PATH MALARIA LEARNING SERIES

Population-Wide Drug-Based Strategies for Malaria Elimination

Assessing impact, operational requirements, and cost across three African settings

PATH

THE PATH MALARIA LEARNING SERIES

The PATH Malaria Learning Series provides concise briefings on the latest evidence in malaria research and science. Each issue will overview important developments in malaria control and elimination and synthesize results from PATH-supported research.

Making progress against malaria requires the involvement and commitment of partners from the national level to the community. PATH collaborates closely with national and subnational partners in malaria-endemic countries, including ministries of health and national malaria control programs, to develop, evaluate, and scale tools and strategies for malaria control and elimination. PATH's partnership model creates opportunities to leverage national capacity, ideas, and enthusiasm in the fight against malaria.

ACKNOWLEDGMENTS

This report was authored by Geoffrey Kirkwood of the Malaria Control and Elimination Partnership in Africa (MACEPA), a program at PATH. It draws on evidence generated by MACEPA in partnership with the Federal Ministry of Health (FMOH) in Ethiopia, the Programme National de Lutte contre le Paludisme (PNLP) in Senegal, and the National Malaria Control Centre (NMCC) in Zambia.

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KEY CONCEPTS:

Population-wide drug-based strategies for malaria elimination*

Population-wide drug-based strategy
Time-limited strategy targeting an entire population for testing and/or treatment to decrease the reservoir of malaria parasites by clearing infections with safe and effective antimalarial drugs

Mass drug administration (MDA)
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

Focal mass drug administration (fMDA)
Testing a population and treating entire households in which one or more infections is detected

Mass test and treat (MTAT)
Testing an entire population and treating individuals with a positive test result

Asymptomatic reservoir
Individuals in a population who carry the malaria parasite and may contribute to onward transmission but who do not exhibit symptoms of malaria

* See World Health Organization, Global Malaria Programme, "WHO malaria terminology," 2016, for definitions of MDA and MTAT. The definition of fMDA is derived from the WHO's definition of mass testing and focal drug administration, modified to align with the fMDA intervention as implemented in Zambia by MACEPA, the Zambia Ministry of Health, and partners.

IN THIS ISSUE

Population-wide drug-based strategies are potentially powerful accelerators for malaria elimination. This issue of the PATH Malaria Learning Series explores their role in rapidly reducing the malaria parasite burden in targeted populations and explains the differences between various population-wide drug-based strategies. It also takes a close look at the results of PATH-supported research into population-wide drug-based strategies in three malaria-endemic countries in Africa.

Working in partnership with national malaria programs and other partners, PATH has evaluated the impact, operational requirements, and costs of population-wide drug-based strategies in Ethiopia, Senegal, and Zambia. Studies evaluating three strategies—mass drug administration (MDA), focal mass drug administration (fMDA), and mass test and treat (MTAT)—indicate that they are operationally achievable across a range of epidemiologic, geographic, and health system settings and suggest that MDA in particular is a promising strategy for accelerating malaria elimination in certain transmission settings when used in a time-limited fashion and in combination with high coverage of vector control and case management and timely surveillance for tracking and investigating cases.

Photo: PATH/Gabe Bienczycki

THE LEARNING AGENDA

Questions about impact, cost, and operational requirements for implementation

Population-wide drug-based strategies are promising approaches to drive down malaria transmission to sufficiently low levels to allow the detection and investigation of all cases. Some of the major questions on the learning agenda concerning their utility as malaria elimination tools and implementation requirements are listed below. PATH-supported operational research is helping to answer some of these questions and to identify areas where more research is needed.

- In what transmission settings are population-wide drug-based strategies effective and feasible?
- What are the relative advantages and disadvantages of mass test and treat strategies in comparison to mass drug administration and focal mass drug administration?
- What is the appropriate, optimal population size, and operationally achievable population size, for population-wide drug-based strategies?
- As population-wide drug-based strategies have an acceleratory function, and cannot be deployed indefinitely at realistic levels of financial and operational resources, what are the trigger conditions and "exit strategies" for their use?
- What is the minimum foundation—in terms of case management, vector control, case investigation, and surveillance and information systems—that must be in place before population-wide drug-based strategies should be considered?
- How many campaign rounds over how many years are optimal for the implementation of a population-wide drug-based strategy, and how should they be targeted seasonally?
- What levels of population coverage are operationally achievable during campaigns and what levels are necessary for significant reductions in malaria transmission that can set the stage for elimination?
- How acceptable are population-wide drug-based strategies to local communities and how can community acceptance be improved and intervention refusal rates lowered?
- How costly are population-wide drug-based strategies and how can their costs be balanced against indefinite maintenance of vector control and case management?
- What is the effect of time-limited implementation of mass drug administration or mass test and treat strategies on molecular markers of antimalarial drug resistance?
- What is the optimal configuration of health personnel to carry out population-wide campaigns?
- Can malaria-specific campaigns be combined with other disease interventions?

Photo: PATH/Gabe Bienczycki

KEY FINDINGS

1. Mass drug administration is a promising strategy for accelerating toward malaria elimination in certain transmission settings.

- In Zambia, a PATH-supported study to evaluate mass drug administration (MDA) and focal mass drug administration (fMDA) in a population of approximately 300,000 showed that MDA targeting the whole population with dihydroartemisinin-piperaquine (DHAP), when added to the standard of care (enhanced case management, insecticide-treated bednets, indoor residual spraying with Actellic-CS®, and robust surveillance including rapid reporting and case investigation), resulted in rapid and substantial reductions in infection prevalence in high- and low-transmission areas.

2. Impact from mass test and treat strategies is limited by sensitivity of current diagnostic tools.

- PATH-supported mass test and treat (MTAT) studies in low malaria transmission areas in Senegal and Ethiopia, where the whole population was tested with a rapid diagnostic test (RDT) and treated only if positive, resulted in only a modest impact on malaria case incidence.

- MTAT can achieve modest near-term incidence reductions, but it appears to be less effective than MDA in reaching the goal of rapid transmission reduction, at least until more sensitive diagnostic tools become available.

3. Population-wide drug-based strategies can achieve high levels of population coverage.

- In Zambia, high coverage (approximately 85 percent of individuals in reached households), high treatment adherence rates, and low intervention refusal rates were achieved for both MDA and fMDA.

- Studies in Senegal and Ethiopia similarly showed that MTAT was operationally feasible in relatively large populations, with effective coverage of 77 percent in Senegal (89 percent household coverage and 86 percent of individuals covered) and 76 percent in Ethiopia (87 percent household coverage and 87 percent of individuals covered).

4. Preliminary data suggest that the cost of MDA implementation may be roughly comparable to fMDA and MTAT (at least in certain operational settings) and that MDA costs may drop considerably after research components are removed.

- In Zambia, the average cost per individual reached (per year, over two rounds of implementation) was estimated to be approximately US$12.10 for MDA and $14.70 for fMDA. The largest cost components include drug procurement, supervision, vehicle rental, training, and daily allowances.

- The average cost per individual reached with MDA (per year, over two rounds of implementation) could decrease to $10 or lower if research costs (such as data collection, staff salaries, and vehicle rentals) are removed.

- In comparison, the estimated average cost per individual reached for the Ethiopia MTAT (per year, for only one round) was approximately $7 and the estimated average cost per individual reached for the Senegal MTAT (per year, for only one round) was approximately $14.

5. Population-wide drug-based strategies may be useful in certain transmission settings as part of a comprehensive malaria elimination strategy that accounts for local variations in malaria transmission intensity and coverage levels for vector control and case management.

- Well-functioning surveillance systems and vector control and case management programs (including case investigation to identify residual or new infections) must be present to ensure that gains from population-wide drug-based strategies can be maintained, documented, and built upon.

- Robust strategy development and operational planning processes can be used to target population-wide drug-based strategies to appropriate areas.

Introduction to population-wide drug-based strategies

Population-wide drug-based strategies have been frequently deployed as part of national control and elimination programs for malaria and other diseases.[1] Population-wide drug-based strategies for malaria aim to decrease the reservoir of malaria parasites in a targeted population by clearing infections with safe and effective antimalarial drugs.[2] They target an entire population at defined points in time to achieve rapid and substantial reductions in malaria transmission. Because these strategies target entire populations for presumptive testing and/or treatment, they can reach asymptomatic individuals who may transmit the disease even though they do not feel sick and have not sought treatment.

Current WHO recommendations on population-wide drug-based strategies

In November 2015, the WHO Global Malaria Programme issued recommendations concerning the role of mass drug administration, mass screening and treatment, and focal screening and treatment for malaria.[2]

Recommendations included the following:

- Use of MDA for the elimination of *Plasmodium falciparum* malaria can be considered in areas approaching interruption of transmission where there is good access to treatment, effective implementation of vector control and surveillance, and a minimal risk of re-introduction of infection.
- In the absence of sufficient evidence, WHO does not recommend the use of MDA in situations other than for areas approaching elimination, epidemics, and complex emergencies…
- Mass screening and treatment and focal screening and treatment for malaria are not recommended as interventions to interrupt malaria transmission.
- WHO supports the need for more research on the optimum methods of implementing MDA programmes, promoting community participation and compliance with treatment, and evaluating their effectiveness. Modeling can help guide the optimum method of administering MDA in different epidemiological circumstances and predict its likely impact.

Mass drug administration (MDA) targets an entire population for treatment and can therefore clear malaria infections in individuals whose infections might not be picked up by diagnostic tools with limited sensitivity. Furthermore, if drugs with a long duration of effect are used, MDA can provide a prophylactic effect to the whole population. MDA has been used historically by many national malaria programs and has received renewed attention in recent years as a potential accelerator for malaria elimination. Mass test and treat (MTAT) campaigns test an entire population for malaria with diagnostic tools such as rapid diagnostic tests (RDTs) and treat only individuals who test positive. MTAT, which relies on the sensitivity of diagnostic tools to identify malaria infections for treatment, has not been implemented as frequently as MDA. MDA has several potential advantages over MTAT which may account for its more frequent usage: it can clear infections that MTAT misses due to limited RDT sensitivity, it can provide a prophylactic period to uninfected individuals who have received treatment, and unlike MTAT it does not require the large-scale procurement of RDTs for mass testing.[3]

Population-wide drug-based strategies are campaign-style interventions in which health personnel go door-to-door to reach as many people as possible in the targeted population in a limited time period. They are often planned for the dry season, so that when the rainy season begins, fewer parasites remain in human hosts for mosquitos to pick up and transmit. Population-wide drug-based strategies seek to reduce malaria transmission to low enough levels that timely surveillance coupled with case investigation can be used to treat any residual and imported cases without being overwhelmed by the number of individuals seeking care. Without a strong surveillance and case investigation system to detect and treat remaining cases, malaria transmission may eventually return to pre-intervention levels.

How can mass drug administration reduce malaria transmission?

> *MDA is conducted in a coordinated manner, so that the drug is taken at approximately the same time by the whole population at risk, often at repeated intervals […] MDA aims to provide therapeutic concentrations of antimalarial drugs to as large a proportion of the population as possible in order to cure asymptomatic infections and to prevent re-infection during the period of post-treatment prophylaxis. To impact on transmission, MDA requires high coverage of the target population which, in turn, demands a high level of community participation and engagement.*
>
> – *WHO Global Malaria Programme, 2015*[2]

STEPS TO ACCELERATE MALARIA ELIMINATION

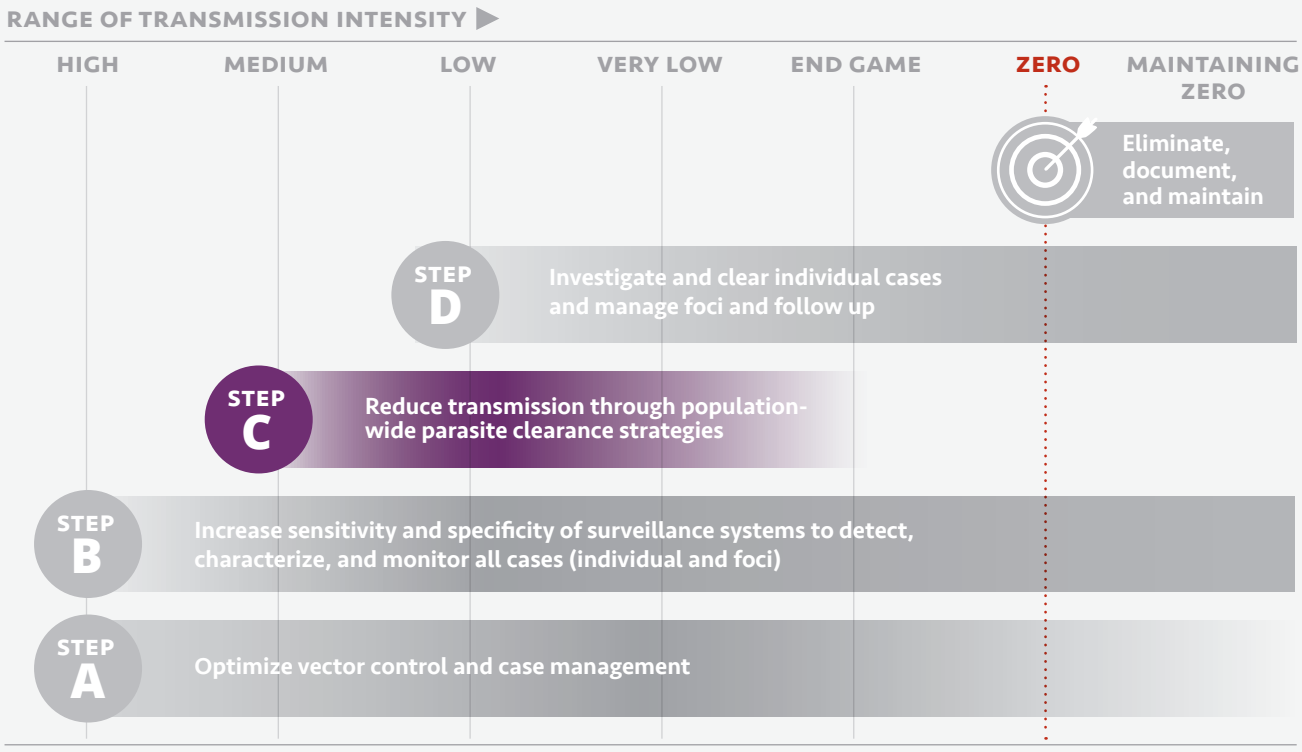
Recent gains in malaria control have led to substantial geographic variation in transmission intensity in many countries. The conceptual framework in Figure 1 shows how an evolving intervention package can be tailored and delivered to address the continuum of a country's diverse malaria transmission intensity—from high to very low—as it moves toward zero.

Across all transmission settings, **Step A** aims to optimize malaria case management and vector control. Ensuring the highest possible access to prevention, diagnosis, and effective treatment can reduce parasite prevalence by 50 percent or more and is essential for building and maintaining gains across all transmission strata in the country.[4] **Step B** aims to increase the sensitivity and specificity of surveillance systems and represents the cornerstone of the framework, as solid information systems allow disease elimination programs to track cases and develop response strategies to prevent or contain onward transmission or reintroduction of infection.

Step C aims to reduce transmission levels and "accelerate" toward elimination through the timely and efficient deployment of population-wide parasite clearance strategies. Step C interventions include population-wide drug-based strategies and potentially supplemental vector control measures and/or parasite-clearing or transmission-blocking vaccines. Step C cannot be considered an end in itself; rather, it consists of a set of time-bound measures that aim to bring transmission to sufficiently low levels so that the relatively few remaining infections can be found and treated as soon as they arise through Step D. Step C is not needed in all transmission settings. Very low transmission areas, for example, may be able to implement the next step—Step D—without deploying Step C as an intermediate step for rapid transmission reduction. Step C should only be used in areas where Step A and Step B interventions are securely deployed and where Step D can be implemented to maintain and build upon gains created by Step C.

Step D is the final additional effort required to achieve and maintain elimination—the detection, treatment, and investigation of the remaining individual cases or foci. This step requires rapid investigation of all cases that are detected by the surveillance system and is feasible only when the number of cases per health catchment area is sufficiently low that health workers and community outreach programs can find and address all cases. Once malaria elimination is achieved, elimination status must be maintained and documented (Step E). Maintaining elimination status will require the continued implementation of Steps A, B, and D, although complete or partial withdrawal of Step A vector control interventions may at some point be considered.

FIGURE 1



When should population-wide drug-based strategies be considered?

Over the past 15 years, there has been tremendous progress in reducing the global burden of malaria. Key to this success has been the scale-up of a set of proven interventions, including case management tools—such as rapid diagnostic tests (RDTs) and artemisinin-based combination therapy (ACT)—to test and treat people, vector control tools—such as long-lasting insecticide-treated nets (LLINs) and indoor residual spraying (IRS) using an evolving set of insecticides—to attack the mosquito, and information systems to monitor and respond to changing patterns of malaria transmission.

Population-wide drug-based strategies are an additional intervention that may be useful to rapidly reduce malaria transmission in certain settings. As with other interventions, population-wide drug-based strategies should be targeted following evidence-based criteria (such as malaria transmission intensity and health system capacity to conduct population-wide campaigns and to investigate remaining cases afterwards) to ensure impact and operational and financial achievability.

ASSESSING IMPACT AND REQUIREMENTS OF POPULATION-WIDE DRUG-BASED STRATEGIES

Population-wide drug-based strategies must demonstrate impact and operational and financial achievability in order to be adopted as evidence-based malaria elimination tools.[5]

IMPACT: Does a time-limited population-wide drug-based strategy succeed in reducing the parasite reservoir in the targeted population rapidly enough to allow surveillance and case investigation systems to maintain and build upon gains through the identification and treatment of residual or imported malaria cases?

OPERATIONAL REQUIREMENTS: Is the health system capable of implementing a population-wide drug-based strategy and achieving high coverage of the targeted population? Are there sufficient numbers of motivated community health workers or other local health personnel to carry out the intervention? Is the targeted population reasonably accessible? Are infrastructure and means of transportation adequate? Is there sufficient information about the target population (including household location, mobility, and community acceptance of the proposed interventions) to achieve high levels of population coverage? Are surveillance systems in place to allow detection and investigation of subsequent individual cases and foci?

FINANCIAL REQUIREMENTS: How much will it cost to implement a population-wide drug-based strategy? Is adequate funding available? Is the strategy cost-effective compared to other interventions? Could it result in long-term savings by eliminating or greatly diminishing the future malaria burden?

Measuring impact and assessing operational and financial requirements will depend on an array of epidemiological, socioeconomic, and fiscal factors. A strategy may be easier in one area compared to another due to variations in transmission intensity; differences in health system capacity, geography, or infrastructure strength; or disparities in funding.

Photo: PATH/Gabe Bienczycki

Evaluating population-wide drug-based strategies for malaria elimination

PATH's Malaria Control and Elimination Partnership in Africa (MACEPA) is collaborating with three African countries—Ethiopia, Senegal, and Zambia—to eliminate local malaria transmission at national or subnational levels. MACEPA provides technical assistance for elimination planning and supports operational research and the programmatic deployment of elimination interventions. As a major part of its work, MACEPA is evaluating the impact, operational requirements, and cost of population-wide drug-based strategies for malaria elimination in the diverse epidemiologic settings in which it works.

ZAMBIA (2014-2016)

STUDY DESIGN: Cluster randomized controlled trial

STRATEGIES EVALUATED:

- Mass Drug Administration (MDA)
- Focal MDA (fMDA)

DRUG: Dihydroartemisinin-piperaquine (DHAP)

SENEGAL (2014-2015)

STUDY DESIGN: Quasi-experimental design

STRATEGIES EVALUATED:

- Mass Test and Treat (MTAT) at the beginning of transmission season followed by weekly mass fever screening, testing, and treatment (PECADOM++)
- Case investigation with focal test and treat (FTAT) and focal screen (for fever), test, and treat (FSTAT)

DRUG: Dihydroartemisinin-piperaquine (DHAP)

ETHIOPIA (2014-2015)

STUDY DESIGN: Quasi-experimental design

STRATEGIES EVALUATED:

- Mass Test and Treat (MTAT) at the beginning of transmission season
- Case investigation with focal test and treat (FTAT)

DRUG: Artemether-lumefantrine (AL)

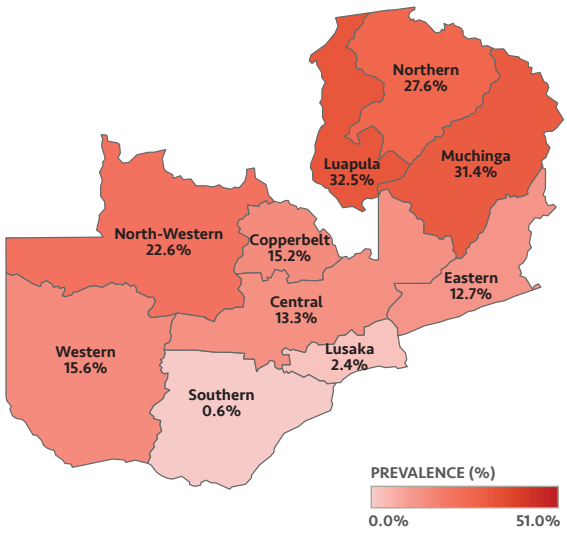
Evaluating Mass Drug Administration and Focal Mass Drug Administration in **ZAMBIA**

In Zambia's Southern Province, MACEPA is partnering with the Zambia Ministry of Health to evaluate mass drug administration (MDA) and focal mass drug administration (fMDA) strategies in which the antimalarial drug dihydroartemisinin-piperaquine (DHAP) is administered to entire populations (MDA) or targeted subsets (fMDA).

Key research objectives

1. Evaluation of the relative effectiveness of MDA or fMDA with DHAP compared to a control population (standard of care for all populations included case management, insecticide-treated bednets, indoor residual spraying with Actellic-CS®, and robust surveillance including rapid reporting and case investigation).
2. Quantification of the coverage of fMDA and MDA.
3. Assessment of adherence to antimalarial medications under programmatic efforts using directly observed therapy.
4. Assessment of individual and community acceptability of fMDA and MDA.

Malaria Parasite Prevalence (%), Zambia 2015

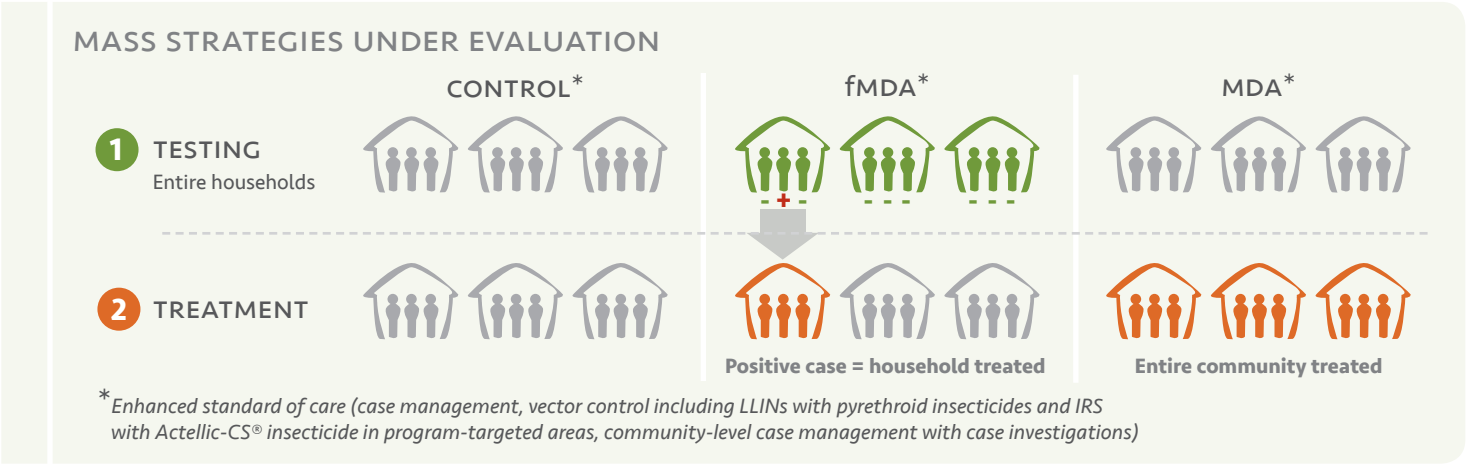


Source: MIS 2015

Study design

Using a community-randomized controlled trial design, health facility catchment areas (HFCAs) in Southern Province were stratified according to the intensity of malaria transmission. Thirty HFCAs with parasite prevalence below 10 percent and 30 HFCAs with parasite prevalence above 10 percent were randomly allocated to MDA, fMDA, or control arms. HFCAs in all trial arms benefited from robust prevention and control programs, including long-lasting insecticide-treated mosquito nets, indoor residual spraying (IRS) with Actellic-CS® insecticide, case management with RDTs and antimalarial drugs, and facility- and community-level rapid reporting and case management with case investigations in all HFCAs.

Control-arm HFCAs were compared with (1) MDA-arm HFCAs where all consenting persons were tested by rapid diagnostic test (RDT) and treated with DHAP regardless of RDT test result and (2) fMDA-arm HFCAs where all consenting persons were tested by RDT and positive test results triggered DHAP treatment of the positive individual, as well as of all household members regardless of test result. Two rounds of MDA or fMDA were conducted each year over two years in the intervention arms. The first two rounds of MDA and fMDA occurred in November 2014–January 2015 and February–March 2015, and the second two rounds occurred in September–October 2015 and February-March 2016. Only Year 1 findings are presented here as Year 2 results are still being analyzed.



Results: Impact

Lower transmission areas

- In the MDA arm, malaria prevalence among children under five years of age dropped significantly from 8.1 to 0.6 percent as measured by RDT in areas of lower transmission between April–May 2014 and April–May 2015 (Figure 2).
- Prevalence dropped substantially in the control arm (from 9.2 to 2.6 percent) in areas of lower transmission, but, unlike in the MDA arm, this decline was not statistically significant.
- The impact of fMDA was more modest and not statistically significant compared to the control arm.

Higher transmission areas

- In areas of higher transmission, parasite prevalence dropped from a baseline of approximately 50 to 15 percent. Results were similar across intervention and control areas (Figure 2).
- The study also evaluated the impact of MDA and fMDA on infection incidence in a longitudinal cohort study conducted in all study arms. For areas of both lower and higher transmission, infection rates were highest in the control arm, intermediate for fMDA, and lowest for the MDA arm. The infection rate difference between the MDA arm and the control arm was statistically significant for both higher and lower transmission areas though this was not the case for fMDA in either lower or higher transmission areas.

Results: Intervention coverage, acceptability and adherence

- Intervention coverage was high. When teams reached households, approximately 85 percent of residents were tested and treated as appropriate (household coverage is still being assessed using satellite imaging and geopositioned data from accessed households). The second round was conducted during the rainy season when some areas were impassable and not reachable by vehicle. As a result, fewer households were reached and fewer people visited in the second round.
- Non-treatment of individuals was mostly due to absence from the household (often due to work or school) or an identified exclusion characteristic (such as first trimester pregnancy or being less than three months of age).
- The overall refusal rate was only 1–2 percent. In light of the low refusal rate and the proportion of individuals with exclusion characteristics, it appears that the highest achievable population coverage for MDA/fMDA may be in the range of 85 percent.
- 82 percent of individuals in MDA and fMDA arms who had received initial treatment with DHAP reported taking a full course of DHAP when visited two days after first visit.

FIGURE 2. Baseline (2014) and follow-up (2015) child parasite prevalence

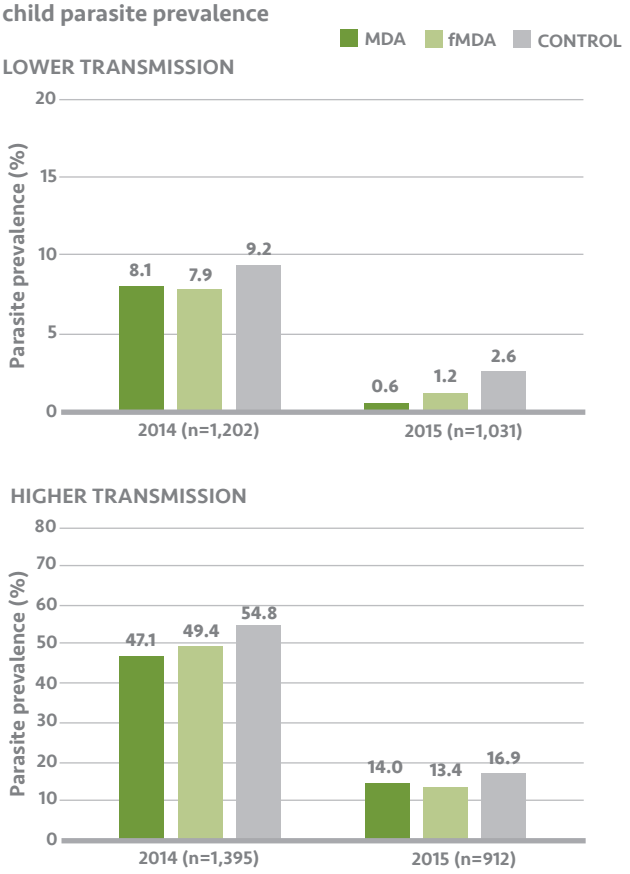


TABLE 1. Population reached by initial two rounds of MDA and fMDA

	Households	People	Courses of DHAP
FIRST ROUND (November 30, 2014, to January 12, 2015)			
MDA	17,692	86,151	79,133
fMDA	15,923	82,354	23,344
SECOND ROUND (February 2, 2015, to March 6, 2015)			
MDA	12,894	62,591	55,124
fMDA	13,957	74,677	15,487

Evaluating Mass Test and Treat in SENEGAL

MACEPA has evaluated a mass test and treat (MTAT) strategy, in combination with weekly household visits to screen for fever cases (PECADOM++, or Prise en charge à domicile++) and case investigation, in low transmission areas in the Matam and Louga regions of Senegal.

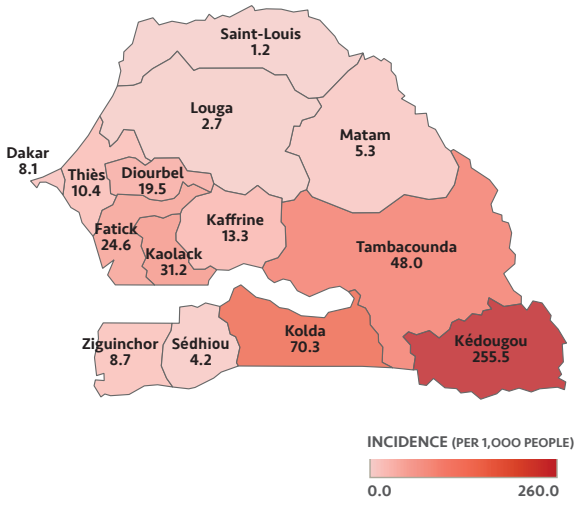
Primary research objective

Evaluation of whether a combination of parasitemia-clearing strategies can substantially decrease malaria incidence in low-transmission areas in three districts (Linguère, Ranérou, and Kanel) of the Matam and Louga regions.

Secondary research objective

Characterization of demographic and spatial patterns of infection and description of the operational feasibility of implementing different parasitemia-clearing strategies.

Malaria Incidence, Senegal 2014



Source: PNLP 2014

Study design

The study used a pilot, quasi-experimental design. Six intervention health post catchment areas were purposefully selected and seven comparison health post catchment areas were selected from the same districts. Villages within the health post catchment areas were stratified according to the 2013 malaria incidence and each stratum received a different package of interventions (Table 1). The primary endpoint was the weekly incidence of passively detected malaria cases confirmed by RDT during the 2014–2015 transmission season.

In intervention areas, Stratum 3 villages received MTAT early in the transmission season (September 2014), followed by PECADOM++ during the rest of the transmission season (October 2014 to January 2015). During the MTAT, in which all households were targeted, all consenting individuals received a rapid diagnostic test (RDT), and RDT-positive individuals received DHAP (or artemether-lumefantrine [AL] in case of contraindications). The PECADOM++ strategy consisted of weekly visits to all households to (1) screen for fever, and test the febrile and treat positives, and (2) in households with a positive RDT, test all household members and treat positives.

Stratum 2 villages only received PECADOM++ from October 2014 to January 2015 and Stratum 1 villages only received case investigation. Case investigation was triggered by the diagnosis of a passively detected *P. falciparum* case (index

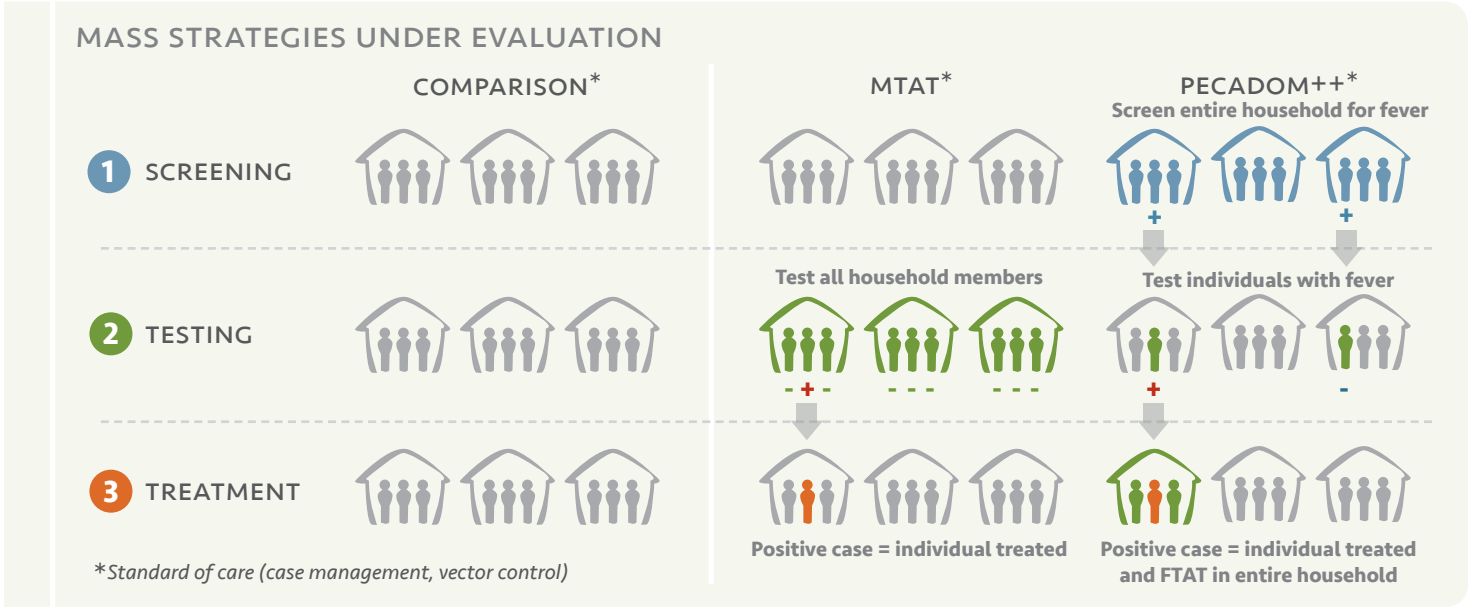


Table 2. Stratification of villages and intervention implemented

Villages within health post catchment areas were stratified by transmission intensity (according to 2013 incidence) and targeted with different interventions.

Stratum	Transmission intensity*	Catchment population in intervention areas	Interventions implemented during high transmission season (Sept 2014 to Jan 2015)
1	**Very low transmission** (<5 cases per 1,000 population per year)	4,753	Case investigation with FTAT/FSTAT
2	**Low transmission** (≥5 and <15 cases per 1,000 population per year)	9,695	PECADOM++
3	**Low-moderate transmission** (≥15 cases per 1,000 population per year)	24,925	MTAT at the beginning of the 2014 transmission season (September 2014) followed by PECADOM++

*Passively detected *Plasmodium falciparum* cases per 1,000 population per year in 2013

case) and consisted of focal testing and treatment (FTAT) in the index case household and focal screening for risk factors, testing, and treatment (FSTAT) in the five closest neighboring households within a 100-meter radius. The comparison areas received the standard of care, which consisted of malaria case management with RDTs and ACTs. Stratum 1 results are not presented here (only 13 case investigations were implemented in this stratum).

Results: MTAT

- Effective coverage of the MTAT intervention was 77 percent (89 percent household coverage and 86 percent of household individuals covered).
- Of all individuals tested, 1.5 percent had a positive RDT result. Village-level RDT-confirmed infection prevalence ranged from 0 to 10.8 percent, and was consistently higher among males in all age groups.
- Adherence to treatment was high, with 86 percent of individuals completing the full treatment (according to observation of blister pack or self-report).
- All reported adverse events after DHAP treatment were mild and tolerable (8.2 percent vomited, 3.5 percent had fever, and 0.4 percent had itching).
- Eighty-two percent of RDT-positive individuals were younger than 20 years of age, and 71 percent were asymptomatic.
- There was a clustering of infections, with 90 percent of households not having any RDT-positive individuals. Forty-three percent of infections occurred in households with at least one other infection.

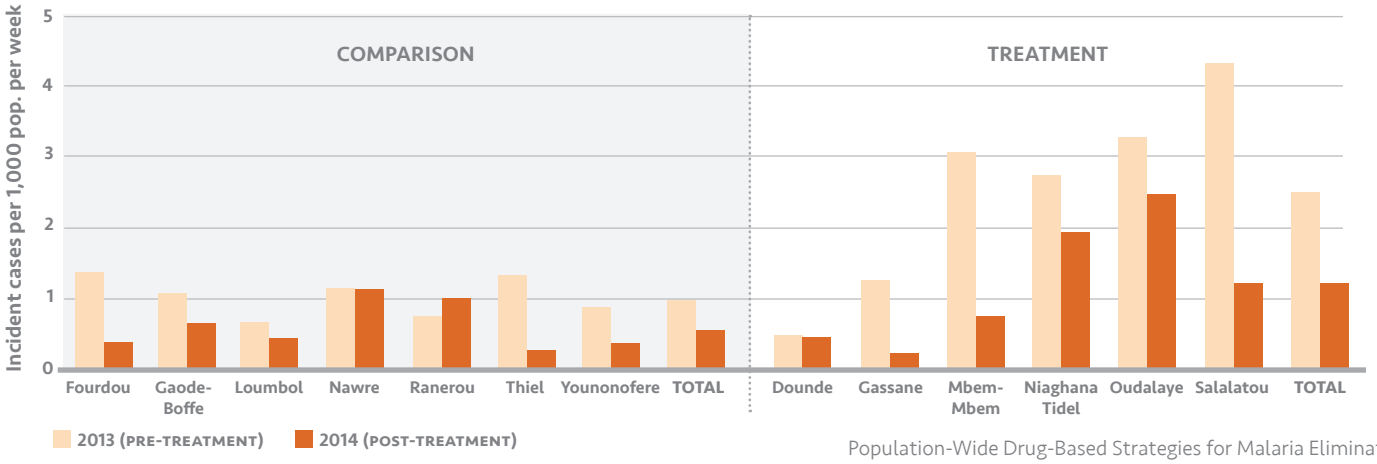
Results: PECADOM++

- Field teams made 40,002 household visits to find and treat 289 RDT-positives (or 7.2 cases per 1,000 household visits).
- 93 percent of the 3,577 households in targeted villages were visited at least once during the implementation period.
- Five percent of visits resulted in the identification of at least one fever case and 6.5 percent of fever cases had a positive RDT result for malaria.
- 9.4 percent of household members in houses where fever cases were identified had a positive RDT result.

Impact evaluation of the combination of interventions (comparison areas versus all intervention areas)

Malaria cases declined by 21 percent during the study period in the comparison and intervention groups combined (Figure 3). The incidence of malaria cases in the intervention group decreased 34 percent more than in comparison areas between the pre- and post-intervention periods, and this difference was statistically significant.

Figure 3. Malaria incidence before and after study (comparison areas versus all intervention areas)



Evaluating Mass Test and Treat in ETHIOPIA

In Ethiopia, MACEPA has evaluated a mass test and treatment (MTAT) strategy followed by case investigation in low-transmission areas in the Amhara region.

Primary research objective

Evaluation of whether a combination of parasitemia-clearing strategies can substantially decrease malaria incidence in the study areas in the Amhara region.

Secondary research objective

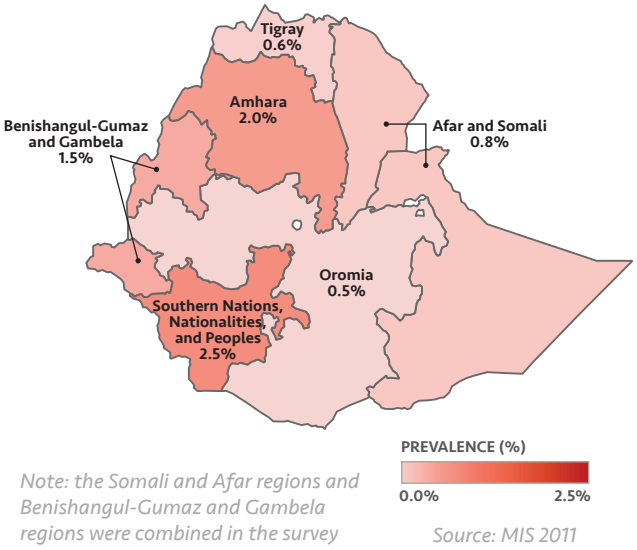
Characterization of demographic and spatial patterns of infection and description of the operational feasibility of implementing different parasitemia-clearing strategies.

Study design

The study was conducted using a pilot, quasi-experimental design. Ten intervention health post catchment areas were purposefully selected and ten comparison health post catchment areas receiving the standard of care were selected from the same districts. The primary endpoint was weekly incidence of passively detected RDT-confirmed malaria during the 2014–2015 transmission season.

MTAT was implemented in the six health post catchment areas with the highest transmission in September 2014, at the beginning of the transmission season. All households were targeted, consenting individuals were tested with RDTs, and positive individuals were treated with the antimalarial drug AL. Case investigation began in October 2014 and was conducted in the ten intervention health post catchment areas during the rest of the transmission season. Case investigation was triggered by the diagnosis of a passively detected index case. Focal test and treat (FTAT) was then done in the index case household and the ten closest households (within a 100 meter radius), during which consenting individuals were tested with an RDT and positive individuals were treated with AL.

Malaria Parasite Prevalence (%), Ethiopia, 2011

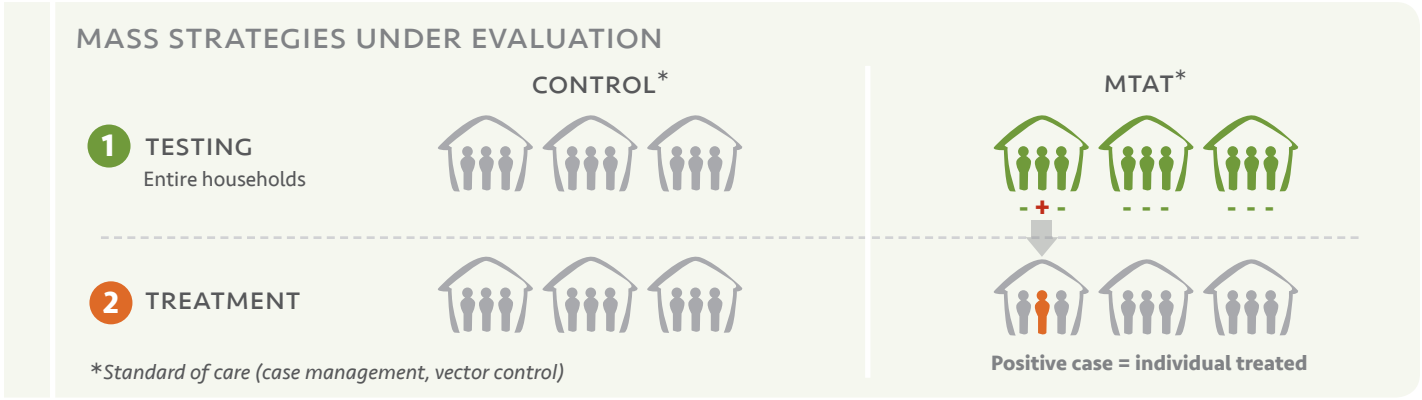


Note: the Somali and Afar regions and Benishangul-Gumaz and Gambela regions were combined in the survey

Source: MIS 2011

MTAT Results

- Effective coverage of the MTAT intervention was 76 percent (87 percent household coverage and 87 percent of household individuals covered).
- The MTAT found and treated only 421 malaria infections, or 1.4 percent of the 30,712 individuals who were tested. Health post-level RDT-confirmed infection prevalence ranged from 0.3 to 5.1 percent. Limited RDT sensitivity likely resulted in missed positives and PCR testing is pending.
- 61 percent of the infections were asymptomatic and 63 percent were in individuals younger than 20 years old (Figure 4).
- Travel history (defined as having spent at least one night away from home in the previous month) was a risk factor for RDT-positivity in individuals aged



ten years and older. Seven percent of RDT-positive individuals had a history of travel.[6]

- Infections were clustered, with 96 percent of households not having any RDT-positive individuals. Fifteen percent of positive households had more than one RDT-positive individual.
- Adherence was assessed in a subsample of participants, with 43 percent reporting completion of all treatment doses and 22 percent being observed to have more than one dose of treatment remaining.
- No adverse events were reported by any individuals after taking AL.

Case investigation results

- Among the 407 *P. falciparum*/mixed index cases that were detected during the high transmission season, 54 percent were able to be investigated. In health posts with a high number of cases, the main reason for non-investigation was that the system was overwhelmed and there was not enough time to investigate all cases.
- In the 914 households where FTAT was conducted, the RDT positivity rate was 4.8 percent in the index case households and 3.6 percent in the neighboring households, which led to finding 127 more RDT-positives.
- Three patterns of malaria transmission were found (Figure 5):
  - Very low transmission (five villages), with very low number of index cases and no importation.
  - High importation and low local transmission (four villages), with high number of index cases, high importation from migrant workers, and low number of secondary cases found during the FTAT.
  - High local transmission (one village), with high number of index cases, low importation, and high number of secondary cases found during the FTAT.

FIGURE 4. Rapid diagnostic test positivity by age and sex, Amhara, Ethiopia

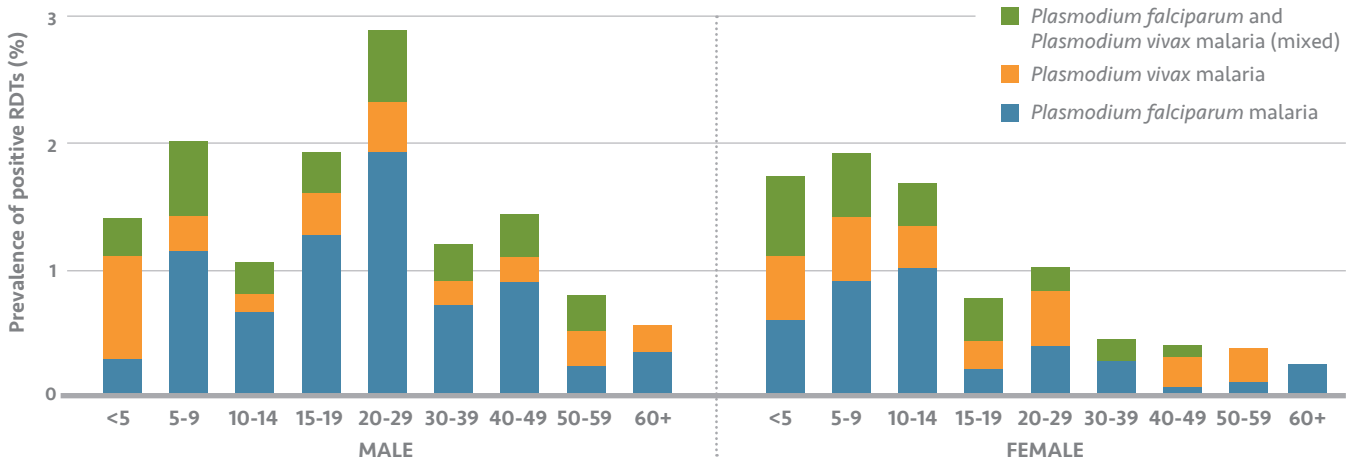
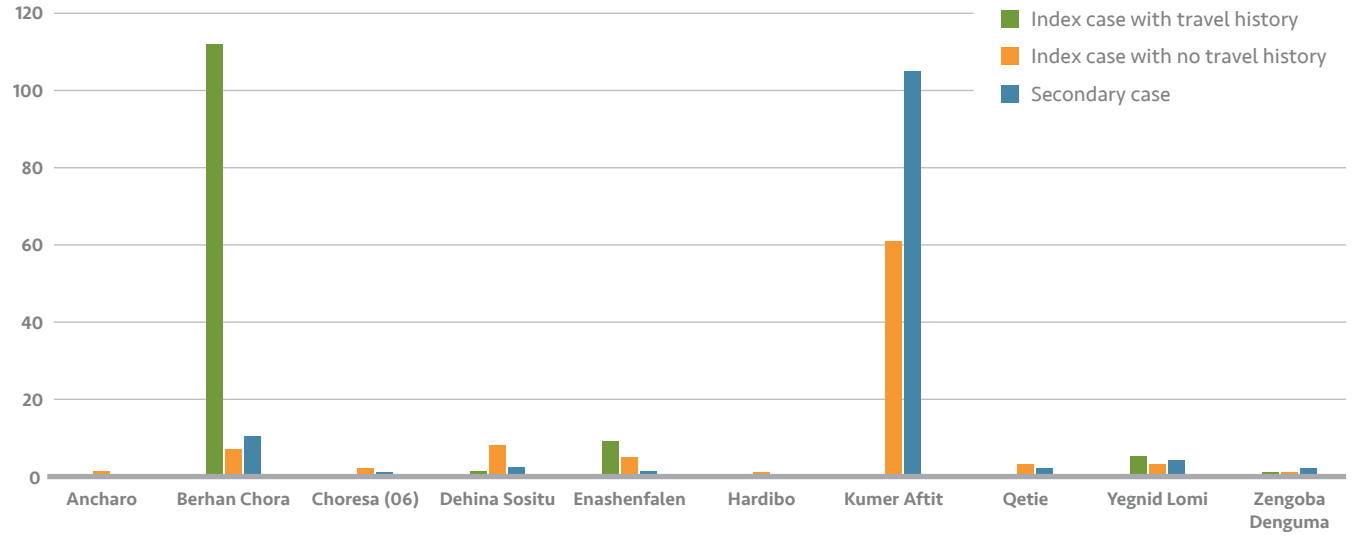


FIGURE 5. Number of index cases (with and without travel history) and secondary cases detected during the FTAT by health post



Impact

MDA and fMDA Impact: Zambia

In lower transmission areas, Year 1 trial results showed large declines in malaria infection across all study arms and a significant reduction in malaria prevalence in the mass drug administration (MDA) arm compared to the control arm. There was a more modest and non-significant reduction in the focal mass drug administration (fMDA) arm compared to the control arm. In areas of higher transmission, the reduction was substantial across all arms. Malaria prevalence at the end of the transmission season in areas of higher transmission approached levels seen in lower transmission health facility catchment areas (HFCAs) at baseline—providing hope that Year 2 interventions can further reduce parasite prevalence rates to very low levels. The study team is investigating the prevalence reductions seen in the control arm in high- and low-transmission areas. Possible contributing factors include increased bednet coverage due to mass distribution of long-lasting insecticide-treated nets in 2014, the change in chemical for indoor residual spraying to Actellic-CS® in 2014–2015, improvements in community case management, or a positive "spillover" effect from the spatial proximity of control arms to MDA and fMDA arms. It is notable that no other province in Zambia experienced prevalence reductions of the magnitude seen in Southern Province, where the study was conducted, during this time period.[7]

Year 1 trial results suggest that MDA with DHAP in particular may be a useful strategy to rapidly clear parasites from a population. In areas of lower transmission, the very low prevalence levels reached after two rounds of MDA with DHAP should permit consideration of discontinuing MDA and focusing on case investigations to identify and treat residual or imported malaria cases without overburdening the health system. In areas of higher transmission, the substantial prevalence reductions after one year of MDA indicate that a second year of MDA might reduce prevalence to levels comparable to those found in low-transmission areas after Year 1. In comparison, fMDA appears to have had less of an impact than MDA, possibly due to the comparatively lower amount of chemoprophylaxis protection provided by DHAP in fMDA areas (where a much smaller proportion of people received the drug) and to rapid diagnostic tests (RDTs) missing low-density infections. It is important to note that MDA/fMDA interventions occurred in areas with high levels of prevention and control coverage, including community case management with case investigations.

MTAT Impact: Senegal

The impact of MTAT implemented one month after the start of the transmission season in low-moderate transmission areas, in combination with PECADOM++ and case investigation, was significant but modest. The MTAT approach resulted in a very small proportion of the population receiving DHAP (only 291 people treated of approximately 22,000 visited). RDT sensitivity is limited and undoubtedly some infections were missed. The results suggest that additional or alternative strategies are needed to complement the modest impact of MTAT to reduce transmission sufficiently to move to case investigation only.

MTAT Impact: Ethiopia

Travel history was a risk factor for RDT positivity during the MTAT. In some villages a large percentage of cases were found to be imported during case investigations. These cases were mainly among migrant workers returning home after performing seasonal agricultural work in areas of higher malaria transmission in western Amhara. This shows that population mobility to higher transmission areas is one of the drivers of malaria transmission in Amhara, making it difficult for a strategy such as MTAT to have a significant impact unless strategies that specifically target migrant workers are implemented in parallel.

Photo: PATH/Gabe Bienczycki

Operational requirements

Zambia

The MDA/fMDA trials indicate that high levels of coverage and adherence are operationally achievable in large populations—the MDA/fMDA trials targeted approximately 300,000 persons in 56,000 households. Approximately 85 percent of reached household members received interventions, and conservative estimates of adherence to a full course of treatment showed high rates of treatment completion. Intervention refusal rates were only 1–2 percent. Although Year 1 MDA/fMDA interventions required substantial human resources and training, the operational model for implementing MDA/fMDA is likely to change if implemented outside of a research study. During Year 1 trials, field teams went house-to-house and enumerators administered household surveys to collect information from study participants. Future MDA/fMDA campaigns without a research component may not require enumerators for data collection and may be able to adopt more efficient intervention delivery strategies, such as centralized DHAP distribution at schools or health facilities.

Senegal

Although its impact appeared to be modest, the Senegal MTAT strategy did indicate that MTAT can achieve effective coverage levels exceeding 75 percent, at least in settings similar to the study areas. Study teams visited 89 percent of the 2,503 households identified in the study area, testing 86 percent of the 22,170 individuals visited in these households, to achieve an effective coverage level of 77 percent. PECADOM++ involved considerable work and does not appear to be an efficient strategy in low transmission areas. Fifty-two field teams had to make 40,000 visits to implement PECADOM++ in the MTAT study arm, identifying only 289 infections during these visits.

Ethiopia

The Ethiopia MTAT strategy similarly suggests that it is operationally feasible to conduct MTAT with effective coverage levels exceeding 75 percent, at least in settings similar to the study area in Amhara. The effective coverage of the MTAT was 76 percent, with 87 percent of households in the intervention areas reached and 87 percent of individuals in the households reached receiving an RDT.

Costs

Across countries

The average cost per individual reached per year over two rounds is estimated to be $12.10 for MDA and $14.70 for fMDA. The largest cost components include drug procurement, supervision, vehicle rental, training, and daily allowances. However, the average cost per individual reached could decrease to $10 or less if research costs (e.g., data collection, staff salaries, and vehicle rentals) are removed. In comparison, the Ethiopia MTAT strategy resulted in an average cost per individual of approximately $7 for only one round per year. The average cost per individual reached for the Senegal MTAT strategy was approximately $14 for only one round per year.

Zambia focus

The cost differences between MDA and fMDA in Zambia are relatively small, and costs are expected to decrease as the operational model evolves. If no rental vehicles or enumerators were utilized during implementation, the average total cost per HFCA per year would decrease substantially. In addition, field teams became more efficient in implementing MDA/fMDA over the course of Year 1 trials and financial efficiencies may be achievable as implementers grow in experience and increase the speed at which visits are conducted. Moreover, MDA and fMDA are time-limited interventions that may be cost-effective over the long-term. "Front-loading" malaria program costs during the MDA/fMDA campaign phase may reduce the subsequent costs of sustaining malaria control measures.

Population-wide drug-based strategies: The way forward

PATH-supported operational research suggests that mass drug administration (MDA) is a particularly promising population-wide drug-based strategy for accelerating malaria elimination in certain transmission settings when used in a time limited fashion and in combination with high coverage of vector control and case management and timely surveillance that allows for tracking and investigation of cases. Further research should provide new information about the impact and operational and financial requirements for population-wide drug-based strategies across different transmission settings. Moving forward, PATH and partners will provide technical assistance and capacity-building to help translate research results into programmatic tools for policymakers in malaria-eliminating countries developing evidence-based plans for malaria elimination. In Zambia, the national government has set the ambitious goal of eliminating malaria nationally by 2020, and its new malaria elimination strategy includes the programmatic implementation of MDA to advance toward that goal. Further demonstrations of impact and achievable resource requirements of population-wide drug-based strategies in Zambia and other malaria-eliminating countries will help generate political momentum, financial resources, and community energy to sustain malaria elimination efforts.

MDA is a particularly promising strategy for accelerating malaria elimination in certain transmission settings when used in a time limited fashion and in combination with high coverage of vector control and case management and timely surveillance that allows for tracking and investigation of cases.

Photo: PATH/Gabe Bienczycki

REFERENCES

1 Poirot E, Skarbinski J, Sinclair D, et al. Administration of antimalarial drugs to whole populations. *Cochrane Database of Systematic Reviews*. 2013;12. doi:10.1002/14651858.CD008846.pub2.

2 WHO Global Malaria Programme. *The role of mass drug administration, mass screening and treatment, and focal screening and treatment for malaria: recommendations*. WHO; 2015. Available at: http://www.who.int/malaria/publications/atoz/role-of-mda-for-malaria.pdf.

3 Walker P, Griffin J, Ferguson N, and Ghani A. Estimating the most efficient allocation of interventions to achieve reductions in Plasmodium falciparum malaria burden and transmission in Africa: a modelling study. *Lancet*. 2016. Published online at http://dx.doi.org/10.1016/S2214-109X(16)30073-0.

4 Bhatt S, Weiss DJ, Cameron, et al. The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. *Nature*. 2016:(526):207. doi:10.1038/nature15535.

5 Moonen B, Cohen J, Tatem A, et al. A framework for assessing the feasibility of malaria elimination. *Malaria Journal*. 2010;9(322). doi:10.1186/1475-2875-9-322.

6 Scott C, Yeshiwondim A, Serda B, et al. Mass testing and treatment for malaria in low transmission areas in Amhara Region, Ethiopia. *Malaria Journal*. 2016:15(305). doi: 10.1186/s12936-016-1333-3.

7 Government of the Republic of Zambia, Ministry of Health, "Zambia National Malaria Indicator Survey 2015."

PATH is a leader in the battle to control and eliminate malaria nationally and regionally, and ultimately to eradicate it worldwide. PATH is partnering with national programs to optimize the delivery of current solutions and approaches, while developing new strategies to eliminate malaria in local and regional settings. With an unparalleled portfolio of malaria projects, PATH is developing the next generation of tools to accelerate efforts to detect, prevent, and treat malaria.

Diagnostics. In collaboration with public and private sector partners, PATH is pioneering the use of diagnostics for malaria elimination. We are improving access to available tests while advancing the development of new ones that support improved case management.

Vaccines. PATH's pipeline of vaccine candidates and approaches, under development with partners from across the globe, is one of the most robust in the world. It includes candidates that would prevent infection and those that attempt to block transmission of the malaria parasite from humans to mosquitoes and back again.

Drugs. PATH is working to improve malaria treatment so that no one who contracts the disease dies from it. We are ensuring a stable supply of malaria drugs and strengthening the existing supply. We are also strengthening health systems and improving the quality of malaria case management in Africa and the Mekong Region.

System and Service Innovations. To develop the science behind how to eliminate malaria in Africa, we are piloting new strategies with the goal of developing a package of approaches that are adoptable and adaptable across the region. These include strategies to stop the transmission of the malaria parasite from humans to mosquitoes and back again through community-wide treatment. We are collaborating closely with endemic countries to create malaria-free zones, the first step on the path to elimination.

Better Data for Decision-Making and Improved Surveillance. PATH is working with partners to use data in new and better ways to track emerging transmission patterns, optimize the way resources are deployed, and eventually track down the last malaria parasite.

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