of diagnostic, FSAT alone could reduce but not eliminate transmission, and the impact was short-lived. The modeled reductions were more pronounced as the sensitivity of diagnostic tool increased, and diagnostic sensitivity had a greater effect on transmission than coverage achieved. Regular implementation of FSAT at borders using a highly sensitive RDT (which was hypothetical when the study was published) was deemed a key component of an integrated elimination strategy.[77]

Four modeling studies sought to determine the proportion of the infected population detected through RACD with various screening radii and in different transmission settings. Three took place in Southern Province, Zambia[13,72,73] and one in the Myanmar-Thailand border.[80] In a Zambia study published in 2013, modeling indicated that RDT-based RACD within a 500m radius of index cases would detect 90% of positive individuals in a moderate transmission setting (23% prevalence), but only 76% in a low transmission setting (8% prevalence).[72] Similarly, a 2016 Zambia modeling study using data from districts with less than 1% prevalence showed that RDT-based RACD within a 140m radius of index cases would detect only 22% of positive individuals, and concluded that RACD is not sufficient to achieve malaria elimination in very low transmission settings.[73] However, the third Zambia study model indicated that RDT-based RACD detects higher proportions of the infectious reservoir in lower prevalence areas versus moderate, likely a result of greater case clustering as transmission levels decline. Using diagnostics with greater sensitivity and implementing RACD with wider search radii will capture more positive individuals in the target population, yet yield was not substantially higher with either approach and both require considerably more human and financial resources. Thus, these approaches may not be operationally feasible for many malaria programs.[13] The Myanmar modeling study in a low transmission setting came to similar conclusions: RDT-based RACD was more effective at detecting a higher proportion of cases with larger screening radii (>150m), but results were no better than random household screening and would require significant investment of resources. In addition, household clustering in this transmission setting is less likely due to high population mobility, occupation-based risk factors, and the occurrence of *P. vivax* relapses; thus, household-based RACD is not an efficient strategy for interrupting transmission.[80]

In two additional studies from Southern Province, Zambia, the optimal scenarios for RACD to reduce transmission were modeled. Standard RACD, whereby treatment is based on individual RDT results, was found to be most effective in settings with low importation and where transmission has recently been reduced. In historically low transmission settings, it was assumed that the bulk of infectious individuals are symptomatic and best treated through strong case management instead.[71] Another study evaluated population-level infection detection strategies. In all transmission settings, RACD + fMDA based on results of RDT in sentinel individual(s) were not effective for transmission reduction. In low transmission settings aiming for elimination, RACD + fMDA did not identify more hotspots already identified by the clinical index case, and other, more proactive strategies using serology to detect infection in the past year (MSAT with treatment of serology-positive individuals, or fMDA with treatment to an entire household based on at least one serology-positive household member) were more effective. However, the model did not take into consideration population mobility, cost, nor operational feasibility of deploying serology-based detection strategies.[70]

Costing/economic studies

Ten papers used empirical data with or without modeling to evaluate the costs and/or cost-effectiveness of MSAT (n=3), FSAT (n=1, of border screening), or RACD (n=6).

The first MSAT study was published in 2005 and compared the costs of microscopy-based MSAT with PCD in Brazil.[25] Despite cost per positive smear being 2.3 times more than PCD (122 versus 52 USD), MSAT was deemed worth the extra investment in light of the additional cases detected and treated. Also, with most of the costs due to start-up and training, cost per positive smear would decrease with increased testing. More recently, a modeling study designed to estimate the cost-effectiveness of MSAT under optimal conditions found that the intervention is most efficient when used to reduce malaria burden in higher transmission settings, particularly if the malaria program has adequate resources and the

capacity to implement regularly at high coverage.[64] In low transmission settings, MSAT was not at all cost-effective for transmission reduction or reduction of malaria burden. The model assumed the use of microscopy or standard RDTs; it was noted that efficiency would likely improve across transmission settings if more sensitive diagnostics were used instead.[64] The findings from the MSAT modeling exercise were borne out in the field, through a cost-effectiveness analysis[82] conducted alongside a previously discussed MSAT intervention study in a moderate transmission setting in Zambia.[42] For reduction of malaria burden, the net cost per disability adjusted life-year (DALY) averted was estimated to be highly cost-effective at 804 USD. The total cost per RDT used and AL treatment course administered across three MSAT rounds in four locations was also reported and found to be low at 4.39 and 34.74 USD, respectively.[82]

The programmatic costs associated with achieving elimination and sustaining a POR campaign were summarized in a case study from Mauritius.[83] During the elimination phase, the malaria program carried out both RACD and proactive case detection through the screening of passengers at ports of entry, and continued the passenger screening during the POR phase. Per capita costs for this strategy declined by 40% when the program transitioned from elimination to POR and personnel and operating costs were integrated into the larger health system. Passenger screening remained one of the most significant overall cost drivers (one-third of total costs) due to the heavy operational and human resource requirements, yet this only represented a small amount (0.70 USD) compared to total annual health expenditures per capita (247 USD).[83]

Six studies examined costs associated with RACD. Two papers, one a study from Zambia and another covering three sites in Asia Pacific, also developed costing frameworks to aid programs in predicting budgetary needs. In a moderate transmission setting in Zambia, mean annual cost per health facility catchment area was 1177 USD, and the main cost drivers were personnel (CHWs) and data review.[84] Rapid diagnostic tests and drugs accounted for less than 10% of total costs. In a POR setting (China), and two very low transmission settings (Indonesia and Thailand) in Asia Pacific, annual case investigation and RACD costs per health facility catchment area were 1688, 719, and 4468 USD, respectively (calculated using data in paper).[30] Higher costs in Thailand could be attributed to the vertical malaria program structure with facilities, personnel, and commodities earmarked for malaria specific activities, while lower costs In China and Indonesia were a result of better integration of malaria elimination/POR activities into the larger health system. There were also fewer index cases and a shorter malaria season in China. As with border screening in the Mauritius POR setting, RACD costs in China during POR accounted for a significant portion (50%) of total monthly malaria expenditures.[30]

A study from a moderate transmission, IDP camp setting in Democratic Republic of Congo compared the costs per case diagnosed and treated of RACD targeting **1)** all household members of positive index cases only, **2)** all household members of positive index cases and negative fever cases, or **3)** only symptomatic household members of positive index cases and negative fever cases.[48] The cost per diagnosed and treated case for the three approaches was 24, 23, and 7 USD, respectively. In comparison, the cost per individual diagnosed and treated through household-based RACD in the aforementioned very low transmission sites in Asia Pacific was 1242 USD in Indonesia and 940 USD in Thailand (calculated using data in paper). These figures reflect not only the more comprehensive capture of costs (including personnel, services, and other costs) versus the IDP camp study, but also the reduced yield of RACD due to lower test positivity rates in very low transmission settings.[30]

In Senegal, the cost-effectiveness of RACD as part of a comprehensive malaria intervention package was assessed based on cost per DALY averted.[85] Specifically, a malaria elimination package of standard interventions plus RACD, implemented in one very low transmission district, was compared to other intervention packages which include standard interventions +/- indoor residual spraying +/- seasonal malaria chemoprevention and are implemented in higher transmission districts. Of the various intervention packages, the RACD package had one of the lowest costs per capita at 0.68 USD; in comparison, the national-level cost for all intervention packages combined was 0.82 USD per capita. At 1591 USD per DALY averted, the RACD package cost was 3 to 21 times higher than the non-RACD packages, but it was still considered cost effective using a reference of three times the GDP per capita. A major limitation of the study, however, was that estimates of DALYs averted were based on observational data (decline in incidence following implementation of the RACD package was fully attributed to the intervention).[85]

A final study not captured in the literature search (but which has since been published) compared the costs and cost-effectiveness of RACD using microscopy versus LAMP in Aceh Besar, Indonesia.[86] The average costs were high (1178 USD per RACD event and 7070 USD per

individual diagnosed and treated), primarily driven by the personnel cost category, but the overall cost per capita per year was low at 0.42 USD. Compared to microscopy, the use of LAMP in RACD was more cost-effective for the detection of infections. The incremental cost effectiveness ratio was 5907 USD per infection detected.[86]

Community acceptability studies

Community acceptability of SAT approaches was the focus of three qualitative studies: one study focused on FSAT, or proactive screening of travelers at ports of entry in a very low transmission setting and the other two focused on MSAT in moderate and high transmission settings in Africa. There were no studies of acceptability of RACD.

In Isabel Province, Solomon Islands, the malaria program was considering implementing SAT of all travelers at ports of entry as part of their elimination strategy and wanted to determine the feasibility and acceptability of this approach.[87] Community perceptions of SAT were elicited through focus group discussions, interviews, and field observations. While most participants were supportive of the strategy and elimination goal, they suggested that compliance would improve through education and awareness campaigns, coordination with private companies, implementation of provincial legislation, and engagement with local chiefs and religious organizations. The program has since determined that port screening is too expensive and logistically challenging, and instead will rely on a more informal system in which community members identify new arrivals and direct them to health facilities for testing.[87]

The other two studies examined community perceptions of MSAT to determine the feasibility of adding the approach to their respective national malaria control strategies.[88,89] In Zambia and Kenya, CHWs and community members were interviewed during and after research-based MSAT campaigns to identify knowledge, attitudes, and barriers to participation. Overall, MSAT was perceived positively by the community, but in both locations there was a general distrust and suspicion related to having blood drawn. In addition, interviews revealed a lack of understanding of asymptomatic malaria and why testing and treatment are necessary in the absence of symptoms. Strategies identified by CHWs and community members to improve acceptability and participation included culturally-appropriate education campaigns, community sensitization through the engagement of local leaders, directly observed treatment, and formal certification of CHWs to elevate their status in the community and instill trust.[88,89]

Of the empirical research already discussed, three of the MSAT intervention studies[41,42,46] and four of the RACD studies[12,51,52,60] discussed challenges related to achieving high coverage, noting that absenteeism and refusals were common. Because both MSAT and RACD are time- and resource-intensive, planning multiple visits to track down those in the target population who were missed is not operationally feasible for malaria programs.[12,46,51,52,60] Similar to the findings above, conducting adequate community sensitization campaigns prior to SAT interventions was deemed important to improve coverage.[41,42,60]

Programmatic experience with SAT

A landscaping of published and grey literature, program documentation, meeting presentations and discussions, and survey responses revealed considerable variation across programs in terms of why and how SAT is implemented, and whether it is useful. Below are program perspectives of **1)** rationale, purpose, and design of SAT, and **2)** benefits and challenges in terms of operational implementation and perceived utility and impact. Operational details gleaned from this landscaping exercise can be found in Appendix D. Twenty-five national/subnational malaria control programs are profiled in this assessment: Bangladesh, Bhutan, Botswana, Brazil, Cambodia, China, Democratic People's Republic of Korea (DPR Korea), Indonesia, Lao PDR, Malaysia, Mauritius, Namibia, Nepal, Republic of Korea, São Tomé and Príncipe, Senegal, Solomon Islands, South Africa, Sri Lanka, Swaziland, Thailand, Vanuatu, Vietnam, Zambia, and Zanzibar.

MSAT

Four of the 25 programs (16%) have piloted or implemented MSAT interventions, including Brazil, Indonesia, São Tomé and Príncipe, and Vietnam. The context in which these interventions are implemented, the intervention objectives, and operational details differ across and even within each program. However, high-level themes emerged.

Rationale, purpose, and design of MSAT

Programs generally conduct MSAT in higher endemic settings, during peak transmission season, and often in rural or difficult to access areas of the country. Most programs report utilizing MSAT to determine malaria prevalence and target asymptomatic infections in order to reduce the parasite reservoir. MSAT is also used by some programs in low transmission settings, such as Indonesia, which implements MSAT when districts enter the program's designated elimination phase (annual

parasite index <1 per 1000 population), and as a follow-up to two or more positive cases detected through RACD in elimination districts.

Benefits and challenges of MSAT

Programs believe that MSAT successfully facilitates the identification and treatment of asymptomatic infections and improves the quality of surveillance data. Brazil reports that the implementation of MSAT interventions in highly endemic and remote areas was leveraged to improve the local health systems, thereby contributing to the campaign's overall cost-effectiveness.

The limited sensitivity of standard diagnostic tools compared to molecular testing is a reported challenge. The impact of MSAT on malaria transmission was reported to be difficult to measure as it is often conducted in conjunction with other interventions. In Indonesia, some low transmission districts implementing MSAT were able to achieve elimination even though not every low-density, asymptomatic infection was treated. In high transmission districts, the Indonesia program reported that the effect of MSAT seems to be negligible or, at best, short-lived. Defining target areas and achieving adequate coverage during MSAT campaigns are additional identified challenges.

FSAT

Sixteen of the 25 programs (64%) report using proactive FSAT through the targeting of high-risk areas or among high-risk population groups.

Rationale, purpose, and design of FSAT

Populations targeted by programs for FSAT include mobile and migrant populations and certain occupational groups (e.g. military personnel, forest-based laborers, returning oversees workers). Programs also report targeting locations, including work sites (e.g. plantations, logging camps, project development sites), and areas of the country that are remote and/or difficult to access due to limited infrastructure or rough terrain. To prevent reintroduction of malaria into areas free of transmission, several countries conduct border screenings of incoming visitors and/or locals returning from malaria endemic areas. Programs also use FSAT within defined geographic foci to prevent perennial outbreaks or reintroduction of transmission in cleared foci with high receptivity. Proactive FSAT is conducted in a range of transmission settings, from high to low to very low (elimination).

Benefits and challenges of FSAT

FSAT is generally believed to be useful for identifying asymptomatic infections. However, benefits for symptomatic malaria were also expressed. FSAT is thought to mitigate low treatment-seeking behavior among at-risk populations, improve prompt diagnosis and treatment, and increase the malaria program's annual blood examination rate.

Programs report various challenges to FSAT, including high population mobility and porous borders, both of which complicate M&E efforts among targeted high-risk populations. For border screening, low positivity rates and false negatives at the time of screening due to incubation period were cited as challenges. Community refusals and gaps in the supply chain were other reported challenges. Limited sensitivity of standard diagnostic tools to detect low-density infections was a common theme.

As with MSAT, Indonesia reports that the impact of FSAT alone is difficult to measure because these activities are typically conducted in combination with other interventions. However, the combined interventions involving FSAT have resulted in major reductions in cases in lower transmission districts. In China, several provinces have favorable views of FSAT using microscopy and/or PCR among high-risk groups such as returning overseas workers. Test positivity rates were sufficiently high for program officers to deem the activity useful.

RACD

Twenty-two of the 25 programs (88%) report implementing RACD strategies, making it by far the most popular SAT method among the countries included in this analysis.

Rationale, purpose, and design of RACD

Most programs using RACD have low transmission and are nearing elimination, or they selectively implement RACD sub-nationally in receptive, low transmission areas of the country.

Programs implement RACD primarily to facilitate the identification and treatment of new cases. Some programs go further: Bhutan considers RACD an effective intervention to prevent outbreaks and DPR Korea reports RACD has the potential to eliminate active foci in low transmission settings. Several programs report that RACD provides robust surveillance data which supports the targeting and stratification of other interventions. For example, in Swaziland, RACD data indicates that FSAT at border posts and network sampling of adult male travelers may be an effective intervention in detecting additional cases. In Zambia, RACD was expanded to increase case management capacity, enhance surveillance granularity, and identify areas of residual transmission. Cambodia reports that it considers RACD among social networks to be a cost-effective intervention. Three programs indicated

that RACD is implemented, at least in part, because it is recommended by global policy bodies, including the WHO, the Global Fund, and the President's Malaria Initiative.

Across and even within programs, RACD approaches differ in terms of radius, target population, the events that trigger a RACD event, response time, diagnostics, epidemiological data collected, and use of co-interventions, but are usually tailored to local factors. All target the index case households, some also target neighboring households, and others target co-exposed individuals (e.g. co-workers and co-travelers). Cambodia, China, Indonesia, Thailand, South Africa, and Swaziland implement RACD as part of a 1-3-7-type of case-based surveillance (case reporting within 1 day, case investigation within 3 days, and RACD within 7 days), or a slightly modified version thereof. Along with blood testing, information collected during RACD events includes occupation and travel history. Surveyed programs from Asia Pacific collected additional information including: contact with other travelers, traveling companions, the time spent at their current residence, and G6PD deficiency status. Some programs report implementing additional interventions as part of their RACD response including: entomological surveillance, focal vector control, environmental management, and health education. More information on the operational details of RACD by country is in Appendix D.

Benefits and challenges of RACD

Many programs report that RACD is a time- and resource-intensive intervention. Several related operational challenges were cited, including inadequate human and financial resources, difficulty ensuring timeliness and completeness of case investigations and reporting, and inconsistent staff knowledge on standard operating procedures (SOPs). Botswana further reports that health workers need more training, incentives, and a better reporting mechanism. Other related challenges include defining the radius and the number of households and individuals to screen, and the development of operationally feasible SOPs.

Many programs report that currently available diagnostic tests limit the effectiveness of RACD interventions. Several programs believe that standard RDTs are not sensitive enough to be used when conducting RACD as these tests miss low-density infections. Swaziland reports it is likely missing infections due to the insensitivity of RDTs but that molecular methods are not practical for use in field settings. In Indonesia, using microscopy for routine diagnosis misses *P. knowlesi* infections and leads to delays in obtaining accurate test results. In China, it was found that PCR samples are difficult to transport and the lag time for confirmation complicates and delays case follow-up. Similarly, Indonesia and Vietnam consider molecular diagnostic methods inadequate for field use due to delays. Several programs report that that molecular testing is too expensive for programmatic use. Vietnam also reports a lack in skills and capacity as a barrier to using molecular methods at the programmatic level.

Several programs mention that mobile populations and cross-border communities complicate RACD efforts. In reference to RACD screening coverage, Bhutan and China report that absenteeism is a major obstacle, and Bhutan went further to explain that case investigation during the work day misses household members, suggesting that best practice is to conduct RACD in the early mornings or evenings. Some country programs in Asia Pacific listed the local transmission dynamics (e.g. forest malaria, outdoor biting, the predominance of *P. vivax* infections) as inherent challenges to RACD. Other challenges cited by programs include: drug safety, low case yields, logistics and coordination, transportation to remote locations, and the procurement of commodities and supply chain delays.

Several programs report that methods to improve the effectiveness of RACD should be based on local transmission dynamics and available resources. In Swaziland, the probability of detecting secondary cases was higher when investigations were done within one week of index case detection. Cambodia and Indonesia report low detection rates (<1%) of additional cases when conducting RACD based on a set radius. As such, Cambodia has found greater success in conducting RACD based on a set of personal risk factors related to outdoor transmission and local vector behavior. Similarly, Indonesia reports that targeting based on personal risk factors (such as forest-related occupation) may be more appropriate than targeting based on a pre-defined radius.

Summary of findings and recommendations

Empirical research overview

Learning points and evidence gaps

- The recent increase in literature on SAT indicates high level of interest, a need for evidence gaps to be filled, and policies to be made and clarified at the global level.
- More evidence is needed from the Americas and Asia Pacific where transmission dynamics—specifically, *Plasmodium* species and high-risk groups—are different.
- Limited sensitivity of point of care diagnostics decreases yield for infection detection and likely limits effectiveness of SAT.

Recommendations

- High-level recommendations (e.g. from WHO Evidence Review Groups) are needed on the objectives and settings in which to use MSAT, FSAT, and RACD.
- Coverage and impact indicators are needed for M&E.
- Current SAT terminology describes geographic targeting of the intervention. Terminology should also be inclusive of non-geographic targeting of SAT (e.g. high risk groups).
- Given the limited sensitivity of standard diagnostics, more sensitive point of care diagnostics should be used in SAT. In the absence of highly sensitive point-of-care diagnostics (e.g. for non-*falciparum* infection), simple molecular methods such as LAMP or the use of high-throughput platforms should be incorporated. Alternatively, MDA or a hybrid SAT/MDA approach (e.g. SAT+focal MDA based on test results in a sentinel population) should be considered.
- See "Future research" below for additional general recommendations.

MSAT empirical research

Learning points and evidence gaps

- Despite the variation in outcomes and short assessment periods, results from intervention studies of RDT- or microscopy-based MSAT +/- fMDA suggest no or limited effect on transmission reduction in all transmission settings. Only one study showed impact on RDT-detectable infection prevalence.[42]
- There were limited data comparing MSAT +/- fMDA to MDA but findings from a trial in Zambia[28] suggest MDA is more effective than MSAT + fMDA in high transmission settings.
- The results of a recent CRCT of community-based MSAT using RDT conducted in a high transmission setting in Kenya[100] have not yet been published, but findings will help further clarify the role of MSAT for reduction of transmission or disease burden.

Recommendations

- Based on current evidence, MSAT using standard RDTs or microscopy should not be implemented for transmission reduction. Until more sensitive diagnostics become available, SAT should be replaced with MDA or a hybrid of SAT and MDA.
- Use of MSAT to decrease disease burden (e.g. DALYs) may be justified if impact is sustainable.

FSAT empirical research

Learning points and evidence gaps

- Using the definition of FSAT as a proactive SAT targeted to a sub village level, there were no empirical research studies of FSAT.
- There is likely a limited role for FSAT as a proactive intervention targeting geographic areas, based on lack of evidence available for its use.
- Further empirical evidence regarding FSAT among high risk groups is needed.

Recommendations

- SAT of high risk geographic foci should mostly be conducted as RACD, rather than proactively.
- For other FSAT recommendations, see Modeling and Programmatic experience sections.

RACD empirical research

Learning points and evidence gaps

- From low and very low transmission *P. falciparum* settings in sub-Saharan Africa, there was consistent evidence that malaria clusters in index and neighboring households of passively detected index cases, providing a rationale for RACD. Beyond the neighboring households of index cases, the yield of RACD to detect infection is generally limited and associated with operational challenges.
- There were limited data on household clustering from *P. vivax*-predominant settings in the Americas, and *P. vivax*- or *P. knowlesi*-predominant settings in Asia Pacific.

- In a few studies from southeast Asia, similar risk of infection among co-workers/co-travelers and higher risk in areas with high incidence (compared to index case households) suggests that socio-behavioral RACD and proactive case detection may be complementary to traditional RACD around households.
- Operational aspects of RACD (e.g. criteria for defining a triggering case, target population, timing and frequency, diagnostic) are not well studied and largely determined by local epidemiology and resource constraints.
- There is limited evidence regarding monitoring and evaluation and quality improvement for SAT.
- RACD is the most commonly implemented SAT strategy and in very low transmission and prevention of reintroduction settings appears to be useful for surveillance, e.g. assessing the extent of transmission in foci.
- Surveillance information obtained from RACD can inform interventions and may indirectly lead to transmission reduction.
- As there are no RACD intervention studies, utility is best assessed according to these outcomes: 1) yield to detecting infections, and 2) percent increase in detection of infection compared to passive case detection alone. Yield to detect foci was not reported but may be another useful outcome.
- Use of molecular methods increased detection of infections by more than two-fold in low and very low transmission settings.
- RACD+fMDA has not been evaluated.
- Two recent trials,[101,102] the results of which have not yet been published, compared the impact on transmission of RACD versus reactive fMDA in low transmission settings in Namibia and Zambia. Control arms without reactive interventions were not included, but once available, findings will help to inform the relative effectiveness of RACD to reactive fMDA. The Namibia trial will additionally enable an assessment of reactive interventions with or without reactive vector control.

Recommendations

- Assessing impact on transmission of RACD will be challenging in low transmission settings. If results from ongoing studies (RACD trials and studies on transmissibility of low-density infections) are inconclusive, novel analytic methods and modeling will likely be needed.
- In order to benefit from the multitude of ongoing RACD programs, the establishment of standard M&E indicators, regular review of findings, and sharing of program experiences may lead to improved effectiveness of programs and impact on malaria transmission.
- In RACD settings where clustering of cases is predictable and sensitivity of diagnostics is known to be inadequate, hybrids of SAT and MDA should be considered.
- In RACD settings where sensitivity of diagnostics is known to be inadequate either for parasite density and/or species, introduction of better-performing tests, even if they are more expensive, should be considered due to the surveillance benefits and potential for transmission reduction.
- Particularly in very low transmission settings and/or areas where *P. vivax* and *P. knowlesi* are present, and in very low transmission settings programs should assess the feasibility of implementing RACD in high risk groups.
- Until data regarding transmission reduction is available, the value of surrogate measures (yield to detect infections, percent increase in infection detection compared to passive case detection alone, and yield to detect foci) should be determined, and the utility of gathered surveillance to inform interventions should be quantified. Accompanying economic metrics should also be assessed (see Economic studies).

Modeling

Learning points and evidence gaps

- SAT modeling studies heavily represent *P. falciparum*-predominant, higher transmission settings in sub-Saharan Africa, with limited studies from Asia Pacific or the Americas.
- Consistent with the empirical research, modeling shows that MSAT will not lead to elimination in most transmission settings. However, addressing a gap from the empirical research, it may be effective at very low transmission levels when using an ultrasensitive diagnostic test.
- Consistent with the empirical research, modeling shows MSAT with vector control is effective in reducing disease burden in higher transmission settings.
- Addressing a gap in the empirical research, modeling of border entry FSAT suggests limited effectiveness

to interrupt transmission alone but important in the context of a package of interventions.

- Addressing a gap in the empirical research, RACD may be most effective in settings with recent decreases in transmission, assuming most infectious individuals in historically low transmission settings will be symptomatic and treated through strong case management. Also, compared to MDA or serology-based approaches, the RDT-based reactive approach for population-level treatment may be less effective for transmission reduction, though other factors (e.g. operational feasibility, acceptability, mobility in the population) should be considered.

Recommendations

- Consistent with recommendations based on empirical research, MSAT using standard diagnostics should not be implemented for transmission reduction in any setting. Based on modeling evidence, MSAT using more sensitive diagnostics should be limited to lower transmission settings due to anticipated ineffectiveness in higher transmission settings.
- For all types of SAT, more representation from *P. vivax*-predominant settings in the Americas and Asia Pacific, and *P. knowlesi*-predominant settings in southeast Asia, is needed in modeling studies. For RACD, more representation from African sites other than Zambia are also needed.
- The value that programs place on epidemiological data gathered through SAT, and the potential for that data to indirectly lead to transmission reduction (via better targeting of interventions) should be incorporated into models.
- Modeling may be able to address the question of when programs should transition to or away from different SAT approaches (based on transmission intensity, availability of resources, targeted groups, program goals, etc.), MDA, and hybrid SAT/MDA. However, models should consider a wider range of possibilities or incorporate empirical data regarding: the relationship between immunity, symptoms, and infection density; the effectiveness of case management; the time between detection of index cases and follow up; the number of neighbors tested; and the diagnostic accuracy of serologic diagnostics and ultrasensitive tests for infection detection and whether such diagnostic tools should be used at all.
- Using empirical data, modeling studies should include evidence-based, realistic, operationally feasible parameters—particularly regarding coverage of SAT and other interventions—in order for their outputs to be helpful to malaria programs.
- Ongoing unpublished modelling work suggests that although coverage of RACD is usually less than that of FSAT or MSAT and fewer infections are detected and removed from the population, it can be more effective in the longer term because these infections are usually removed every week instead of once, or at most a few times, a year.

Economic studies

Learning points and evidence gaps

- Studies are few and report different measures of costs and cost-effectiveness. Without empiric evidence on transmission reduction, no studies quantified the cost-effectiveness of MSAT, FSAT, or RACD to prevent cases or decrease transmission.
- SAT costs are mainly driven by start-up costs, training, and personnel (not the costs of the diagnostic test and drugs).
- There are no costing or cost-effectiveness studies of SAT utilizing highly sensitive diagnostics.

Recommendations

- Because the main drivers of overall SAT costs are personnel and start-up costs rather than diagnostic tests, the extra costs associated with highly sensitive diagnostics should not be a deterrent to using them.
- To inform budgets and assess cost-effectiveness, there is a need for further economic studies and consensus on the appropriate costing and cost-effectiveness outcome measures. These should be guided by the outcome measures used to assess effectiveness or utility of SAT.

Acceptability

Learning points and evidence gaps

- While local circumstances may vary, SAT is generally acceptable to communities.
- Acceptability may change if interventions are implemented over many rounds and/or years, or if an alternative approach is preferred (e.g. MDA).

Recommendations

- Prior to implementation of SAT, multiple visits and community sensitization through educational campaigns and engagement of local leaders and

implementers (e.g. community health workers) are critical to maintaining trust, allaying fears, and maximizing coverage.

- Acceptability of SAT does not need to be a major area of investment for research, but qualitative and quantitative assessments (the latter assessed through refusal rates) can be built into new or ongoing SAT studies or programs.

Programmatic experience

Learning points and evidence gaps

- MSAT was generally found to be conducted in higher endemic settings and beneficial for measuring prevalence, targeting asymptomatic infections, and improving case management.
- While some programs reported use of proactive FSAT in geographic foci, most reported use to target high risk groups such as mobile and migrant populations, certain occupational groups, travelers, and groups with limited health care access.
- Most programs reported using RACD in low and very low transmission settings.
- Programs already implement SAT and are unlikely to stop due to the perceived benefits, including: identification and treatment of new cases, outbreak prevention, elimination of active foci in low transmission settings, provision of robust and granular surveillance data that supports the targeting and stratification of other interventions, increase case management capacity, and targeting of high risk groups (when social networks are screened).
- Despite these perceived benefits, it was unclear as to whether programs actually use data gathered through SAT to direct interventions/targeting.
- For both FSAT and RACD, logistical challenges with reaching the target population were reported due to mobile populations and people not being available/at home during visits.
- Better diagnostics, optimization of procedures, improved program management, and increased funding allocation for these activities is needed.

Recommendations

- Guidance is not needed on whether to implement SAT; rather, it is needed to support optimal implementation (including use of better diagnostics for low-density and non-*falciparum* infections), M&E, and when to change interventions.
- Tools, SOPs, technical assistance, capacity building, and systems are needed to support programs to:
  - design practical and epidemiologically appropriate SAT strategies.
  - develop and implement SAT M&E to ensure timeliness, completeness, and coverage of procedures.
  - analyze and interpret the data and then use findings to inform the targeting of interventions.

Future research to address evidence gaps

- Better consensus is needed regarding the appropriate outcome measures for SAT trials, observational studies, and programmatic M&E. In addition to standard surrogate measures of transmission, outcomes should include surveillance measures and capture how surveillance data guides targeting of interventions.
- As SAT interventions may have a delayed impact on the infectious reservoir, evaluations need to be for more than one year (particularly for reactive interventions carried out in low transmission settings).
- For intervention studies, comparison to a control of no SAT (versus SAT using standard diagnostics, MDA, or SAT/MDA hybrid) is more likely to show difference but may be unethical.
- For intervention studies, factorial designs or other methods should be employed to better quantify the relative impact of MSAT compared to vector control.
- For intervention studies, novel study designs may be needed to improve statistical power and/or integrate multiple outcomes of interest.[91]
- Modeling infectivity data from other sites can complement intervention and observational studies to help answer questions about the effectiveness of SAT to reduce transmission.
- Ideally, intervention studies of SAT should take place in the transmission settings in which they would be recommended. However, where infeasible or where there is urgency to reduce or interrupt transmission (e.g. elimination goals are fast approaching), evidence should be gathered through "learning by doing." Implementation with quality M&E still provides opportunities to gather evidence (quasi experimental designs such as pre/post, staged implementation).

Appendices

Appendix A:
SAT survey for malaria program managers/ surveillance officers

Appendix B:
Studies assessed for inclusion in the study (n=164)

Appendix C:
Studies included in analysis, by category (n=84)

Appendix D:
Programmatic SAT operational details

Appendix A:

SAT survey for malaria program managers/ surveillance officers

Question 1:
In the table on the next page, please describe any active screen and treat intervention(s) your program is **currently implementing**, or plans to implement within the next year (do not include routine passive case detection within health facilities). **Please provide details on target groups or administrative areas and the diagnostic tests used**. These interventions may include:

- Mass screen and treat/mass blood surveys
- Focal screen and treat
    - Reactive case detection among household residents and/or neighbors of an index case
    - Reactive case detection within the social networks/peer groups of an index case
    - Proactive case detection among high risk groups or other special populations
    - Proactive case detection along borders and at ports of entry
- Any other SAT strategies (please describe)

Question 2:
Why is your program implementing the screen and treat intervention(s) described in the table – what is your rationale for including these interventions in your national strategic plan for malaria elimination? Examples of rationale are below – please include any that are applicable in the table (you may select more than one) or provide your own explanation.

- There is existing evidence from other countries that the intervention(s) have reduced/are reducing malaria transmission (please describe)
- There is existing evidence from my country that the intervention(s) have reduced/are reducing malaria transmission (please describe)
- I believe the intervention(s) has potential to reduce malaria transmission (please describe)
- The intervention(s) was recommended by WHO/ Global Fund/other international stakeholders (please describe)
- The intervention(s) provides valuable surveillance data on malaria case trends and transmission patterns that I use to improve targeting/ stratification (please describe)
- The intervention(s) is accepted by the target community and I can achieve high coverage (please describe)
- The intervention(s) is cost-effective and fits in my annual budget (please describe)
- Other rationale (please describe)

SAT intervention	Target group/s or administrative areas	Diagnostic test(s) used	Rationale for intervention choice

Question 3:
What factors would affect your choice of SAT interventions in the future and in what way? Please select any applicable responses from the list below (you may select more than one) and **provide supporting detail**:

1. New published research proves the intervention(s) is effective in reducing malaria transmission (please describe)

2. Other program managers are implementing the intervention(s) and believe it to be effective (please describe)

3. WHO/Global Fund/other international stakeholders issues a new policy or guidelines on the use of SAT interventions for malaria elimination (please describe)

4. More sensitive diagnostics become available

5. Diagnostics become more affordable

6. Diagnostics become easier to use in field settings

7. Malaria transmission patterns change (increase or decrease in burden, more/less focal, etc) (please describe)

8. My budget increases or decreases (please describe)

9. My program's human resources capacity (number of trained staff) increases or decreases (please describe)

10. Other (please describe)

Appendix B:

Studies assessed for inclusion (n=164)

The *87 excluded studies are in italics* and the **40 empirical research studies are in bold** (note that the 40 empirical research studies were subdivided into 46 total studies in the analysis).

1. Abeyasinghe RR, Galappaththy GNL, Smith Gueye C, Kahn JG, Feachem RGA. Malaria control and elimination in Sri Lanka: documenting progress and success factors in a conflict setting. PLoS ONE 2012; 7(8): e43162.
2. **Aidoo EK, Afrane YA, Machani MG, Chebore W, Lawson BW, et al. Reactive case detection of Plasmodium falciparum in western Kenya highlands: effective in identifying additional cases, yet limited effect on transmission. Malar J 2018; 17:111.**
3. *Atkinson JA, Johnson ML, Wijesinghe R, Bobogare A, Losi L, et al. Operational research to inform a sub-national surveillance intervention for malaria elimination in Solomon Islands. Malar J 2012; 11:101.*
4. *Aydin-Schmidt B, Xu W, Gonzalez IJ, Polley SD, Bell D, et al. Loop mediated isothermal amplification (LAMP) accurately detects malaria DNA from filter paper blood samples of low density parasitaemias. PLoS ONE 2014; 9(8): e103905.*
5. *Aydin-Schmidt B, Morris U, Ding XC, Jovel I, Msellem MI, et al. Field evaluation of a high throughput loop mediated isothermal amplification test for the detection of asymptomatic Plasmodium infections in Zanzibar. PLoS ONE 2017; 12(1) e0169037.*
6. *Baltzell KA, Shakely D, Hsiang M, Kemere J, Ali AS, et al. Prevalence of PCR detectable malaria infection among febrile patients with a negative Plasmodium falciparum specific rapid diagnostic test in Zanzibar. Am J Trop Med Hyg 2013; 88(2): 289-291.*
7. *Barbosa S, Gozze AB, Lima NF, Batista CL, da Silva Bastos M, et al. Epidemiology of disappearing Plasmodium vivax malaria: a case study in rural Amazonia. PLoS Negl Trop Dis 2014; 8(8): e3109.*
8. *Baum E, Sattabongkot J, Sirichaisinthop J, Kiattibutr K, Jain A, et al. Common asymptomatic and submicroscopic malaria infections in Western Thailand revealed in longitudinal molecular and serological studies: a challenge to malaria elimination. Malar J 2016; 15:333.*
9. *Bell D, Fleurent AE, Hegg MC, Boomgard JD, McConnico CC. Development of new malaria diagnostics: matching performance and need. Malar J 2016; 15:406.*
10. Bjorkman A, Cook J, Sturrock H, Msellem M, Ali A, et al. Spatial distribution of falciparum malaria infections in Zanzibar: implications for focal drug administration strategies targeting asymptomatic parasite carriers. Clin Infect Dis 2017; 64(9): 1236-1243.
11. **Bousema T, Stresman G, Baidjoe AY, Bradley J, Knight P, et al. The impact of hotspot-targeted interventions on malaria transmission in Rachuonyo South District in the Western Kenyan highlands: a cluster-randomized controlled trial. PLoS Med 2016; 13(4): e1001993.**
12. *Bousema T, Okell L, Felger I, Drakeley C. Asymptomatic malaria infections: detectability, transmissibility and public health relevance. Nat Rev Microbiol 2014; 12(1): 833-840.*
13. *Bousema T, Griffin JT, Sauerwein RW, Smith DL, Churcher TS, et al. Hitting hotspots: spatial targeting of malaria for control and elimination. PLoS Med 2012; 9(1): e1001165.*
14. **Branch O, Casapia WM, Gamboa DV, Hernandez JN, Alava FF, et al. Clustered local transmission and asymptomatic Plasmodium falciparum and Plasmodium vivax malaria infections in a recently emerged, hypoendemic Peruvian Amazon community. Malar J 2005; 4:27.**
15. *Campillo A, Daily J, Gonzalez IJ. International survey to identify diagnostic needs to support malaria elimination: guiding the development of combination highly sensitive rapid diagnostic tests. Malar J 2017; 16:385.*
16. *Canier L, Khim N, Kim S, Sluydts V, Heng S, et al. An innovative tool for moving malaria PCR detection of parasite reservoir into the field. Malar J 2013; 12:405.*
17. Cao J, Sturrock HJW, Cotter C, Zhou S, Zhou H, et al. Communicating and monitoring surveillance and response activities for malaria elimination: China's "1-3-7" strategy. PLoS Med 2014; 11(5): e1001642.
18. *Chen SC, Chang HL, Chen KT. The epidemiology of imported malaria in Taiwan between 2002-2013: the importance of sensitive surveillance and implications for pre-travel medical advice. Int J Environ Res Public Health 2014; 11(6): 5651-5664.*
19. **Chihanga S, Haque U, Chanda E, Mosweunyane T, Moakofhi K, et al. Malaria elimination in Botswna, 2012-2014: achievements and challenges. Parasit Vectors 2016; 9:99.**
20. *Chourasia MK, Raghavendra K, Bhatt RM, Swain DK, Valecha N, Kleinschmidt I. Burden of asymptomatic malaria among a tribal population in a forested village of central India: a hidden challenge for malaria control in India. R Soc Pub Health 2017; 147: 92-97.*
21. *Cohen R, Cardona JS, Navarro ES, Padilla N, Reyes L, et al. Outbreak investigation of Plasmodium vivax malaria in a region of Guatemala targeted for malaria elimination. Am J Trop Med Hyg 2017; 96(4) 819-825.*
22. *Congpuong K, SaeJeng A, Sug-aram R, Aruncharus S, Darakapong A, et al. Mass blood survey for malaria: pooling and real-time PCR combined with expert microscopy in north-west Thailand. Malar J 2012; 11:288.*
23. **Cook J, Xu W, Msellem M, Vonk M, Bergstrom B, et al. Mass screening and treatment on the basis of results of a Plasmodium falciparum-specific rapid diagnostic test did not reduce malaria incidence in Zanzibar. J Infect Dis 2014; 211(9): 1476-1483.**

24. **Cook J, Aydin-Schmidt B, Gonzalez IJ, Bell D, Edlund E, et al. Loop-mediated isothermal amplification (LAMP) for point-of-care detection of asymptomatic low-density malaria parasite carriers in Zanzibar. Malar J 2015; 14:43.**

25. **Cotter C, Sudathip P, Herdiana H, Cao Y, Liu Y, et al. Piloting a programme tool to evaluate malaria case investigation and reactive case detection activities: results from 3 settings in the Asia Pacific. Malar J 2017; 16:347.**

26. *Cotter C, Sturrock HJW, Hsiang MS, Liu J, Phillips AA, et al. The changing epidemiology of malaria elimination: new strategies for new challenges. Lancet 2013; 382(9895): 900-911.*

27. Crowell V, Brief OJT, Hardy D, Chitnis N, Maire N, et al. Modeling the cost-effectiveness of mass screening and treatment for reducing Plasmodium falciparum malaria burden. Malar J 2012; 11(Suppl 1): P19.

28. *de AW Gunasekera WMKT, Abeyasinghe RR, Premawansa S, Fernando SD. Usefulness of polymerase chain reaction to supplement field microscopy in a pre-selected population with a high probability of malaria infections. Am J Trop Med Hyg 2011; 85(1): 6-11.*

29. **Deutsch-Feldman M, Hamapumbu H, Lubinda J, Musonda M, Katowa B, et al. Efficiency of a malaria-reactive test-and-treat program in southern Zambia: a prospective, observational study. Am J Trop Med Hyg 2018; 98(5): 1382-1388.**

30. *Ding XC, Ade MP, Baird JK, Cheng Q, Cunningham J, et al. Defining the next generation of Plasmodium vivax diagnostic tests for control and elimination: target product profiles. PLoS Negl Trop Dis 2017; 11(4): e0005516.*

31. **Donald W, Pasay C, Guintran JO, Iata H, Anderson K, et al. The utility of malaria rapid diagnostic tests as a tool in enhanced surveillance for malaria elimination in Vanuatu. PLoS ONE 2016; 11(11): e0167136.**

32. *Dondorp AM, Smithius FM, Woodrow C, von Seidlein L. How to contain artemisinin- and multidrug-resistant falciparum malaria. Trends Parasitol 2017; 33(5): 353-363.*

33. **Eisele TP, Bennett A, Silumbe K, Finn TP, Chalwe V, et al. 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 2016; 214(12): 1831-1839.**

34. *Ekawati LL, Herdiana H, Sumiwi ME, Barussanah C, Ainun C, et al. A comprehensive assessment of the malaria microscopy system of Aceh, Indonesia, in preparation for malaria elimination. Malar J 2015; 14:240.*

35. *Elbadry MA, Al-Khedery B, Tagliamonte MS, Yowell CA, Raccurt CP, et al. High prevalence of asymptomatic malaria infections: a cross-sectional study in rural areas in six departments in Haiti. Malar J 2015; 14:510.*

36. Faye S, Cico A, Gueye AB, Baruwa E, Johns B, Ndiop M, Alilio M. Scaling up malaria intervention "packages" in Senegal: using cost effectiveness data for improving allocative efficiency and programmatic decision-making. Malar J 2018; 17(1):159.

37. **Feng J, Tu H, Zhang L, Zhang S, Jiang S, Xia Z, Zhou S. Mapping transmission foci to eliminate malaria in the People's Republic of China, 2010-2015: a retrospective analysis. BMC Infect Dis 2018; 18(1): 115.**

38. Feng J, Liu J, Feng X, Zhang L, Xiao H, Xia Z. Towards malaria elimination: monitoring and evaluation of the "1-3-7" approach at the China-Myanmar border. Am J Trop Med Hyg 2016; 95(4): 806-810.

39. *Fernando SD, Ainan S, Premaratne RG, Rodrigo C, Jayanetti SR, Rajapakse S. Challenges to malaria surveillance following elimination of indigenous transmission: findings from a hospital-based study in rural Sri Lanka. Int Health 2015; 7(5): 317-323.*

40. **Fontoura PS, Finco BF, Lima NF, de Carvalho Jr JF, Vinetz JM, et al. Reactive case detection for Plasmodium vivax malaria elimination in rural Amazonia. PLoS Negl Trop Dis 2016; 10(12): e0005221.**

41. Gerardin J, Bever CA, Bridenbecker D, Hamainza B, Silumbe K, et al. Effectiveness of reactive case detection for malaria elimination in three archetypical transmission settings: a modelling study. Malar J 2017; 16:248.

42. Gerardin J, Bever CA, Hamainza B, Miller JM, Eckhoff PA, Wenger EA. Optimal population-level infection detection strategies for malaria control and elimination in a spatial model of malaria transmission. PLoS Comput Biol 2016; 12(1): e1004707.

43. Gerardin J, Ouedraogo AL, McCarthy KA, Eckhoff PA, Wenger EA. Characterization of the infectious reservoir of malaria with an agent-based model calibrated to age-stratified parasite densities and infectiousness. Malar J 2015; 14:231.

44. Gerardin J, Eckhoff P, Wenger EA. Mass campaigns with antimalarial drugs: a modelling comparison of artemether-lumefantrine and DHA-piperaquine with and without primaquine as tools for malaria control and elimination. BMC Infect Dis 2015; 15:144.

45. *Gosling RD, Okell L, Mosha J, Chandramohan D. The role of antimalarial treatment in the elimination of malaria. Clin Microbiol Infect 2011; 17(11): 1617-1623.*

46. *Grietens KP, Gryseels C, Dierickx S, Bannister-Tyrrell M, Trienekens S, et al. Characterizing types of human mobility to inform differential and targeted malaria elimination strategies in northeast Cambodia. Sci Rep 2015; 5:15837.*

47. Griffin JT, Hollingsworth TD, Okell LC, Churcher TS, White M, et al. Reducing Plasmodium falciparum malaria transmission in Africa: a model-based evaluation of intervention strategies. PLoS Med 2010; 7(8): e1000324.

48. *Hamainza B, Moonga H, Sikaala CH, Kamuliwo M, Bennett A, et al. Monitoring, characterization and control of chronic, symptomatic malaria infections in rural Zambia through monthly household visits by paid community health workers. Malar J 2014; 13:128.*

49. **Hamze H, Charchuk R, Jean Paul MK, Claude KM, Leon M, Hawkes MT. Lack of household clustering of malaria in a complex humanitarian emergency: implications for active case detection. Pathog Glob Health 2016; 110(6): 223-227.**

50. *Harris I, Sharrock WW, Bain LM, Gray KA, Bobogare A, et al. A large proportion of asymptomatic Plasmodium infections with low and sub-microscopic parasite densities in the low transmission setting of Temotu Province, Solomon Islands: challenges for malaria diagnostics in an elimination setting. Malar J 2010; 9:254.*

51. **Herdiana H, Cotter C, Coutrier FN, Zarlinda I, Zelman BW, et al. Malaria risk factor assessment using active and passive surveillance data from Aceh Besar, Indonesia, a low endemic, malaria elimination setting with Plasmodium knowlesi, Plasmodium vivax, and Plasmodium falciparum. Malar J 2016; 15:468.**

52. *Herdiana H, Fuad A, Asih PBS, Zubaedah S, Arisanti RR, et al. Progress towards malaria elimination in Sabang Municipality, Aceh, Indonesia. Malar J 2013; 12:42.*

53. *Hiwat H, Hardjopawiro LS, Takken W, Villegas L. Novel strategies lead to pre-elimination of malaria in previously high-risk areas in Suriname, South America. Malar J 2012; 11:10.*

54. **Hoyer S, Nguon S, Kim S, Habib N, Khim N, et al. Focused screening and treatment (FSAT): a PCR-based strategy to detect malaria parasite carriers and contain drug resistant P. falciparum, Pailin, Cambodia. PLoS ONE 2012; 7(10): e45797.**

55. *Hsiang MS, Greenhouse B, Rosenthal PJ. Point of care testing for malaria using LAMP, loop mediated isothermal amplification. J Infect Dis 2014; 210(8): 1167-1169.*

56. *Hsiang MS, Hwang J, Kunene S, Drakeley C, Kandula D, et al. Surveillance for malaria elimination in Swaziland: a national cross-sectional study using pooled PCR and serology. PLoS ONE 2012; 7(1): e29550.*

57. **Hustedt J, Canavati SE, Rang C, Ashton RA, Khim N, et al. Reactive case-detection of malaria in Pailin Province, Western Cambodia: lessons from a year-long evaluation in a pre-elimination setting. Malar J 2016; 15:132.**

58. *Jeffree SM, Ahmed K, Safian N, Hassan R, Mihat O, et al. Falciparum malaria outbreak in Sabah linked to an immigrant rubber tapper. Am J Trop Med Hyg 2018; 98(1): 45-50.*

59. *Kalantari M, Soltani Z, Ebrahimi M, Yousefi M, Amin M, et al. Monitoring of Plasmodium infection in humans and potential vectors of malaria in a newly emerged focus in southern Iran. Pathog Glob Health 2017; 111(1): 49-55.*

60. Kern SE, Tiono AB, Makanga M, Gbadoe AD, Premji Z, et al. Community screening and treatment of asymptomatic carriers of Plasmodium falciparum with artemether-lumefantrine to reduce malaria disease burden: a modelling and simulation analysis. Malar J 2011; 10:210.

61. *Koita K, Novotny J, Kunene S, Zulu Z, Ntshalintshali N, Gandhi M, Gosling R. Targeting imported malaria through social networks: a potential strategy for malaria elimination in Swaziland. Malar J 2013; 12:219.*

62. *Landier J, Parker DM, Thu AM, Carrara VI, Lwin KM, et al. The role of early detection and treatment in malaria elimination. Malar J 2016; 15:363.*

63. *Larsen DA, Winters A, Cheelo S, Hamainza B, Kamuliwo M, Miller JM, Bridges DJ. Shifting the burden or expanding access to care? Assessing malaria trends following scale-up of community health worker malaria case management and reactive case detection. Malar J 2017; 16(1):441.*

64. **Larsen DA, Ngwenya-Kangombe T, Cheelo S, Hamainza B, Miller J, et al. Location, location, location: environmental factors better predict malaria-positive individuals during reactive case detection than index case demographics in Southern Province, Zambia. Malar J 2017; 16:18.**

65. **Larsen DA, Chisha Z, Winters B, Mwanza M, Kamuliwo M, et al. Malaria surveillance in low-transmission areas of Zambia using reactive case detection. Malar J 2015; 14:465.**

66. **Larsen DA, Bennett A, Silumbe K, Hamainza B, Yukich JO, et al. Population-wide malaria testing and treatment with rapid diagnostic tests and artemether-lumefantrine in Southern Zambia: a community randomized step-wedge control trial design. Am J Trop Med Hyg 2015; 92(5): 913-921.**

67. Larson Ba, Ngoma T, Silumbe K, Rutagwera MI, Hamainza B, et al. A framework for evaluating the costs of malaria elimination interventions: an application to reactive case detection in Southern Province of Zambia, 2014. Malar J 2016; 15:408.

68. **Lee PW, Liu CT, Rampao HS, do Rosario VE, Shaio MF. Pre-elimination of malaria on the island of Principe. Malar J 2010; 9:26.**

69. *Lek D, Popovici J, Ariey F, Vinjamuri SB, Meek S, et al. National malaria prevalence in Cambodia: microscopy versus polymerase chain reaction estimates. Am J Trop Med Hyg 2016; 95(3): 588-594.*

70. *Lennon SE, Miranda A, Henao J, Vallejo AF, Perez J, et al. Malaria elimination challenges in Mesoamerica: evidence of submicroscopic malaria reservoirs in Guatemala. Malar J 2016: 15:441.*

71. *Lin JT, Saunders DL, Meshnick SR. The role of submicroscopic parasitemia in malaria transmission: what is the evidence? Trends Parasitol 2014; 30(4): 183-190.*

72. *Lindblade KA, Steinhardt L, Samuels A, Kachur SP, Slutsker L. The silent threat: asymptomatic parasitemia and malaria transmission. Expert Rev Anti Infect Ther 2013; 11(6): 623-639.*

73. *Linn AM, Ndiaye Y, Hennessee I, Gaye S, Linn P, et al. Reduction in symptomatic malaria prevalence through proactive community treatment in rural Senegal. Trop Med Int Health 2015; 20(11): 1438-1446.*

74. **Littrell M, Sow GD, Ngom A, Ba M, Mboup BM, et al. Case investigation and reactive case detection for malaria elimination in northern Senegal. Malar J 2013; 12:331.**

75. Lohfeld L, Kangombe-Ngwenya T, Winters AM, Chisha Z, Hamainza B, et al. A qualitative review of implementer perceptions of the national community-level malaria surveillance system in Southern Province, Zambia. Malar J 2016; 15:400.

76. *Lourenco C, Kandula D, Haidula L, Ward A, Cohen JM. Strengthenin malaria diagnosis and appropriate treatment in Namibia: a test of case management training interventions in Kavango Region. Malar J 2014; 13:508.*

77. Lu G, Liu Y, Beiersmann C, Feng Y, Cao J, Muller O. Challenges in and lessons learned during the implementation of the 1-3-7 malaria surveillance and response strategy in China: a qualitative study. Infect Dis Poverty 2016; 5:94.

78. *Ma S, Lawpoolsri S, Soonthornworasiri N, Khamsiriwatchara A, Jandee K, et al. Effectiveness of implementation of electronic malaria information system as the national malaria surveillance system in Thailand. JMIR Public Health Surveill 2016; 2(1): e20.*

79. Macauley C. Aggressive active case detection: a malaria control strategy based on the Brazilian model. Soc Sci Med 2005; 60(3): 563-573.

80. *malERA Consultative Group on Monitoring, Evaluation, and Surveillance. A research agenda for malaria eradication: monitoring, evaluation, and surveillance. PLoS Med 2011; 8(1): e1000400.*

81. *Manjurano A, Okell L, Lukindo T, Reyburn H, Olomi R, et al. Association of sub-microscopic malaria parasite carriage with transmission intensity in north-eastern Tanzania. Malar J 2011; 10:370.*

82. *Marshall JM, Bennett A, Kiware SS, Sturrock HJW. The hitchhiking parasite: why human movement matters to malaria transmission and what we can do about it. Trends Parasitol 2016; 32(10): 752-755.*

83. **Molina Gomez K, Caicedo MA, Gaitan A, Herrera-Varela M, Arce MI, et al. Characterizing the malaria rural-to-urban transmission interface: the importance of reactive case detection. PLoS Negl Trop Dis 2017; 11(7): e0005780.**

84. *Moonen B, Cohen JM, Snow RW, Slutsker L, Drakeley C, et al. Operational strategies to achieve and maintain malaria elimination. Lancet 2010; 376(9752): 1592-1603.*

85. *Morris U, Khamis M, Aydin-Schmidt B, Abass AK, Msellem MI, et al. Field deployment of loop-mediated isothermal amplification for centralized mass-screening of asymptomatic malaria in Zanzibar: a pre-elimination setting. Malar J 2015; 14:205.*

86. Mosha JF, Sturrock HJW, Greenhouse B, Greenwood B, Sutherland CJ, et al. Epidemiology of subpatent Plasmodium falciparum infection: implications for detection of hotspots with imperfect diagnostics. Malar J 2013; 12:221.

87. *Motshoge T, Ababio GK, Aleksenko L, Read J, Peloewetse E, et al. Molecular evidence of high rates of asymptomatic P. vivax infection and very low P. falciparum malaria in Botswana. BMC Infect Dis 2016; 16:520.*

88. *Mwingira F, Genton B, Kabanywanyi ANM, Felger I. Comparison of detection methods to estimate asexual Plasmodium falciparum parasite prevalence and gametocyte carriage in a community survey in Tanzania. Malar J 2014; 13:433.*

89. *Nikolov M, Bever CA, Upfill-Brown A, Hamainza B, Miller JM, et al. Malaria elimination campaigns in the Lake Kariba region of Zambia: a spatial dynamical model. PLoS Comput Biol 2016; 12(11): e1005192.*

90. *Noor AM, Mohamed MB, Mugyenyi CK, Osman MA, Guessod HH, et al. Establishing the extent of malaria transmission and challenges facing pre-elimination in the Republic of Djibouti. BMC Infect Dis 2011; 11:121.*

91. *Nourein AB, Abass MA, Nugud AHD, El Hassan I, Snow RW, Noor AM. Identifying residual foci of Plasmodium falciparum infections for malaria elimination: the urban context of Khartoum, Sudan. PLoS ONE 2011; 6(2): e16948.*

92. *Nwe TW, Oo T, Wai KT, Zhou S, van Griensven J, et al. Malaria profiles and challenges in artemisinin resistance containment in Myanmar. Infect Dis Poverty 2017; 6:76.*

93. *Nygren D, Isaksson AL. Battling malaria in rural Zambia with modern technology: a qualitative study on the value of cell phones, geographical information systems, asymptomatic carriers and rapid diagnostic tests to identify, treat and control malaria. J Public Health Afr 2014; 5(1): 171.*

94. O'Sullivan M, Kenilorea G, Yamaguchi Y, Bobogare A, Losi L, et al. Malaria elimination in Isabel Province, Solomon Islands: establishing a surveillance-response system to prevent introduction and reintroduction of malaria. Malar J 2011; 10:235.

95. *Okell LC, Bousema T, Griffin JT, Ouedraogo AL, Ghani AC, Drakeley CJ. Factors determining the occurrence of submicroscopic malaria infections and their relevance for control. Nat Commun 2012; 3:1237.*

96. Parker DM, Landier J, von Seidlein L, Dondorp A, White L, et al. Limitations of malaria reactive case detection in an area of low and unstable transmission on the Myanmar-Thailand border. Malar J 2016; 15:571.

97. *Parker DM, Matthews SA, Yan G, Zhou G, Lee MC, et al. Microgeography and molecular epidemiology of malaria at the Thailand-Myanmar border in the malaria pre-elimination phase. Malar J 2015; 14:198.*

98. *Phommasone K, Adhikari B, Henriques G, Pongvongsa T, Phongmany P, et al. Asymptomatic Plasmodium infections in 18 villages of southern Savannakhet Province, Lao PDR (Laos). Malar J 2016; 15:296.*

99. **Pinchoff J, Henostroza G, Carter BS, Roberts ST, Hatwiinda S, et al. Spatial patterns of incident malaria cases and their household contacts in a single clinic catchment area of Chongwe District, Zambia. Malar J 2015; 14:305.**

100. *Pongvongsa T, Nonaka D, Iwagami M, Nakatsu M, Phongmany P, et al. Household clustering of asymptomatic malaria infections in Xepon district, Savannakhet province, Lao PDR. Malar J 2016; 15:508.*

101. *Rajakaruna RS, Alifrangis M, Amerasinghe PH, Konradsen F. Pre-elimination stage of malaria in Sri Lanka: assessing the level of hidden parasites in the population. Malar J 2010; 9:25.*

102. *Ray AP. The discipline and dynamics of active case detection procedure under surveillance operations in a malaria eradication programme. WHO/Mal/453. Geneva: World Health Organization; 1964.*

103. **Rogawski ET, Congpuong K, Sudathip P, Satimai W, Sug-aram R, et al. Active case detection with pooled real-time PCR to eliminate malaria in Trat Province, Thailand. Am J Trop Med Hyg 2012; 86(5): 789-791.**

104. *Rosas-Aguirre A, Speybroeck N, Llanos-Cuentas A, Rosanas-Urgell A, Carrasco-Escobar G, et al. Hotspots of malaria transmission in the Peruvian Amazon: rapid assessment through a parasitological and serological survey. PLoS ONE 2015; 10(9): e0137458.*

105. *Rosas-Aguirre A, Llanos-Cuentas A, Speybroeck N, Cook J, Contreras-Mancilla J, et al. Assessing malaria transmission in a low endemicity area of north-western Peru. Malar J 2013; 12:339.*

106. Rosas-Aguirre A, Erhart A, Llanos-Cuentas A, Branch O, Berkvens D, et al. Modelling the potential of focal screening and treatment as elimination strategy for Plasmodium falciparum malaria in the Peruvian Amazon Region. Parasit Vectors 2015; 8:261.

107. **Rossi G, Van den Bergh R, Nguon C, Debackere M, Vernaeve L, et al. Adapting reactive case detection strategies for falciparum malaria in a low-transmission area in Cambodia. Clin Infect Dis 2018; 66(2): 296-298.**

108. **Rossi G, Vernaeve L, Van den Bergh R, Nguon C, Debackere M, et al. Closing in on the reservoir: pro-active case detection in high-risk groups as a strategy to detect Plasmodium falciparum asymptomatic carriers in Cambodia. Clin Infect Dis 2018; 66(10): 1610-1617.**

109. *Ruktanonchai NW, DeLeenheer P, Tatem AJ, Alegana VA, Caughlin TT, et al. Identifying malaria transmission foci for elimination using human mobility data. PLoS Comput Biol 2016; 12(4): e1004846.*

110. **Rulisa S, Kateera F, Bizimana JP, Agaba S, Dukuzumuremyi J, et al. Malaria prevalence, spatial clustering and risk factors in a low endemic area of Eastern Rwanda: a cross sectional study. PLoS ONE 2013; 8(7): e69443.**

111. *Sanders K, Smith Gueye C, Phillips AA, Gosling R. Active case detection for malaria elimination: a confusion of acronyms and definitions. Malar Chemother Control Elimin 2012; 1(1): 1-5.*

112. **Scott CA, Yeshiwondim AK, Serda B, Guinovart C, Tesfay BH, et al. Mass testing and treatment for malaria in low transmission areas in Amhara Region, Ethiopia. Malar J 2016; 15:305.**

113. **Searle KM, Hamapumbu H, Lubinda J, Shields TM, Pinchoff J, et al. Evaluation of the operational challenges in implementing reactive screen-and-treat and implications of reactive case detection strategies for malaria elimination in a region of low transmission in southern Zambia. Malar J 2016; 15:412.**

114. Searle KM, Shields T, Hamapumbu H, Kobayashi T, Mharakurwa S, et al. Efficiency of household reactive case detection for malaria in rural southern Zambia: simulations based on cross-sectional surveys from two epidemiological settings. PLoS ONE 2013; 8(8): e70972.

115. *Searle KM, Katowa B, Kobayashi T, Siame MNS, Mharakurwa S, et al. Distinct parasite populations infect individuals identified through passive and active case detection in a region of declining malaria transmission in southern Zambia. Malar J 2017; 16:154.*

116. Shuford K, Were F, Awino N, Samuels A, Ouma P, et al. Community perceptions of mass screening and treatment for malaria in Siaya County, western Kenya. Malar J 2016; 15:71.

117. Silal SP, Little F, Barnes KI, White LJ. Hitting a moving target: a model for malaria elimination in the presence of population movement. PLoS ONE 2015; 10(12): e0144990.

118. Silal SP, Little F, Barnes KI, White LJ. Predicting the impact of border control on malaria transmission: a simulated focal screen and treat campaign. Malar J 2015; 14:268.

119. Silal SP, Little F, Barnes KI, White LJ. Towards malaria elimination in Mpumalanga, South Africa: a population-level mathematical modelling approach. Malar J 2014; 13:297.

120. Silumbe K, Yukich JO, Hamainza B, Bennett A, Earle D, et al. Costs and cost-effectiveness of a large-scale mass testing and treatment intervention for malaria in Southern Province, Zambia. Malar J 2015; 14:211.

121. Silumbe K, Chiyende E, Finn TP, Desmond M, Puta C, et al. A qualitative study of perceptions of a mass test and treat campaign in Southern Zambia and potential barriers to effectiveness. Malar J 2015; 14:171.

122. *Singh N, Bharti PK, Kumre NS. Active v. passive surveillance for malaria in remote tribal belt of Central India: implications for malaria elimination. Pathog Glob Health 2016; 110(4-5): 178-184.*

123. Slater HC, Ross A, Ouedraogo AL, White LJ, Nguon C, et al. Assessing the impact of next-generation rapid diagnostic tests on Plasmodium falciparum malaria elimination strategies. Nature 2015; 528: S94-S101.

124. **Smith JL, Auala J, Tambo M, Haindongo E, Katokele S, et al. Spatial clustering of patent and sub-patent malaria infections in northern Namibia: implications for surveillance and response strategies for elimination. PLoS ONE 2017; 12(8): e0180845.**

125. Smith Gueye C, Sanders KC, Galappaththy GNL, Rundi C, Tobgay T, et al. Active case detection for malaria elimimation: a survey among Asia Pacific countries. Malar J 2013; 12:358.

126. **Stresman GH, Kamanga A, Moono P, Hamapumbu H, Mharakurwa S, et al. A method of active case detection to target reservoirs of asymptomatic malaria and gametocyte carriers in a rural area in Southern Province, Zambia. Malar J 2010; 9:265.**

127. **Stresman GH, Baidjoe AY, Stevenson J, Grignard L, Odongo W, et al. Focal screening to identify the subpatent parasite reservoir in an area of low and heterogeneous transmission in the Kenya highlands. J Infect Dis 2015; 212(11): 1768-1777.**

128. Stuckey EM, Miller JM, Littrell M, Chitnis N, Steketee R. Operational strategies of anti-malarial drug campaigns for malaria elimination in Zambia's Southern Province; a simulation study. Malar J 2016; 15:148.

129. **Sturrock HJW, Novotny JM, Kunene S, Dlamini S, Zulu Z, et al. Reactive case detection for malaria elimination: real-life experience from an ongoing program in Swaziland. PLoS ONE 2013; 8(5): e63830.**

130. *Sturrock HJW, Hsiang MS, Cohen JM, Smith DL, Greenhouse B, et al. Targeting asymptomatic malaria infections: active surveillance in control and elimination. PLoS Med 2013; 10(6): e1001467.*

131. **Sutanto I, Kosasih A, Elyazar IRF, Simanjuntak DR, Larasati TA, et al. Negligible impact of mass screening and treatment on meso-endemic malaria transmission at West Timor in Eastern Indonesia: a cluster-randomised trial. Clin Infect Dis 2018; DOI: 10.1093/cid/ciy231.**

132. **Sutcliffe CG, Kobayashi T, Hamapumbu H, Shields T, Mharakurwa S, et al. Reduced risk of malaria parasitemia following household screening and treatment: a cross-sectional and longitudinal cohort study. PLoS ONE 2012; 7(2): e31396.**

133. *Sutcliffe CG, Kobayashi T, Hamapumbu H, Shields T, Kamanga A, et al. Changing individual-level risk factors for malaria with declining transmission in southern Zambia: a cross-sectional study. Malar J 2011; 10:324.*

134. *Tadesse FG, Pett H, Baidjoe A, Lanke K, Grignard L, et al. Submicroscopic carriage of Plasmodium falciparum and Plasmodium vivax in a low endemic area in Ethiopia where no parasitaemia was detected by microscopy or rapid diagnostic test. Malar J 2015; 14:303.*

135. Tatarsky A, Aboobakar S, Cohen JM, Gopee N, Bheecarry A, et al. Preventing the reintroduction of malaria in Mauritius: a programmatic and financial assessment. PLoS ONE 2011; 6(9): e23832.

136. **Tejedor-Garavito N, Dlamini N, Pindolia D, Soble A, Ruktanonchai NW, et al. Travel patterns and demographic characteristics of malaria cases in Swaziland, 2010-2014. Malar J 2017; 16:359.**

137. *Thanh PV, Hong NV, Van NV, Malderen CV, Obsomer V, et al. Epidemiology of forest malaria in Central Vietnam: the hidden parasite reservoir. Malar J 2015: 14:86.*

138. *Tietje K, Hawkins K, Clerk C, Ebels K, McGray S, et al. The essential role of infection-detection technologies for malaria elimination and eradication. Trends Parasitol 2014; 30(5): 259-266.*

139. Tiono AB, Kangoye DT, Rehman AM, Kargougou DG, Kabore Y, et al. Malaria incidence in children in South-West Burkina Faso: comparison of active and passive case detection methods. PLoS ONE 2014; 9(1): e86936.

140. **Tiono AB, Ouedraogo A, Ogutu B, Diarra A, Coulibaly S, et al. A controlled, parallel, cluster-randomized trial of community-wide screening and treatment of asymptomatic carriers of Plasmodium falciparum in Burkina Faso. Malar J 2013; 12:9.**

141. *Tseroni M, Baka A, Kapizioni C, Snounou G, Tsiodras S, et al. Prevention of malaria resurgence in Greece through the association of mass drug administration (MDA) to immigrants from malaria-endemic regions and standard control measures. PLoS Negl Trop Dis 2015; 9(11): e0004215.*

142. Tsoka-Gwegweni JM, Okafor U. Asymptomatic malaria in refugees living in a non-endemic South African city. PLoS ONE 2014; 9(9): e107693.

143. Tun STT, von Seidlein L, Pongvongsa T, Mayxay M, Saralamba S, et al. Towards malaria elimination in Savannakhet, Lao PDR: mathematical modelling driven strategy design. Malar J 2017; 16(1):483.

144. *Turki H, Raeisi A, Malekzadeh K, Ghanbarnejad A, Zoghi S, et al. Efficiency of nested-PCR in detecting asymptomatic cases toward malaria elimination program in an endemic area of Iran. Iran J Parasitol 2015; 10(1): 39-45.*

145. *Vallejo AF, Chaparro PE, Benavides Y, Alvarez A, Quintero JP, et al. High prevalence of sub-microscopic infections in Colombia. Malar J 2015; 14:201.*

146. *Vallejo AF, Martinez NL, Gonzalez IJ, Arevalo-Herrera M, Herrera S. Evaluation of the loop mediated isothermal DNA amplification (LAMP) kit for malaria diagnosis in P. vivax endemic settings of Colombia. PLoS Negl Trop Dis 2015; 9(1): e3453.*

147. **van Eijk AM, Ramanathapuram L, Sutton PL, Kanagaraj D, Priya GSL, et al. What is the value of reactive case detection in malaria control? A case-study in India and a systematic review. Malar J 2016; 15:67.**

148. *Vasquez-Jimenez JM, Arevalo-Herrera M, Henao-Giraldo J, Molina-Gomez K, Arce-Plata M, et al. Consistent prevalence of asymptomatic infections in malaria endemic populations in Colombia over time. Malar J 2016; 15:70.*

149. *Vitor-Silva S, Siqueira AM, Sampaio VS, Guinovart C, Reyes-Lecca RC, et al. Declining malaria transmission in rural Amazon: changing epidemiology and challenges to achieve elimination. Malar J 2016; 15:266.*

150. *von Seidlein, L. The failure of screening and treating as a malaria elimination strategy. PLoS Med 2014; 11(1): e1001595.*

151. **Wang D, Cotter C, Sun X, Bennett A, Gosling RD, Xiao N. Adapting the local response for malaria elimination through evaluation of the 1-3-7 system performance in the China-Myanmar border region. Malar J 2017; 16:54.**

152. *Wang CM, Hu SC, Hung WS, Chang HL, Wu HS, et al. The absence of endemic malaria transmission in Taiwan from 2002 to 2010: the implications of sustained malaria elimimation in Taiwan. Travel Med Infect Dis 2012; 10(5-6): 240-246.*

153. Wangdi K, Banwell C, Gatton ML, Kelly GC, Namgay R, Clements ACA. Development and evaluation of a spatial decision support system for malaria elimination in Bhutan. Malar J 2016; 15:180.

154. Wen S, Harvard KE, Smith Gueye C, Canavati SE, Chancellor A, et al. Targeting populations at higher risk for malaria: a survey of national malaria elimination programmes in the Asia Pacific. Malar J 2016; 15:271.

155. *West N, Gyeltshen S, Dukpa S, Khoshnood K, Tashi S, et al. An evaluation of the national malaria surveillance system of Bhutan, 2006-2012 as it approaches the goal of malaria elimination. Front Public Health 2016; 4:167.*

156. Wickremasinghe R, Fernando SD, Thillekaratne J, Wijeyaratne PM, Wickremasinghe AR. Importance of active case detection in a malaria elimination programme. Malar J 2014; 13:186.

157. *Wu L, van den Hoogen LL, Slater H, Walker PGT, Ghani AC, et al. Comparison of diagnostics for the detection of asymptomatic Plasmodium falciparum infections to inform control and elimination strategies. Nature 2015; 528:S86-S93.*

158. Yukich J, Bennett A, Yukich R, Stuck L, Hamainza B, et al. Estimation of malaria parasite reservoir coverage using reactive case detection and active community fever screening from census data with rapid diagnostic tests in southern Zambia: a re-sampling approach. Malar J 2017; 16:317.

159. *Zaw MT, Thant M, Hlaing TM, Aung NZ, Thu M, et al. Asymptomatic and sub-microscopic malaria infection in Kayah State, eastern Myanmar. Malar J 2017; 16:138.*

160. *Zeng XC, Sun XD, Li JX, Chen MN, Deng DW, et al. Assessment of malaria control consultation and service posts in Yunnan, P.R. China. Infect Dis Poverty 2016; 5:102.*

161. **Zhang X, Yao L, Sun J, Pan J, Chen H, Zhang L, Ruan W. Malaria in Southeastern China from 2012 to 2016: analysis of imported cases. Am J Trop Med Hyg 2018; 98(4): 1107-1112.**

162. Zhou SS, Zhang SS, Zhang L, Rietveld AEC, Ramsay AR, et al. China's 1-3-7 surveillance and response strategy for malaria elimination: is case reporting, investigation and foci response happening according to plan? Infect Dis Poverty 2015; 4:55.

163. *Zhu M, Ruan W, Fei SJ, Song JQ, Zhang Y, et al. Approaches to the evaluation of malaria elimination at county level: case study in the Yangtze River Delta. Adv Parasitol 2014; 86:135-182.*

164. *Zoghi S, Mehrizi AA, Raeisi A, Haghdoost AA, Turki H, et al. Survey for asymptomatic malaria cases in low transmission settings of Iran under elimination programme. Malar J 2012; 11:126.*

Appendix C:

Studies included in analysis, by category (n=84)

Note: the 6 studies in bold were further subdivided for analysis, bringing the total to 84 studies

1. Abeyasinghe et al 2012[92]
   Programmatic experience
2. Aidoo et al 2018[51]
   Empirical research
3. Bjorkman et al 2017[78]
   Modeling
4. Bousema et al 2016[38]
   Empirical research
5. Branch et al 2005[23]
   Empirical research
6. Cao et al 2014[93]
   Programmatic experience
7. Chihanga et al 2016[54]
   Empirical research
   Programmatic experience
8. Cook et al 2015(a)[33]
   Empirical research
9. Cook et al 2015(b)[41]
   Empirical research
10. **Cotter et al 2017[30]**
    Empirical research
    Programmatic experience
    Costing
11. Crowell et al 2013[64]
    Modeling
    Costing
12. Deutsch-Feldman et al 2018[59]
    Empirical research
13. **Donald et al 2016[31]**
    Empirical research
    Programmatic experience
14. **Eisele et al 2016[28]**
    Empirical research
15. Faye et al 2018[85]
    Costing
16. Feng et al 2018[57]
    Empirical research
17. Feng et al 2016[94]
    Programmatic experience
18. Fontoura et al 2016[24]
    Empirical research
19. Gerardin et al 2017[71]
    Modeling
20. Geradin et al 2016[70]
    Modeling
21. Gerardin et al 2015(a)[65]
    Modeling
22. Gerardin et al 2015(b)[69]
    Modeling
23. Griffin et al 2010[66]
    Modeling
24. Hamze et al 2016[48]
    Empirical research
    Costing
25. Herdiana et al 2016[35]
    Empirical research
    Programmatic experience
26. Hoyer et al 2012[34]
    Empirical research
27. Hustedt et al 2016[53]
    Empirical research
28. Kern et al 2011[67]
    Modeling
29. Larsen et al 2017[55]
    Empirical research
30. **Larsen et al 2015(a)[29]**
    Empirical research
    Programmatic experience
31. Larsen et al 2015(b)[42]
    Empirical research
    Programmatic experience
32. Larson et al 2016[84]
    Costing
33. Lee et al 2010[44]
    Empirical research
    Programmatic experience
34. Littrell et al 2013[60]
    Empirical research
35. Lohfeld et al 2016[90]
    Programmatic experience
36. Lu et al 2016[95]
    Programmatic experience
37. Macauley et al 2005[25]
    Programmatic experience
    Costing

38. Molina Gomez et al 2017[26]
    Empirical research
39. Mosha et al 2013[79]
    Modeling
40. O'Sullivan et al 2011[87]
    Community acceptability
41. Parker et al 2016[80]
    Modeling
42. Pinchoff et al 2015[62]
    Empirical research
43. Rogawski et al 2012[37]
    Empirical research
44. Rosas-Aguirre et al 2015[27]
    Modeling
45. Rossi et al 2018(a)[36]
    Empirical research
46. **Rossi et al 2018(b)[32]**
    Empirical research
47. Rulisa et al 2013[49]
    Empirical research
48. Scott et al 2016[46]
    Empirical research
49. Searle et al 2016[73]
    Programmatic experience
    Modeling
50. Searle et al 2013[72]
    Modeling
51. Shuford et al 2016[88]
    Community acceptability
52. Silal et al 2015(a)[76]
    Modeling
53. Silal et al 2015(b)[77]
    Modeling
54. Silal et al 2014[75]
    Modeling
55. Silumbe et al 2015(a)[82]
    Costing
56. Silumbe et al 2015(b)[89]
    Community acceptability
57. Slater et al 2015[68]
    Modeling
58. Smith et al 2017[52]
    Empirical research
59. Smith Gueye et al 2013[21]
    Programmatic experience
60. Stresman et al 2010[50]
    Empirical research
61. Stresman et al 2015[45]
    Empirical research
62. Stuckey et al 2016[74]
    Modeling
63. Sturrock et al 2013[61]
    Empirical research
    Programmatic experience
64. Sutanto et al 2018[39]
    Empirical research
65. Sutcliffe et al 2012[43]
    Empirical research
66. Tatarsky et al 2011[83]
    Programmatic experience
    Costing
67. Tejedor-Garavito et al 2017[58]
    Empirical research
    Programmatic experience
68. Tiono et al 2013[40]
    Empirical research
69. Tun et al 2017[81]
    Modeling
70. **van Eijk et al 2016[12]**
    Empirical research
71. Wang et al 2017[56]
    Empirical research
    Programmatic experience
72. Wangdi et al 2016[96]
    Programmatic experience
73. Wen et al 2016[22]
    Programmatic experience
74. Wickremasinghe et al 2014[97]
    Programmatic experience
75. Yukich et al 2017[13]
    Modeling
76. Zhang et al 2018[47]
    Empirical research
77. Zhou et al 2015[98]
    Programmatic experience

Appendix D:
Programmatic SAT operational details

Appendix Table 1: Proactive MSAT

	BRA	IDN	STP	VNM
Transmission setting:				
Higher transmission / control	●	●		
Lower transmission / elimination		●	●	
Outbreak response				●
Frequency:				
Monthly	●			
Annually		●	●	
Once, as needed		●		●
Locations targeted:				
Hard-to-reach / rural	●	●		
Work sites				
International border area				
Diagnostics used:				
RDT		●	●	
Microscopy	●	●	●	
PCR		●		
Serology				
Other interventions co-deployed:				
Vector control (IRS, LLIN)		●		
Reactive case detection		●		
Seasonal malaria chemoprevention				

BRA Brazil
IDN Indonesia
STP São Tomé and Príncipe
VNM Vietnam
RDT rapid diagnostic test
PCR polymerase chain reaction
IRS indoor residual spraying
LLIN long lasting insecticide-treated net

Appendix Table 2: Proactive FSAT

	BGD	BTN	KHM	CHN	IDN	LAO	MYS	MUS	NAM	NPL	KOR	ZAF	LKA	SWZ	THA	VUT
Transmission setting:																
Higher transmission / control	●	●	●		●										●	
Lower transmission / elimination	●				●											
Active foci		●	●	●							●					
Epidemic response													●			
Targeting based on population group demographics:																
Migrants and mobile populations		●			●	●	●		●					●		●
Occupational groups at high risk (e.g. returning overseas workers, armed forces)	●			●		●	●			●	●		●		●	
Asymptomatic/ low-density infections					●										●	
Other (e.g. travel history, fever screening)			●					●						●	●	
Targeting based on location/s:																
Drug resistance															●	
Hard-to-reach					●	●	●									
Work sites		●			●		●									
International border area / ports of entry		●	●				●	●		●		●	●			●

	BGD	BTN	KHM	CHN	IDN	LAO	MYS	MUS	NAM	NPL	KOR	ZAF	LKA	SWZ	THA	VUT
Diagnostics:																
RDT	●	●														
(HS-RDT trial site)						●										
Microscopy		●		●											●	●
PCR				●			●								●	
Serology																

BGD	Bangladesh	MUS	Mauritius	THA	Thailand
BTN	Bhutan	NAM	Namibia	VUT	Vanuatu
KHM	Cambodia	NPL	Nepal	RDT	rapid diagnostic test
CHN	China	KOR	Republic of Korea	HS-RDT	highly sensitive rapid diagnostic test
IDN	Indonesia	ZAF	South Africa	PCR	polymerase chain reaction
LAO	Lao PDR	LKA	Sri Lanka		
MYS	Malaysia	SWZ	Swaziland		

Appendix Table 3: RACD

	BGD	BTN	BWA	KHM	CHN	IDN	MYS	MUS	NAM	NPL	PRK	KOR	SEN	SLB	ZAF	LKA	SWZ	THA	VUT	VNM	ZAN	ZMB
Transmission Setting:																						
Lower transmission / elimination	●			●	●						●	●	●	●	●	●			●	●		●
Receptive areas																	●					
Intervention details:																						
Timeline based on 1-3-7				●	●	●									●			●				
Triggers for RACD:																						
Single index case		●	●		●		●				●	●		●		●	●	●				
>1 case within specified radius						●				●			●						●			
Imported cases																				●		
Action taken / information collected:																						
Case investigation	●	●		●	●	●	●	●	●	●				●	●	●	●	●	●	●		
Case mapping						●	●			●	●					●			●			
Other interventions co-deployed		●						●	●							●						
Travel history		●			●	●	●	●		●				●	●	●	●	●	●			
Travel companions					●			●		●												
G6PD status						●	●															
Time at current residence						●	●			●						●		●	●			
Occupation		●				●	●			●				●		●		●	●	●		
Contact with travelers/ immigrants						●	●			●						●		●	●			

	BGD	BTN	BWA	KHM	CHN	IDN	MYS	MUS	NAM	NPL	PRK	KOR	SEN	SLB	ZAF	LKA	SWZ	THA	VUT	VNM	ZAN	ZMB
Screening based on:																						
Index case HH			●	●	●	●			●		●	●			●	●	●				●	
Target radius based on unit of length (500m-1km)	●	●	●			●*		●	●			●	●				●					●**
Target radius based on # of HH / # of people				●	●							●						●				●***
Risk factors (e.g. history of fever, occupation, travel companions)		●		●	●												●					
Village-wide											●											
Diagnostics:																						
RDT		●		●	●	●			●	●	●	●	●		●	●		●		●	●	●
Microscopy		●		●		●	●		●	●	●			●	●	●		●	●	●	●	
PCR					●	●	●				●							●				
Serology											●											

* or 10-20 HH

** rural

*** urban

BGD	Bangladesh
BTN	Bhutan
BWA	Botswana
KHM	Cambodia
CHN	China
IDN	Indonesia
MYS	Malaysia
MUS	Mauritius
NAM	Namibia
NPL	Nepal
PRK	People's Democratic Republic of Korea
KOR	Republic of Korea
SEN	Senegal
SLB	Solomon Islands
ZAF	South Africa
LKA	Sri Lanka
SWZ	Swaziland
THA	Thailand
VUT	Vanuatu
VNM	Vietnam
ZAN	Zanzibar
ZMB	Zambia
G6PD	glucose-6-phosphate dehydrogenase
HH	household
RDT	rapid diagnostic test
PCR	polymerase chain reaction

References

1 Global Malaria Programme. A framework for malaria elimination. 2017. http://www.who.int/malaria/publications/atoz/WHO-malaria-elimination-framework-2017-presentation-en.pdf (accessed Nov 27, 2017).

2 Moonen B, Cohen JM, Snow RW, et al. Operational strategies to achieve and maintain malaria elimination. The Lancet 6; 376: 1592–603.

3 Battle KE, Bisanzio D, Gibson HS, et al. Treatment-seeking rates in malaria endemic countries. Malar J 2016; 15: 20.

4 Sturrock HJW, Hsiang MS, Cohen JM, et al. Targeting Asymptomatic Malaria Infections: Active Surveillance in Control and Elimination. PLoS Med 2013; 10: e1001467.

5 Lindblade KA, Steinhardt L, Samuels A, Kachur SP, Slutsker L. The silent threat: asymptomatic parasitemia and malaria transmission. Expert Rev Anti Infect Ther 2014; 11: 623–39.

6 malERA Refresh Consultative Panel. malERA: An updated research agenda for characterising the reservoir and measuring transmission in malaria elimination and eradication. PLOS Med 2017; 14: e1002452.

7 PATH. PATH Malaria Learning Series: A Conceptual Framework for Malaria Elimination. 2017. http://www.makingmalariahistory.org/wp-content/uploads/2017/10/MalariaLearningSeries_Steps_FINAL.pdf (accessed Nov 27, 2017).

8 Global Malaria Programme. WHO malaria terminology. 2017. http://apps.who.int/iris/bitstream/10665/208815/1/WHO_HTM_GMP_2016.6_eng.pdf (accessed Nov 27, 2017).

9 WHO Evidence Review Group. Mass drug administration, mass screening and treatment and focal screening and treatment for malaria. Geneva: World Health Organization, 2015 http://www.who.int/malaria/mpac/mpac-sept2015-erg-mda-report.pdf (accessed Nov 27, 2017).

10 Bousema T, Okell L, Felger I, Drakeley C. Asymptomatic malaria infections: detectability, transmissibility and public health relevance. Nat Rev Microbiol 2014; 12: 833–40.

11 WHO Evidence Review Group. Meeting report of the WHO Evidence Review Group on low-density malaria infections. Geneva: World Health Organization, 2017 http://www.who.int/malaria/mpac/mpac-oct2017-erg-malaria-low-density-infections-session2.pdf (accessed Dec 14, 2017).

12 van Eijk AM, Ramanathapuram L, Sutton PL, et al. What is the value of reactive case detection in malaria control? A case-study in India and a systematic review. Malar J 2016; 15: 67.

13 Yukich J, Bennett A, Yukich R, et al. Estimation of malaria parasite reservoir coverage using reactive case detection and active community fever screening from census data with rapid diagnostic tests in southern Zambia: a re-sampling approach. Malar J 2017; 16: 317.

14 Poirot E, Skarbinski J, Sinclair D, Kachur SP, Slutsker L, Hwang J. Mass drug administration for malaria. In: Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd, 2013. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008846.pub2 (accessed Dec 11, 2017).

15 Newby G, Koita K, Slutsker L, et al. Review of Mass Drug Administration for Malaria and Its Operational Challenges. Am J Trop Med Hyg 2015; 93: 125–34.

16 Global Malaria Programme. Recommendations: the role of mass drug administration, mass screening and treatment, and focal screening and treatment for malaria. 2015. http://www.who.int/malaria/publications/atoz/role-of-mda-for-malaria.pdf (accessed Nov 27, 2017).

17 Sanders K, Gueye CS, Phillips AA, Gosling R. Active Case Detection for Malaria Elimination: A Confusion of Acronyms and Definitions. Malar Chemother Control Elimin 2012; 1: 1–5.

18 Asia Pacific Malaria Elimination Network. About APMEN. 2018. http://apmen.org/about/ (accessed Dec 1, 2017).

19 Elimination 8. About the E8. 2016. https://malariaelimination8.org/about-us/ (accessed Dec 1, 2017).

20 APROG. Antiparasite Rollout Group Meeting Summary. 2017. http://www.shrinkingthemalariamap.org/sites/www.shrinkingthemalariamap.org/files/content/resource/attachment/antiparasite-rollout-meeting-summary.pdf (accessed May 10, 2018).

21 Smith Gueye C, Sanders KC, Galappaththy GN, et al. Active case detection for malaria elimination: a survey among Asia Pacific countries. Malar J 2013; 12: 358.

22 Wen S, Harvard KE, Gueye CS, et al. Targeting populations at higher risk for malaria: a survey of national malaria elimination programmes in the Asia Pacific. Malar J 2016; 15: 271.

23 Branch O, Casapia WM, Gamboa DV, et al. Clustered local transmission and asymptomatic Plasmodium falciparum and Plasmodium vivax malaria infections in a recently emerged, hypoendemic Peruvian Amazon community. Malar J 2005; 4: 1.

24 Fontoura PS, Finco BF, Lima NF, et al. Reactive Case Detection for Plasmodium vivax Malaria Elimination in Rural Amazonia. PLoS Negl Trop Dis 2016; 10: e0005221.

25 Macauley C. Aggressive active case detection: a malaria control strategy based on the Brazilian model. Soc Sci Med 2005; 60: 563–73.

26 Molina Gómez K, Caicedo MA, Gaitán A, et al. Characterizing the malaria rural-to-urban transmission interface: The importance of reactive case detection. PLoS Negl Trop Dis 2017; 11: e0005780.

27 Rosas-Aguirre A, Erhart A, Llanos-Cuentas A, et al. Modelling the potential of focal screening and treatment as elimination strategy for Plasmodium falciparum malaria in the Peruvian Amazon Region. Parasit Vectors 2015; 8: 261.

28 Eisele TP, Bennett A, Silumbe K, et al. 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 2016; 214: 1831–9.

29 Larsen DA, Chisha Z, Winters B, et al. Malaria surveillance in low-transmission areas of Zambia using reactive case detection. Malar J 2015; 14: 465.

30 Cotter C, Sudathip P, Herdiana H, et al. Piloting a programme tool to evaluate malaria case investigation and reactive case detection activities: results from 3 settings in the Asia Pacific. Malar J 2017; 16: 347.

31 Donald W, Pasay C, Guintran J-O, et al. The Utility of Malaria Rapid Diagnostic Tests as a Tool in Enhanced Surveillance for Malaria Elimination in Vanuatu. PLoS ONE 2016; 11: e0167136.

32 Rossi G, Vernaeve L, Van den Bergh R, et al. Closing in on the Reservoir: Proactive Case Detection in High-Risk Groups as a Strategy to Detect Plasmodium falciparum Asymptomatic Carriers in Cambodia. Clin Infect Dis 2018; 66(10): 1610-1617.

33 Cook J, Aydin-Schmidt B, González IJ, et al. Loop-mediated isothermal amplification (LAMP) for point-of-care detection of asymptomatic low-density malaria parasite carriers in Zanzibar. Malar J 2015; 14: 43.

34 Hoyer S, Nguon S, Kim S, et al. Focused Screening and Treatment (FSAT): A PCR-Based Strategy to Detect Malaria Parasite Carriers and Contain Drug Resistant P. falciparum, Pailin, Cambodia. PLoS ONE 2012; 7: e45797.

35 Herdiana H, Cotter C, Coutrier FN, et al. Malaria risk factor assessment using active and passive surveillance data from Aceh Besar, Indonesia, a low endemic, malaria elimination setting with Plasmodium knowlesi, Plasmodium vivax, and Plasmodium falciparum. Malar J 2016; 15: 468.

36 Rossi G, Van den Bergh R, Nguon C, et al. Adapting Reactive Case Detection Strategies for falciparum Malaria in a Low-Transmission Area in Cambodia. Clin Infect Dis 2018; 66: 296–8.

37 Rogawski ET, Congpuong K, Sudathip P, et al. Active Case Detection with Pooled Real-Time PCR to Eliminate Malaria in Trat Province, Thailand. Am J Trop Med Hyg 2012; 86: 789–91.

38 Bousema T, Stresman G, Baidjoe AY, et al. The Impact of Hotspot-Targeted Interventions on Malaria Transmission in Rachuonyo South District in the Western Kenyan Highlands: A Cluster-Randomized Controlled Trial. PLOS Med 2016; 13: e1001993.

39 Sutanto I, Kosasih A, Elyazar IR, et al. Negligible Impact of Mass Screening and Treatment on Meso-endemic Malaria Transmission at West Timor in Eastern Indonesia: A Cluster-Randomised Trial. Clin Infect Dis 2018; published online March 22. DOI:10.1093/cid/ciy231.

40 Tiono AB, Ouedraogo A, Ogutu B, et al. A controlled, parallel, cluster-randomized trial of community-wide screening and treatment of asymptomatic carriers of Plasmodium falciparum in Burkina Faso. Malar J 2013; 12: 79.

41 Cook J, Xu W, Msellem M, et al. Mass screening and treatment on the basis of results of a Plasmodium falciparum-specific rapid diagnostic test did not reduce malaria incidence in Zanzibar. J Infect Dis 2015; 211: 1476–83.

42 Larsen DA, Bennett A, Silumbe K, et al. Population-wide malaria testing and treatment with rapid diagnostic tests and artemether-lumefantrine in southern Zambia: a community randomized step-wedge control trial design. Am J Trop Med Hyg 2015; 92: 913–21.

43 Sutcliffe CG, Kobayashi T, Hamapumbu H, et al. Reduced Risk of Malaria Parasitemia Following Household Screening and Treatment: A Cross-Sectional and Longitudinal Cohort Study. PLoS ONE 2012; 7: e31396.

44 Lee P-W, Liu C-T, Rampao HS, do Rosario VE, Shaio M-F. Pre-elimination of malaria on the island of Príncipe. Malar J 2010; 9: 26.

45 Stresman GH, Baidjoe AY, Stevenson J, et al. Focal Screening to Identify the Subpatent Parasite Reservoir in an Area of Low and Heterogeneous Transmission in the Kenya Highlands. J Infect Dis 2015; 212: 1768–77.

46 Scott CA, Yeshiwondim AK, Serda B, et al. Mass testing and treatment for malaria in low transmission areas in Amhara Region, Ethiopia. Malar J 2016; 15: 305.

47 Zhang X, Yao L, Sun J, et al. Malaria in Southeastern China from 2012 to 2016: Analysis of Imported Cases. Am J Trop Med Hyg 2018; 98: 1107–12.

48 Hamze H, Charchuk R, Jean Paul MK, Claude KM, Léon M, Hawkes MT. Lack of household clustering of malaria in a complex humanitarian emergency: implications for active case detection. Pathog Glob Health 2016; 110: 223–7.

49 Rulisa S, Kateera F, Bizimana JP, et al. Malaria Prevalence, Spatial Clustering and Risk Factors in a Low Endemic Area of Eastern Rwanda: A Cross Sectional Study. PLoS ONE 2013; 8: e69443.

50 Stresman GH, Kamanga A, Moono P, et al. A method of active case detection to target reservoirs of asymptomatic malaria and gametocyte carriers in a rural area in Southern Province, Zambia. Malar J 2010; 9: 1.

51 Aidoo EK, Afrane YA, Machani MG, et al. Reactive case detection of Plasmodium falciparum in western Kenya highlands: effective in identifying additional cases, yet limited effect on transmission. Malar J 2018; 17: 111.

52 Smith JL, Auala J, Tambo M, et al. Spatial clustering of patent and sub-patent malaria infections in northern Namibia: Implications for surveillance and response strategies for elimination. PLoS ONE 2017; 12: e0180845.

53 Hustedt J, Canavati SE, Rang C, et al. Reactive case-detection of malaria in Pailin Province, Western Cambodia: lessons from a year-long evaluation in a pre-elimination setting. Malar J 2016; 15: 132.

54 Chihanga S, Haque U, Chanda E, et al. Malaria elimination in Botswana, 2012-2014: achievements and challenges. Parasit Vectors 2016; 9: 99.

55 Larsen DA, Ngwenya-Kangombe T, Cheelo S, et al. Location, location, location: environmental factors better predict malaria-positive individuals during reactive case detection than index case demographics in Southern Province, Zambia. Malar J 2017; 16: 18.

56 Wang D, Cotter C, Sun X, Bennett A, Gosling RD, Xiao N. Adapting the local response for malaria elimination through evaluation of the 1-3-7 system performance in the China–Myanmar border region. Malar J 2017; 16: 54.

57 Feng J, Tu H, Zhang L, et al. Mapping transmission foci to eliminate malaria in the People's Republic of China, 2010–2015: a retrospective analysis. BMC Infect Dis 2018; 18: 115.

58 Tejedor-Garavito N, Dlamini N, Pindolia D, et al. Travel patterns and demographic characteristics of malaria cases in Swaziland, 2010–2014. Malar J 2017; 16: 359.

59 Deutsch-Feldman M, Hamapumbu H, Lubinda J, et al. Efficiency of a Malaria Reactive Test-and-Treat Program in Southern Zambia: A Prospective, Observational Study. Am J Trop Med Hyg 2018; 98: 1382–8.

60 Littrell M, Sow GD, Ngom A, et al. Case investigation and reactive case detection for malaria elimination in northern Senegal. Malar J 2013; 12: 331.

61 Sturrock HJW, Novotny JM, Kunene S, et al. Reactive case detection for malaria elimination: real-life experience from an ongoing program in Swaziland. PLoS ONE 2013; 8: e63830.

62 Pinchoff J, Henostroza G, Carter BS, et al. Spatial patterns of incident malaria cases and their household contacts in a single clinic catchment area of Chongwe District, Zambia. Malar J 2015; 14: 305.

63 World Health Organization. Malaria Surveillance, Monitoring & Evaluation: A Reference Manual. 2018. http://www.who.int/malaria/publications/atoz/9789241565578/en/ (accessed April 2, 2018).

64 Crowell V, Briët OJ, Hardy D, et al. Modelling the cost-effectiveness of mass screening and treatment for reducing Plasmodium falciparum malaria burden. Malar J 2013; 12: 4.

65 Gerardin J, Ouédraogo AL, McCarthy KA, Eckhoff PA, Wenger EA. Characterization of the infectious reservoir of malaria with an agent-based model calibrated to age-stratified parasite densities and infectiousness. Malar J 2015; 14: 231.

66 Griffin JT, Hollingsworth TD, Okell LC, et al. Reducing Plasmodium falciparum malaria transmission in Africa: A model-based evaluation of intervention strategies. PLoS Med 2010; 7(8): e1000324.

67 Kern SE, Tiono AB, Makanga M, et al. Community screening and treatment of asymptomatic carriers of Plasmodium falciparum with artemether-lumefantrine to reduce malaria disease burden: a modelling and simulation analysis. Malar J 2011; 10: 210.

68 Slater HC, Ross A, Ouédraogo AL, et al. Assessing the impact of next-generation rapid diagnostic tests on Plasmodium falciparum malaria elimination strategies. Nature 2015; 528: S94-101.

69 Gerardin J, Eckhoff P, Wenger EA. Mass campaigns with antimalarial drugs: a modelling comparison of artemether-lumefantrine and DHA-piperaquine with and without primaquine as tools for malaria control and elimination. BMC Infect Dis 2015; 15: 144.

70 Gerardin J, Bever CA, Hamainza B, Miller JM, Eckhoff PA, Wenger EA. Optimal Population-Level Infection Detection Strategies for Malaria Control and Elimination in a Spatial Model of Malaria Transmission. PLoS Comput Biol 2016; 12: e1004707.

71 Gerardin J, Bever CA, Bridenbecker D, et al. Effectiveness of reactive case detection for malaria elimination in three archetypical transmission settings: a modelling study. Malar J 2017; 16: 248.

72 Searle KM, Shields T, Hamapumbu H, et al. Efficiency of Household Reactive Case Detection for Malaria in Rural Southern Zambia: Simulations Based on Cross-Sectional Surveys from Two Epidemiological Settings. PLoS ONE 2013; 8: e70972.

73 Searle KM, Hamapumbu H, Lubinda J, et al. Evaluation of the operational challenges in implementing reactive screen-and-treat and implications of reactive case detection strategies for malaria elimination in a region of low transmission in southern Zambia. Malar J 2016; 15: 412.

74 Stuckey EM, Miller JM, Littrell M, Chitnis N, Steketee R. Operational strategies of anti-malarial drug campaigns for malaria elimination in Zambia's southern province: a simulation study. Malar J 2016; 15: 148.

75 Silal SP, Little F, Barnes KI, White LJ. Towards malaria elimination in Mpumalanga, South Africa: a population-level mathematical modelling approach. Malar J 2014; 13: 297.

76 Silal SP, Little F, Barnes KI, White LJ. Hitting a moving target: a model for malaria elimination in the presence of population movement. PLoS ONE 2015; 10: e0144990.

77 Silal SP, Little F, Barnes KI, White LJ. Predicting the impact of border control on malaria transmission: a simulated focal screen and treat campaign. Malar J 2015; 14: 268.

78 Björkman A, Cook J, Sturrock H, et al. Spatial Distribution of Falciparum Malaria Infections in Zanzibar: Implications for Focal Drug Administration Strategies Targeting Asymptomatic Parasite Carriers. Clin Infect Dis 2017; 64: 1236–43.

79 Mosha JF, Sturrock HJ, Greenhouse B, et al. Epidemiology of subpatent Plasmodium falciparum infection: implications for detection of hotspots with imperfect diagnostics. Malar J 2013; 12: 221.

80 Parker DM, Landier J, von Seidlein L, et al. Limitations of malaria reactive case detection in an area of low and unstable transmission on the Myanmar–Thailand border. Malar J 2016; 15: 571.

81 Tun STT, von Seidlein L, Pongvongsa T, et al. Towards malaria elimination in Savannakhet, Lao PDR: mathematical modelling driven strategy design. Malar J 2017; 16: 483.

82 Silumbe K, Yukich JO, Hamainza B, et al. Costs and cost-effectiveness of a large-scale mass testing and treatment intervention for malaria in Southern Province, Zambia. Malar J 2015; 14: 211.

83 Tatarsky A, Aboobakar S, Cohen JM, et al. Preventing the reintroduction of malaria in Mauritius: a programmatic and financial assessment. PLoS ONE 2011; 6: e23832.

84 Larson BA, Ngoma T, Silumbe K, et al. A framework for evaluating the costs of malaria elimination interventions: an application to reactive case detection in Southern Province of Zambia, 2014. Malar J 2016; 15: 408.

85 Faye S, Cico A, Gueye AB, Baruwa E, Johns B, Ndiop. Scaling up malaria intervention "packages" in Senegal: using cost effectiveness data for improving allocative efficiency and programmatic decision-making. Malar J 2018; 17: 159.

86 Zelman BW, Baral R, Zarlinda I, et al. Costs and cost-effectiveness of malaria reactive case detection using loop-mediated isothermal amplification compared to microscopy in the low transmission setting of Aceh Province, Indonesia. Malar J 2018; 17: 220.

87 O'Sullivan M, Kenilorea G, Yamaguchi Y, et al. Malaria elimination in Isabel Province, Solomon Islands: establishing a surveillance-response system to prevent introduction and reintroduction of malaria. Malar J 2011; 10: 235.

88 Shuford K, Were F, Awino N, et al. Community perceptions of mass screening and treatment for malaria in Siaya County, western Kenya. Malar J 2016; 15: 71.

89 Silumbe K, Chiyende E, Finn TP, et al. A qualitative study of perceptions of a mass test and treat campaign in Southern Zambia and potential barriers to effectiveness. Malar J 2015; 14: 171.

90 Lohfeld L, Kangombe-Ngwenya T, Winters AM, et al. A qualitative review of implementer perceptions of the national community-level malaria surveillance system in Southern Province, Zambia. Malar J 2016; 15: 400.

91 Evans SR, Rubin D, Follmann D, et al. Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR). Clin Infect Dis 2015; 61: 800–6.

92 Abeyasinghe RR, Galappaththy GNL, Smith Gueye C, Kahn JG, Feachem RGA. Malaria control and elimination in Sri Lanka: documenting progress and success factors in a conflict setting. PLoS ONE 2012; 7: e43162.

93 Cao J, Sturrock HJW, Cotter C, et al. Communicating and monitoring surveillance and response activities for malaria elimination: China's "1-3-7" strategy. PLoS Med 2014; 11: e1001642.

94 Feng J, Liu J, Feng X, Zhang L, Xiao H, Xia Z. Towards Malaria Elimination: Monitoring and Evaluation of the '1-3-7' Approach at the China-Myanmar Border. Am J Trop Med Hyg 2016; 95: 806–10.

95 Lu G, Liu Y, Beiersmann C, Feng Y, Cao J, Müller O. Challenges in and lessons learned during the implementation of the 1-3-7 malaria surveillance and response strategy in China: a qualitative study. Infect Dis Poverty 2016; 5: 94.

96 Wangdi K, Banwell C, Gatton ML, Kelly GC, Namgay R, Clements ACA. Development and evaluation of a spatial decision support system for malaria elimination in Bhutan. Malar J 2016; 15: 180.

97 Wickremasinghe R, Fernando SD, Thillekaratne J, Wijeyaratne PM, Wickremasinghe AR. Importance of active case detection in a malaria elimination programme. Malar J 2014; 13: 186.

98 Zhou S-S, Zhang S-S, Zhang L, et al. China's 1-3-7 surveillance and response strategy for malaria elimination: Is case reporting, investigation and foci response happening according to plan? Infect Dis Poverty 2015; 4. DOI:10.1186/s40249-015-0089-2.

99 Global Malaria Programme. World Malaria Report 2017. Geneva: World Health Organization, 2017. http://apps.who.int/iris/bitstream/handle/10665/259492/9789241565523-eng.pdf;jsessionid=0DF4A4A3412AC19F760D3A755FFF8192?sequence=1 (accessed April 2, 2018).

100 Samuels AM, Awino N, Odongo W, et al. Community-based intermittent mass testing and treatment for malaria in an area of high transmission intensity, western Kenya: study design and methodology for a cluster randomized controlled trial. Malar J 2017; 16:240.

101 Bridges DJ, Miller JM, Chalwe V, et al. Community-led Responses for Elimination (CoRE): a study protocol for a community randomized controlled trial assessing the effectiveness of community-level, reactive focal drug administration for reducing Plasmodium falciparum infection prevalence and incidence in Southern Province, Zambia. Trials 2017; 18:511.

102 Medzihradsky OF, Kleinschmidt I, Mumbengegwi D, et al. Study protocol for a cluster randomised controlled factorial design trial to assess the effectiveness and feasibility of reactive focal mass drug administration and vector control to reduce malaria transmission in the low endemic setting of Namibia. BMJ Open 2018; 8:e019294.

shrinkingthemalariamap.org