PATH/Sarah McGray

Zanzibar Trip Report

Project DIAMETER (Diagnostics for Malaria Elimination Toward Eradication)

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MAILING ADDRESS
PO Box 900922
Seattle, WA 98109
USA

ADDRESS
2201 Westlake Avenue
Suite 200
Seattle, WA 98121
USA

TEL: 206.285.3500
FAX: 206.285.6619

www.path.org

PATH

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Abbreviations

AEIOU	Activity, Environment, Interaction, Object, and User
DIAMETER	Diagnostics for Malaria Elimination Toward Eradication
DMSO	District Malaria Surveillance Officer
ELISA	enzyme-linked immunosorbent assay
FSAT	focal screening and treatment
GPS	Geographic Positioning System
IRS	indoor residual spraying
ITN	insecticide-treated nets
JOC	Jobs-Outcomes-Constraints
MCN	malaria case notification
MEEDS	Malaria Epidemic Early Detection System
MIS	Malaria Indicator Survey
PCR	polymerase chain reaction
PHCC	primary health care center
PHCU	primary health care unit
PMI	President's Malaria Initiative
QA	quality assurance
QC	quality control
RACD	reactive case detection
RDT	rapid diagnostic test
SOP	standard operating procedures
TPP	target product profile
USAID	United States Agency for International Development
WHO	World Health Organization
ZAMRUKI	Zanzibar Malaria Research Unit Karolinska Institute
ZMCP	Zanzibar Malaria Control Program

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Introduction

The DIAMETER project

The goal of the Diagnostics for Malaria Elimination Toward Eradication (DIAMETER) project is to define the diagnostic needs unique to malaria-elimination settings with sufficient clarity so that all stakeholders can act with confidence to develop, commercialize, and efficiently implement the most promising, cost-effective, and impactful technologies for malaria elimination.

Recent progress in malaria control has enabled countries to reduce malaria transmission rates. Existing diagnostic technologies—microscopy and rapid diagnostic tests (RDTs)—have played a critical role in this success by enabling many regions to achieve transmission rates near the threshold that defines the elimination phase. However, it is not clear whether these same tests are the most efficient and cost-effective tools to achieve accurate infection detection at low levels of parasitemia which is critical to achieving elimination goals. Furthermore, there is a lack of clarity and agreement on the use scenarios, target product profiles (TPPs), standardized methods of assay validation, and market potential for the malaria diagnostic tools best suited for cost-effective detection in elimination settings. The resulting ambiguity hinders the development of new infection-detection technologies as well as strategic application of existing and nearly ready tools.

PATH has developed a rigorous approach to identifying the most promising solutions to diagnostic challenges in low-resource settings. This involves aggregating and analyzing user needs, market needs, and technical requirements to generate the comprehensive evidence base necessary to inform program development, commercialization, and strategic program operations. Thus, through extensive field research and collaboration with malaria-elimination experts, the DIAMETER project team will evaluate and hone the use scenarios and TPPs for infection detection in elimination scenarios. To this end, stakeholder interviews will be conducted in a selection of countries in Asia, Africa, and South America that are nearing malaria elimination. Information gathered will be collated to inform product development of new diagnostics and areas where further research is required. This report presents findings from stakeholder interviews conducted in Zanzibar in May 2013.

Background on malaria in Zanzibar

Zanzibar consists of two main islands—Unguja and Pemba—and has an estimated population of 1.3 million, 40% of whom live in urban areas. Zanzibar has two rainy seasons: a long rainy season from March through June, with an average precipitation of 950 mm, and a short rainy season from October through December, with an average precipitation of 450 mm. The public health care system consists of a network of primary health care units (PHCU) complemented by secondary (district and primary health care centers [PHCC]) and tertiary referral centers (Table 1). PHCUs provide only outpatient services,

while PHCCs and hospitals include in-patient services. The private health care sector comprises 3 hospitals, 200 clinics, 60 registered pharmacies, and over 200 over-the-counter outlets.[1,2]

Table 1: Levels of public health care in Zanzibar.

Facility type	Level	Number	Malaria diagnostic tests performed
Primary health care unit	Primary	104	Rapid diagnostic test (RDT)
Primary health care unit-plus	Primary	32	RDT and microscopy*
Primary health care center	Secondary	4	Microscopy
District hospital	Secondary	3	Microscopy
Referral hospital	Tertiary	1 (+ maternity & mental health annexes)	Microscopy
Total:		**144**	

*Microscopy is dependent on the availability of a laboratory technician and electricity.

The scale-up of malaria intervention activities and high coverage rates of indoor residual spraying (IRS) and insecticide-treated nets (ITN) achieved over the years have resulted in a dramatic decline in malaria prevalence. Zanzibar recorded ITN ownership in 76% of households in 2010 and has recorded more than 90% coverage rates of IRS since 2006.[3] The overall prevalence obtained during the Malaria Indicator Survey (MIS) in 2010 was 0.07%.[4] Unpublished data from public health facilities from 2010 through 2012 indicate that children under five years of age constitute only 18% to 20% of all RDT-positive cases (personal communication, Zanzibar Malaria Control Program [ZMCP]). The RDT testing rate among all attendants at public health facilities from 2011 through 2012 was approximately 32% (Appendix A). *Plasmodium falciparum* (*P. falciparum*) is the predominant species, accounting for about 97% of infections in Zanzibar. *Plasmodium malariae* is seen in about 3% of cases, and *Plasmodium ovale* is very rarely seen. The high transmission rate of malaria in mainland Tanzania, however, renders Zanzibar vulnerable, particularly as it has many unauthorized entry routes.

Although Zanzibar has had two failed attempts at elimination, its government has recently expressed its interest to move from control to elimination. In 2008, the ZMCP, in collaboration with several partners, conducted an assessment of the feasibility of eliminating malaria. They concluded that elimination of malaria was possible with currently available interventions. Nevertheless, they acknowledged that it would be operationally and financially challenging to prevent reintroduction if the importation risk remains high.[2] The 2008–2012 strategic plan targeted a 70% reduction in facility-based malaria morbidity (from 35% in 2006 to 10% in 2012).[4] The strategies to achieve this objective included:

- Ensuring effective case management by providing prompt access to parasitological diagnosis (by microscopy or RDT) and artemisinin-based combination therapy.
- Providing effective epidemic preparedness and response by ensuring that for more than 90% of health facilities, case reports are provided to the ZMCP on time, investigation of reported epidemics is initiated within 24 hours, and supplies are at hand to mount a response if necessary.
- Assessing the potential for sustainable elimination of malaria from Zanzibar using newly available data from surveillance and operational research as well as experience from implementation.

The ZMCP's vision is a Zanzibar free of malaria, and its mission is to provide quality, affordable, and cost-effective malarial interventions to all people within the country's borders. The ZMCP is currently in the process of developing its strategic plan for the period 2013 through 2018. The goal is to have zero locally acquired malaria cases by 2017.[5] Funding for the ZMCP's activities is mainly provided by the Government of Zanzibar, the President's Malaria Initiative (PMI) led by the United States Agency for International Development (USAID), and the Global Fund. In addition, ZMCP has collaborations for research and strategy implementation with World Health Organization (WHO), Ifakara Health Institute, and the Clinton Health Access Initiative.

Purpose of the report

1. To consolidate and document country-specific information derived from stakeholder interviews.
2. To disseminate summarized information to key informants who participated in the data collection process, to PATH staff in-country, and to other stakeholders.

Methods

In order to capture a complete picture of the current state of malaria elimination in each country, the DIAMETER project combines thorough desk research on malaria control and elimination efforts with theory-driven qualitative research targeting the opinions and actions of key players within the country's malaria program.

Literature review

Prior to initiating the qualitative research component, a literature review of relevant documents was undertaken. This desk research helped the team position where Zanzibar lies along the spectrum from control to elimination, clearly understand the strategies and priorities of the ZMCP, and gain perspective on previously completed and ongoing research in the country. Qualitative data collection tools were developed based on this desk research, and key informants were identified.

Interviews with key informants

Eight key informant interviews were conducted along with visits to one PHCC and three PHCUs. A list of stakeholders is provided in Appendix B. Interview guides and observation checklists were developed in advance to encourage systematic and uniform data-collection techniques within the tenets of Contextual Inquiry methodology and using a hybrid of two frameworks—Jobs-Outcomes-Constraints (JOC) and Activity, Environment, Interaction, Object, and User (AEIOU)—to organize concepts. Contextual Inquiry approaches qualitative data collection with the objective of describing how actors, objects, and rules influence and are influenced by the larger system in which they exist. This method exposes tacit knowledge that informants may not be aware of and encourages the informant (rather than the reviewer) to prioritize concepts.

Interview guides and observational checklists were used for each category of key informant: program manager, thought leader, surveillance officer, clinician, and drug dispenser. The data collection tools were developed using a hybrid JOC-AEIOU framework, which prompted the interviewers to describe the main elements of the system (AEIOU) and then define the barriers to successfully achieving the intended objectives (JOC).

Following data collection, key concepts from each interview were summarized by the research team, mapped to the corresponding use scenarios and settings, and aggregated across all 12 data sets (8 interviews and 4 observational visits). A spreadsheet mapping key concepts to use scenarios and settings is included as Appendix C.

Malaria diagnostic tests used in Zanzibar

RDTs and microscopy constitute the mainstay of malaria diagnostics under programmatic conditions in Zanzibar.

The test performance, suitability to the local malaria epidemiology, and storage temperature are some of the criteria the ZMCP considers in selecting an RDT. Paracheck was previously used; however, the SD BIOLINE Malaria Ag P.f/Pan test has been in use since 2010 as this test detects other *Plasmodium* species in addition to *P. falciparum*. Some desirable features of the SD BIOLINE Malaria Ag P.f/Pan RDT are its ease of use and the individually packaged buffer solutions. Although the use of a pipette as a blood transfer device is preferred over the loop (as was the case with Paracheck), there are challenges in drawing and transferring the required volume of blood for the test. Drawbacks with RDT use are the absence of a quality control (QC) system and the lack of capacity to perform lot testing locally. There have been instances of test kits having empty buffer pouches and of buffer solutions being yellowish instead of clear. The RDT test kits do not include gloves. While RDTs are procured with PMI funds, gloves and other consumables for microscopy are procured with funds from the Global Fund. This leads to occasional shortages because gloves meant for microscopy are used for RDTs. Sometimes District Malaria Surveillance Officers (DMSOs) do not change gloves between tests. It is unclear if this is a time-saving measure. DMSOs nonetheless stated their preference for gloves to be included in test kits. The estimated annual RDT requirement for 2013 is about 366,000 test kits.

Though not widely available in most public health facilities, microscopy is considered the gold standard. There is a well-established system for QC; all positive blood slides and a random selection of 10% negative blood slides are sent to the ZMCP lab for reading. Between July 2011 and March 2012, 528 positive slides and 7,756 negative slides from 52 public and private health facilities were read at the ZMCP laboratory as a QC measure. The agreement between the readers was 93.8% and 99.7% for positive and negative slides, respectively.[4] Microscopy has the added advantage of providing information on parasite density, parasite species, and stage. There is some concern about the loss of skills of microscopists with the decreasing prevalence of malaria.

Polymerase chain reaction (PCR) tests are only performed under research conditions in collaboration with the Zanzibar Malaria Research Unit Karolinska Institute (ZAMRUKI). Dried blood spots and/or used RDTs are sent out of the country for analyses under such circumstances.

Malaria diagnostic scenarios in Zanzibar

The main use scenarios employed in Zanzibar are passive case detection, reactive case detection (RACD), focal screening and treatment (FSAT), and surveys. In spite of the high importation risk, there are currently no border screening activities. Appendix C summarizes the use scenarios, settings, and constraints.

Passive case detection

Zanzibar's primary strategy for identifying malaria cases relies on passive case detection using microscopy (primary) and RDTs (secondary). Passive case detection occurs in both public and private health sectors, but only public-sector facilities are supplied by the ZMCP and Central Medical Store. Private health facilities are expected to have malaria diagnostic capacity before they are granted authorization to operate, but the extent to which this is enforced is not known. RDTs were only introduced into the private sector in 2013, and the ZMCP currently has no data on the diagnostic tests being used in this sector. Private health facilities procure their RDTs from wholesalers who are authorized to sell the ZMCP-recommended RDTs. It is unknown how many private-sector providers adhere to ZMCP treatment guidelines. There are ongoing efforts to include private-sector facilities in ZMCP guidance and surveillance, but these mechanisms are not fully implemented, and only some facilities report case detection data into the surveillance system.

The ZMCP treatment guidelines require all patients seen at a facility with current fever or a history of fever (in past 48 hours) to be tested by RDT or microscopy. The use of RDTs was introduced to the country in 2005, and following the detection of mono-infections with *P. malariae*, the ZMCP phased out *P. falciparum*-only tests in favor of P.f/Pan RDTs (SD BIOLINE). RDTs alone, microscopy alone, or a combination of the two may be used depending on the level of infrastructure and the availability of a laboratory technician. RDT results are often ready within 15 to 30 minutes, whereas microscopy results are obtained after about an hour. There is a dedicated malaria laboratory at the referral hospital where all out-patients are tested using microscopy. RDTs were used in 126 public health facilities in 2011–2012 (Appendix A).

Microscopy is the preferred method of diagnosis when available; secondary and tertiary centers use microscopy almost exclusively for malaria diagnosis. Microscopists may use thick smear, thin smear, or both, depending on the individual. Microscopists typically provide information on the presence of parasitemia and parasite density to the clinician for patient management. The primary-level facilities, PHCUs, typically use only RDTs. However, some units (PHCU-plus) have basic laboratory facilities

(microscope, water, intermittent power), and therefore use both microscopy and RDTs depending on the availability of electricity and a laboratory technician.

Reactive case detection

The RACD process is triggered when cases are identified at the health facilities. DMSOs follow up with the households of index cases to test and treat household members. RACD relies on a robust surveillance system established by the ZMCP (Appendix D). In 2008, the ZMCP, in collaboration with PMI, developed and implemented a health facility-based Malaria Epidemic Early Detection System (MEEDS) to detect sudden increases in transmission of *P. falciparum*. MEEDS has been implemented in all 144 public health facilities and is being introduced into the private sector.[6] This RACD strategy pairs a DMSO assigned to each of the ten districts with the health facilities within the district. For each malaria case detected at the health facility, the DMSO will track that case back to his or her home and test and treat the index case household and proximal households as needed.

Cases are reported to the DMSO via text message from the health facility within 24 hours of case identification. The ZMCP provides all DMSOs and public health facilities with cell phones and phone credit to facilitate information flow. In addition, DMSOs are provided with tablet PCs with Geographic Positioning System (GPS) capabilities which are used to record and transmit RACD data. DMSOs follow up at the health facility within 24 hours of receiving the alert to collect basic patient information, including name and address, for follow up at the household level. This RACD is usually carried out within 24 hours of collecting the basic patient information.

DMSOs often receive notification of three to five cases per day during the high transmission season and zero to one case per day during the low transmission season. Workload can be very high for the DMSOs because each household has between five and ten members, each of whom has to be tested. Additionally, households may be far apart. DMSOs spend an average of one hour in each household. They often run the RDTs on family members concurrently. The ZMCP provides all logistics and supplies for the DMSOs including motor bikes, thermometers, RDTs, gloves, and artemisinin-based combination therapies. The RDTs are kept in their homes. However, these RDTs are exposed to the weather as the DMSOs carry them in their backpacks when they go about their daily duties on motor bikes. An issue of concern is the risk of getting pricked by the used lancets and of subsequent exposure to blood-borne pathogens such as HIV, especially as there is no post-exposure prophylaxis. DMSOs place all used items in a plastic bag for disposal at the nearest health facility. Yet sometimes, the waste is burned within the community when DMSOs are too far from a health facility at the end of a day's work.

All household members are tested and are treated when they test positive. A brief questionnaire is administered to obtain information on ITN use, recent IRS, and any travels. Axillary temperatures are taken for all household members and GPS coordinates of the household obtained. Up to four neighboring households are screened and treated if more than three people in the index household test positive for malaria. No further follow-up visits are carried out to these households. Table 2 below summarizes the DMSO's tasks.

At the facility, health care workers also submit weekly data summaries to a central server at the ZMCP by calling a toll-free number on their cell phones. The summary data submitted include the week in the year for which a report is being submitted, total outpatient attendance, number testing positive for malaria, and number testing negative for malaria. This information is presented for both persons under five years of age and those five years and older. This enables the ZMCP to make data-driven decisions such as when and where to investigate sudden increases in transmission.

Table 2: Summary of DMSO tasks.

- Receive malaria case notification (MCN) from health facility via text message to cell phone.
- Collect patient details from health facility within 24 hours of notification.
- Travel to household.
- Document Global Positioning System coordinates.
- Administer questionnaire.
- Take temperature of all household members.
- Test all household members with an RDT.
- Provide treatment to all household members who test positive.
- Use tablet PC to transmit results.

Focal screening and treatment

FSAT takes place under two circumstances. Firstly, it is conducted proactively in known "hotspots"[*] twice a year just before the rainy seasons. Each round of FSAT activity is carried out in two phases with a four-week interval by teams of DMSOs who go from house to house. There are usually about 16 teams of two who see about 80 to 100 people per day. GPS coordinates of households are taken during this activity.

FSAT also takes place when data from MEEDS show an abnormal increase in number of cases over a period. Here, a team of DMSOs, medical officers, and laboratory technicians is organized and dispatched to the community. The media is often used to sensitize and mobilize the community to enable the team to set up work stations within the community (e.g., at schools). RDTs are used for this activity, but blood slides are taken for persons who have been treated for malaria within the past two weeks because of the persistence of *P. falciparum* HRP2 antigens and also for persons whose RDTs are inconclusive (e.g., very faint test lines).

Surveys

Two main surveys are conducted in Zanzibar: 1) the MIS, which is usually conducted in a nationally representative sample; and 2) sentinel site cross-sectional surveys, which are conducted in collaboration with ZAMRUKI. The first MIS was carried out in 2002 and has subsequently been conducted every two

[*] Hotspots are large or small geographically clustered regions identified as having comparatively higher levels of transmission. Hotspots may fuel transmission to surrounding areas, and, therefore, interventions targeting hotspots are believed to be useful in elimination settings.

years. The purpose is to determine the parasite prevalence in the population and coverage of interventions such as ITN use and IRS. Previously, blood slides were collected for microscopy, but RDTs were used in 2010. Approximately 1% (n=13,526) of the total population was tested during the 2010 MIS. As a result of the low prevalence (0.07%) obtained during the 2010 MIS and the high coverage rates of the various interventions, combined with a shifting donor-sponsored funding environment, the ZMCP has stopped the conduct of nationally representative surveys. This decision was made because of the large sample size that would be required and the associated logistic and cost implications.

The cross-sectional surveys conducted by ZAMRUKI, however, are purely for research purposes and have been carried out every year in two sentinel districts. These sentinel districts were selected on each of the islands in 2003 because they were representative of malaria epidemiology on the islands at the time. Samples are collected during such surveys for RDTs and for dried blood spots. The latter are subsequently sent to Karolinska-affiliated labs in Europe for PCR analyses and the results shared with the ZMCP. Results from these surveys can take a significantly long time to be reported back to Zanzibar. Clearly, the withdrawal of this support from the Karolinska Institute would have a negative impact on the ZMCP's activities. ZAMRUKI has begun collaboration (November 2013) with the Foundation for Innovative New Diagnostics to carry out some trials using loop-mediated isothermal amplification.

Malaria diagnostic settings in Zanzibar

Malaria diagnostics (microscopy and RDT) are used at all levels of the health system as a routine response to fever. The level of the health system, infrastructure available, and human resources available are the primary determinants of when microscopy is used and when an RDT is used. Appendix E illustrates the types of facilities, diagnostic tests used, common use scenarios at the facility, and infrastructure and human resources available.

Referral lab

The referral lab at Mnazi Mmoja Hospital in Stone Town is the highest-level capacity on the main island, although it does not have PCR capability. Although the national reference lab on Pemba Island has PCR, the ZMCP does not seem to use this resource and has only used technical support from microscopists at this lab for quality assurance (QA) and QC of blood slides (100% positives and 10% negatives) in the past. The referral hospital lab is fully equipped with independent space for hematology, histopathology, parasitology, microbiology, and tuberculosis labs. While there are no PCR capabilities at present, the structural space and infrastructural requirements are available should development of PCR capabilities become a programmatic priority and funding became available. Presently, two to three lab technicians at a time operate in a dedicated parasitology lab where microscopes are used exclusively for malaria diagnosis.

Constraints

Throughout the lab, there were several pieces of broken equipment or equipment that was unused due to stockout of consumables. Replacement and repair of capital equipment can be challenging due to slow response times of the suppliers. About 50% of observed pipettes were recently calibrated, while the other half had not been calibrated for more than six months.

Research laboratories

The ZMCP has an on-site laboratory which performs QC on 10% of negative blood slides and all positive slides from all public health facilities and some private-sector facilities. There is one national reference laboratory which is located on Pemba Island; however, samples from the main island, Unguja, are rarely sent to this lab due to the time and expense. We did not visit this reference lab. The ZMCP lab has capacity for research and QC purposes but is not a clinical laboratory. In addition to purified water, reliable power, cold storage, and microscopy capabilities, the ZMCP lab also has enzyme-linked immunosorbent assay (ELISA) capabilities, though at this time ELISA is used only for entomological purposes. This lab is staffed by ZMCP staff and lab technician students completing their two-year degree.

Another research laboratory set up by ZAMRUKI at the Kivunge PHCC was also visited. This lab was fully equipped for research purposes but also did not have PCR capability. The lab is used only when funded by a research project; it is not used for general clinical purposes. When not in use for research, the lab remains closed, so it is unclear how the lab is staffed when open. This lab also has water purification, a back-up generator to supply reliable electricity, and 4°C and -70°C storage.

District hospitals

All three district hospitals in Zanzibar are located on Pemba Island and were not visited on this trip. However, district hospitals have laboratories and use microscopy.

Primary health care center

The PHCC visited at Kivunge has a small lab with basic clinical analysis capabilities. In addition to two microscopes for tuberculosis and malaria diagnosis, the lab contains a centrifuge and 4°C cold storage and has a back-up generator to ensure constant power supply (shared with the research lab in the adjacent building) as well as tap water. The available pipettes in the lab were functional but older and not recently calibrated. The lab runs 30 to 50 malaria slides per day during the rainy season taken from patients reporting at the PHCC with fever and does thick and thin smear for each slide from which they capture parasitemia and speciation. This lab is staffed by two to four lab technicians with two-year degrees.

Constraints

The district supplies procurement officer noted that he preferred microscopy to RDTs due to the local availability of the supplies for microscopy (Giemsa stain). Availability of RDT supplies can be problematic whereas microscopy supplies can be procured from the private sector in a pinch.

Primary health care unit-plus

At the PHCU-plus level, a basic lab with a single microscope and sink is available for malaria diagnosis. Generally, this level facility would not include other supplies. Power from the mains is generally available, but there is no back-up generator. One microscopist reported power cuts between one and three times per week for periods lasting 5 to 30 minutes. When power is not available, RDTs can be used instead of microscopy. In addition, RDTs may be used in combination with microscopy for RDT-positive patients when patient load is high and speed is required.

Constraints

During one observational visit, the microscopist reported that she does not retain slides for QC, implying that oversight may be less rigorous at this level of health facility. In addition, at both facilities visited, the microscopist did only thick-smear slides, indicating that not all surveillance data on microscopy-positive malaria cases will include parasite species.

At this level, patients may be more likely to mistrust the RDT; one microscopist reported that she occasionally follows up a negative RDT with microscopy to convince a disbelieving patient.

Primary health care unit

This is the most peripheral facility within the Zanzibari public health system and has the fewest resources available. The facility we visited did not have power, and water was available from a tap outside. In a PHCU, a single clinician (four-year degree) provides all testing, treatment, and dispensary services; there is no separate laboratory room or dispensary. Only RDTs are used in this setting. At the facility we visited, the clinician sees approximately 15 febrile patients per day.

Constraints

At this level facility, where RDTs are the only tool used, minimal constraints were identified beyond those of limited infrastructure.

Challenges and strengths for achieving malaria elimination

As Zanzibar intensifies its efforts to implement strategies toward malaria elimination, ZMCP will need to address specific challenges which may impede success, while simultaneously leveraging its strengths to maximize sustained impact.

Challenges

Need for more sensitive tests: ZAMRUKI performed PCR tests on 6,000 samples that had previously been tested by RDTs, and demonstrated that RDTs are less sensitive in detecting positive cases. This is of grave concern to the ZMCP given its reliance on RDTs for most of its activities and prevailing low levels of parasitemia.

Human resource shortages: Lack of trained microscopists.

System breakdown: The QA system in place includes monthly auditing of 100% of positive slides and 10% of negative slides. However, it doesn't appear that significant action is taken if a discrepancy is found.

Meeting WHO requirements for certification of malaria elimination: One of the preconditions for certification by WHO is "high-quality laboratory services to diagnose malaria, based on microscopy."[7] The ZMCP recognizes the importance of establishing parasite counts and presence of gametocytes, but microscopy is not widely available in Zanzibar due to infrastructural challenges and the scarcity of laboratory technicians. In addition, there is misalignment between donor priorities and WHO elimination-certification requirements. For example, PMI is funding a national rollout of RDTs, while the Global Fund supports only microscopy in alignment with WHO requirements.

Determination of causes of non-malarial fevers: With the declining prevalence of malaria, a greater proportion of those who present with fever are testing negative for malaria. This poses a challenge for providers when an obvious cause of fever is absent, particularly for those at the lower levels of the health care system where there is limited diagnostic capacity. It also leads to patients' mistrust of negative RDT results in particular. Other tests that may be conducted in health facilities that have the diagnostic capacity when fever presents as a symptom include the Widal test for typhoid, microscopic examination of urine for urinary tract infection, and, in cases of persistent fever, RDTs for HIV and Ziehl-Neelsen stain for tuberculosis. Nonetheless, clinicians are often faced with a dilemma when these test results are negative.

Funding: Zanzibar obtains most of its funding for malaria-control activities from international donors. Therefore, a shift in donors' interest toward other high-burden diseases could threaten the gains made so far.

Strengths

Strong health system structure: Zanzibar boasts a structured matrix of health facilities with communication and reporting protocols that enable integrated care and data reporting across facilities. This well-structured network has enabled the success of the MEEDs RACD strategy, and will continue to be a key component of data sharing and reporting once elimination has been achieved. ZMCP would benefit from advanced planning to forecast what adaptations to this network will be needed to accommodate evolving surveillance strategies in an elimination scenario.

Adaptive training programs: Zanzibar is fortunate to be home to the Zanzibar Association for Medical and Laboratory Scientific Officers, which provides training, supervision, and standard operating procedures (SOP) development for microscopists. As Zanzibar approaches elimination, access to training resources that can be adapted to the changing landscape of malaria can enable a robust workforce to implement a seamless progression into and maintained status of elimination.

Strong partnerships: Zanzibar has an established history of partnerships with institutions that are laying the groundwork and setting the agenda for malaria elimination at the regional and global levels. Continuing to identify opportunities for collaboration on mutual objectives for elimination in Zanzibar may provide avenues for funding and other resources needed to help Zanzibar achieve elimination.

Summary

RDTs and microscopy constitute the mainstay of malaria diagnostics under programmatic conditions in Zanzibar. PCR is used only for research purposes when external collaborators are involved. The use scenarios employed by the ZMCP are passive case detection, RACD, FSAT, and surveys. The level of the health system, infrastructure available, and human resources available are the primary determinants of when microscopy or RDTs are used for passive case detection. RACD, FSAT, and surveys occur at the household and community levels, and RDTs are used for these use scenarios. The main constraints identified in the use of microscopy are its dependence on electricity and trained lab technicians, liability to reading errors, and being labor intensive. There is also concern about the loss of microscopists' skills as the country moves toward elimination. Major constraints associated with RDTs are the lack of a QC system, inability to differentiate current infections from past infections due to HRP2 persistence, inability to detect all cases, and inability to differentiate between parasite species. Time to RDT results was considered to be too long for RACD and FSAT activities.

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Appendix A: Rapid diagnostic tests performed in public health facilities in the ten districts of Zanzibar, 2011–2012

District	Estimated population	No. of health facilities	2011					2012				
			Total attendance	Number tested	Number positive			Total attendance	Number tested	Number positive		
					Pf	Pan	Pf+pan			Pf	Pan	Pf+Pan
Wete	124,654	18	94,061	24,680	59	-	-	80,220	32,482	205	1	20
Chakechake	102,280	7	44,130	13,691	36	-	-	41,526	14,617	50	-	1
Mkoani	113,878	13	53,905	11,761	136	-	-	51,751	14,618	137	6	3
Micheweni	101,603	11	83,800	23,496	255	-	-	71,201	21,818	494	1	7
North "A"	105,339	10	54,995	18,155	100	7	23	49,912	14,429	64	1	13
North "B"	65,696	12	42,346	17,178	159	5	101	41,236	14,956	293	8	-
South	38,542	9	35,826	11,334	179	20	182	33,528	10,453	43	-	3
Central	75,400	23	64,937	22,647	462	7	256	55,566	13,774	218	10	70
Urban	306,570	11	40,531	14,389	18	-	16	42,463	12,927	26	1	9
West	274,497	12	68,194	23,384	248	4	308	61,444	17,298	161	-	6
Total (%)	**1,308,459**	**126**	**582,725**	**180,715**	**1652 (0.9)**	**43 (0.02)**	**886 (0.5)**	**528,847**	**167,372**	**1691 (1.0)**	**28 (0.02)**	**132 (0.08)**

Pf = *Plasmodium falciparum*

Pan = pan *Plasmodium*

Appendix B: List of stakeholders

Name	Position
Dr. Ali Abdullah	Program Manager, Zanzibar Malaria Control Program (ZMCP)
Dr. Mohammed Jiddawi	Principal Secretary, Ministry of Health
Ali Khamis	Head, Diagnostic Unit-ZMCP
Abdul-wahid Al-mafazy	Head, Surveillance Unit-ZMCP
Haji Haji	Head, Case Management-ZMCP
Dr. Ali Amour	Private provider and pediatrician at Mnazi Mmoja Referral Hospital
Shija Joseph Shija	Pharmacist, ZMCP
Dr. Pierre Kahozi	World Health Organization Liaison Officer
Dr. Salum Seif	Head, Zanzibar Association for Medical and Laboratory Officers
Dr. Jackie Cook	Researcher, Zanzibar Malaria Research Unit Karolinska Institute
Ali Suleiman	District Malaria Surveillance Officer (DMSO)-ZMCP
Habiba	DMSO-ZMCP
Hamis	DMSO-ZMCP
Wadi	Laboratory Technician, Kivunge Primary Health Care Center (PHCC)
Abdulla	Clinical Officer, Kivunge PHCC

Special thanks to Mwinyi I. Msellem, Medical Laboratory Scientist, ZMCP, for sharing insight and facilitating the completion of these interviews.

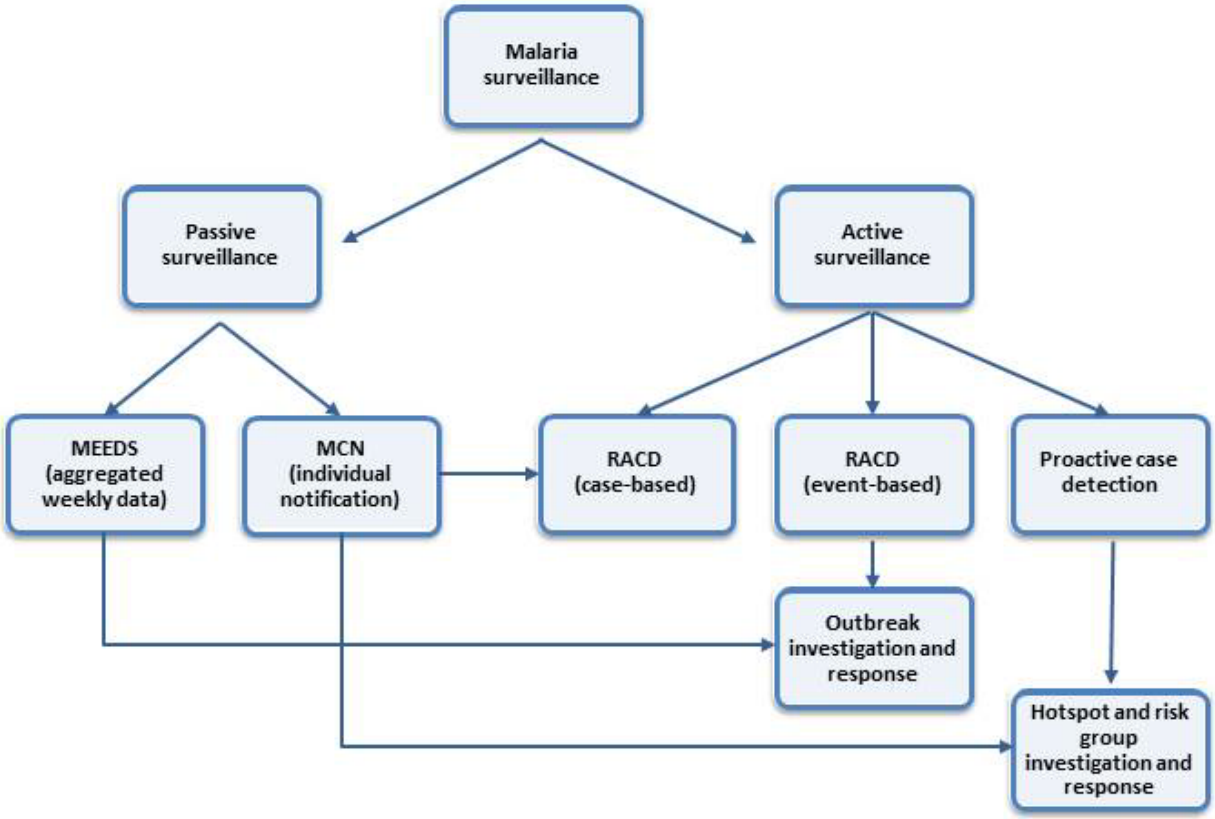
Appendix C: Use Scenarios for Malaria Diagnostic Tests in Zanzibar

Use Scenario	Setting*	Inputs				Outcomes	Constraints	Other Notes/Comments
		Diagnostics	Process	Who performs test?	Infrastructure/Supplies			
Passive Case Detection (PCD)	Primary Health Care Unit	Rapid diagnostic test (RDT) (*Pf* /Pan), SD Bioline, (previously Paracheck)	• Patient presents with fever or a history of fever in past 48 hours • Clinician tests with RDT	• Clinician with four-year degree (doctor, nurse, pharmacist)	• Cell phone to initiate reactive case detection follow-up by district malaria surveillance officer (DMSO) and for weekly surveillance reports to malaria epidemic early detection system (MEEDS) • Zanzibar Malaria Control Program (ZMCP) provides cell phone (including replacements) and phone credit • Intermittent electricity • Water tap outside • Rural, proximal to main (paved) road	• Detect and treat patients with current infection • Document detailed patient information in Malaria Case Register (MCR) • Send Malaria Case Notification (MCN) via text message (sms) to DMSO and ZMCP • Send weekly summary data via sms to MEEDS at ZMCP	• No quality control • Patient mistrust of negative results • Loss of buffer when opening pouch • Retained buffer in tip of pouch • Cannot differentiate between parasite species • Positive test does not always signify current infection • Does not detect all cases • Uncertainty of effect that buffer color change has on test results • Leakage of blood/buffer along sides of cassette • Faint result lines subject to wrong interpretation • Cannot determine other causes of fever • Some difficulty in drawing and dispensing exactly 5µl of blood using pipette	• Results obtained within a short time • Easy to train • Used RDTs are disposed of by burning in pits • Sometimes, positive RDTs may be retained depending on the research needs of Zanzibar Malaria Research Unit Karolinska Institute (ZAMRUKI)
	Primary Health Care Unit plus	RDT (*Pf* /Pan) and microscopy	• Patient presents with fever or having a history of fever in past 48 hours • Test ordered by clinician, done in clinic laboratory (same building) • Test used depends on patient load and availability of electricity • RDTs used when power is out, or when laboratory technician is backlogged; otherwise, microscopy • Results go back to clinician for patient follow-up	• Laboratory technician with two-year degree	• Inconsistent power, sink • No back-up generator • Cell phones for RACD follow-up and weekly surveillance reports	• Detect and treat patients with current infection • Document detailed patient information in MCR • Send MCN via sms to DMSO and ZMCP • Send weekly summary data via sms to MEEDS at ZMCP	**Microscopy and RDTs:** • Use is dependent on the availability of trained laboratory technicians • Electricity • Time consuming • Labor intensive • Liable to reading errors • Technician errors (e.g., reading slides, not preparing fresh stock of Giemsa stain daily)	• All positive slides and random selection of 10% of negative slides are sent to ZMCP monthly (98% agreement) • Use of either test is dependent on laboratory technician's discretion • Reagents available locally • Can determine parasite density, species with microscopy • Can monitor treatment with microscopy • RDT results obtained within a short time
	Primary Health Care Center	Microscopy	• Test all patients presenting with fever or having a history of fever in past 48 hours • Patient goes to clinic laboratory for fingerstick and test • Results take about an hour to get back to clinician • Results go back to clinician for patient follow-up	• Laboratory technician with two-year degree	• Power from mains with back-up generator • Microscope/Reagents • Fresh stock of Giemsa stain daily • Cell phone for transmitting data	• Detect and treat patients with any level of parasitemia • Obtain parasite density and species • Document detailed patient information in MCR • Send MCN via sms to DMSO and ZMCP • Provide DMSO with patient details • Send weekly summary data to ZMCP • Monitor treatment • Send all positive slides and 10% of negative slides to ZMCP monthly	• Requires trained laboratory technician • Time consuming • Labor intensive • Liable to reading errors • Same laboratory technician may have to perform other tests as well	• All positive slides and random selection of 10% of negative slides are sent to ZMCP monthly (98% agreement) • Have back-up generators • Foreseeable challenges with competencies as progress is made toward elimination
	Referral hospital	Microscopy	• Test all patients presenting with fever or a history of fever in past 48 hours	• Laboratory technician with two-year degree	• Power from mains with back-up generator • Microscope/Reagents • Fresh stock of Giemsa stain daily • Cell phone for transmitting data	• Detect and treat patients with any level of parasitemia • Obtain parasite density and species • Document detailed patient information in MCR • Send MCN via sms to DMSO and ZMCP • Provide DMSO with patient details • Send weekly summary data to ZMCP • Monitor treatment • Send all positive slides and 10% of negative slides to ZMCP monthly	• Requires trained laboratory technician • Time consuming for laboratory technician • Labor intensive	• All positive slides and random selection of 10% of negative slides are sent to ZMCP monthly (98% agreement) • Foreseeable challenges with competencies as progress is made toward elimination
Reactive Case Detection (RACD)	Household	RDT	• Receive sms notification from health facility (HF) • Follow up with HF to obtain patient details from MCR within 24 hours and feed into tablet PC • Visit households (HHs) to test all members (+/- neighbors) • Collect supplies from ZMCP, store at home, carry daily needs in backpack	• DMSO: two-week training course	• None—no water or electricity • Floor is work surface • Supplies carried in backpack on motorbike • Potentially walking beyond end of road to reach HH • Cell phone and tablet for data receiving and transmission (syncs when he reaches service area) • Thermometer • Questionnaire (insecticide-treated bednet [ITN], indoor residual spraying [IRS]) • GPS	• Treat all HH members (+/- neighbors) testing positive • Feed test results and information on ITN use, IRS, travels, auxiliary temperature, and GPS coordinates onto tablet • Transfer information to MEEDS • Determine origin of infection • Put waste in plastic bag and dispose at nearest HF (if far, burn in community)	• Time to results is too long given daily workload (sometimes results are read in ten minutes) • No quality control • Loss of buffer when opening pouch • Retained buffer in tip of pouch • Disposal of cassettes/needles • Cannot differentiate between parasite species • Positive test does not always mean current infection • Does not detect all cases • Exposure to weather (test kits are kept in backpacks and DMSOs use motorbikes) • Uncertainty of effect of buffer color change on test results • Leakage of blood/buffer along sides of cassette • No gloves in kit - no change of gloves between tests • Risk of exposure to bloodborne pathogens from used lancets • Fingersticks are painful • Some tests have empty buffer pouches • Some difficulty in drawing and dispensing exactly 5µl of blood using pipette • No electricity or water	• Active case detection is triggered by passive case detection MCN on same day • Usually follow up at HF to collect information on patient and follow up at HH level within 24 hours • Usually focus on just HH, including neighbors when more than three people test positive in index HH (about one hour spent per HH) • Five to ten HHs per day • US President's Malaria Initiative supports procurement of RDTs but not gloves • Preference for pipette as a transfer device • Uncertain whether negative test results are due to performance of the test or imported cases which have not yet resulted in local transmission

Use Scenario	Setting*	Inputs				Outcomes	Constraints	Other Notes/Comments
		Diagnostics	Process	Who performs test?	Infrastructure/Supplies			
Focal Screening and Treatment (FSAT)	Hotspots (household level) - regular (2x/yr)	RDT	• Surveillance teams visit known "hotspots" twice per year based on existing data • House-to-house visits, up to 20 HHs per team of two per day; all HH members are screened by RDT and treated	• Varies; pairs DMSOs (two-week training) with clinicians, laboratory technicians, ZMCP managers	• Cars/Vans for transport • Supplies carried in by vehicle • No electricity • No reliable clean water source	• Detect and treat all persons positive by RDT • Determine travel history • Take GPS coordinates	• Time to results is long • Exposure to weather • Risk of exposure to bloodborne pathogens from used lancets • Fingersticks are painful and may lead to community fatigue • No quality control • Loss of buffer when opening pouch • Retained buffer in tip of pouch • Cannot differentiate between parasite species • Positive test does not always mean current infection • Does not detect all cases (RDT may not be appropriate for pre-elimination as it may miss low-level parasitemia) • Uncertainty of effect of buffer color change on test results • Leakage of blood/buffer along sides of cassette • Some tests have empty buffer pouches • Some difficulty in drawing and dispensing exactly 5µl of blood using pipette • No electricity, water	• In high-risk populations before peak of transmission (twice per year) • GPS coordinates taken • Repeated after four weeks • Sixteen teams of two working with about 80-100 people per day • HH size about five to ten • Test kits carried in backpacks • Teams composed of DMSOs, clinicians, laboratory technicians, and program managers
	Static points in community (set up table in community center, school, etc.) - in response to abnormal increase in prevalence	RDT	• Data from MEEDS • Use media to mobilize community members • Assemble team from ZMCP to set up workstations in community • Label RDTs to link to individuals	• Varies; pairs DMSOs (two-week training) with clinicians, laboratory technicians, ZMCP managers	• Cars/vans for transport • Supplies carried in by vehicle • No electricity • No reliable clean water source	• Detect and treat all persons having any level of parasitemia • Take blood slides for those who have had antimalarial treatment in past two weeks or for whom there were RDT readability issues	• Inadequate space on cassette to write patient name, start and end time for test, as a number of tests may be taken at a time • Time to results is long (do not want to keep people waiting for too long) • No quality control • Loss of buffer when opening pouch • Retained buffer in tip of pouch • Cannot differentiate between parasite species • Positive test does not always mean current infection • Does not detect all persons with parasitemia • Uncertainty of effect of buffer color change on test results • Leakage of blood/buffer along sides of cassette • Some tests have empty buffer pouches • Some difficulty in drawing and dispensing exactly 5µl of blood using pipette • No electricity or water	• Done in response to unusual increase in cases using MEEDs data • Team of about ten comprising DMSOs, medical doctors, and laboratory technicians • Set up work stations in community • RDTs used, blood slides taken for cases which have readability problems and for those who have taken antimalarials within past two weeks (due to the persistence of HRP2) - these are read at ZMCP laboratory • Possibility of using a portable generator
Surveys	Sentinel districts (research)	RDT - dried blood spot (DBS) for polymerase chain reaction (PCR)	• Samples drawn from sentinel districts may or may not include treatment following diagnosis (referral for treatment at facility if positive) • Informed consent obtained, RDT completed, result given to patient • DBS taken, stored for drying and shipping at laboratory • PCR done abroad	• Unclear—study staff drawn from ZMCP, so probably same mix of staff as FSAT, combining DMSOs with program managers	• Cars/Vans for transport • Supplies carried in by vehicle • No electricity • No reliable clean water source	• Prevalence • Drug sensitivity • Determination of parasite origin • Species/Gametocytes	• Research activity • RDTs unable to identify low levels of parasitemia • Drying DBS in field can be a challenge; dried at laboratory overnight • Time to PCR results is long (greater than one year) • Fingersticks invasive and painful; some refusal - need tests that use other body fluids, especially as people are asymptomatic	• Cross-sectional surveys carried out twice a year in collaboration with ZAMRUKI in randomly selected HHs • Findings from a recent survey - 12/6,000 test positives by RDT and PCR on same samples yielded 80 positives • Plans to include species, gametocytes, resistance studies and determination of parasite origin in next survey in June 2013 • House-to-house visits
	National level (Malaria Indicator Survey)	RDT (microscopy used previously)	• Nationally representative sample	• Varies; pairs DMSOs (two-week training) with clinicians, laboratory technicians, ZMCP managers	• Cars/Vans for transport • Supplies carried in by vehicle • No electricity • No reliable clean water source	• Prevalence • Coverage of various interventions	• Huge sample sizes will be required for subsequent surveys (logistics, costs) due to very low prevalence	• Last survey conducted in 2010/2011 • No more surveys
Determine Origin of Infection	Community, household	RDT	• Interview about history of overnight travel in past two weeks	• DMSO: two-week training course	• None—no water or electricity • Floor is work surface • Supplies carried in backpack on motorbike • Potentially walking beyond end of road to reach HH • Cell phone and tablet for data receiving and transmission (syncs when he reaches service area) • Thermometer • Questionnaire (ITN, IRS) • GPS	• Assign infection as being locally acquired or imported	• This determination is not conclusive	

* Private sector: Not evaluated. Unknown how many private-sector providers adhere to ZMCP treatment guidelines. Ongoing efforts to include private-sector facilities in ZMCP guidance and surveillance; mechanisms not fully implemented.

Appendix D: Conceptual framework of malaria surveillance and response in Zanzibar



MEEDS = Malaria Epidemic Early Detection System

MCN = Malaria case notification

RACD = Reactive case detection

Appendix E: Settings where malaria diagnostics are used

Infrastructure	Description/ Tests used	Setting	Users	Detection strategies
Only lab on main island (not including Pemba) with complete referral capacity, sans polymerase chain reaction (PCR) (Pemba has PCR). Distilled water, cold storage, back-up generator.	Independent hematology, histopathology, parasitology, microbiology, tuberculosis labs. No PCR capabilities, microscopes only for malaria. Throughout the lab, several pieces of broken equipment or equipment unused due to stockout of consumables.	**Referral Lab**	Lab technicians with two-year degree.	Passive case detection, confirmation/quality assurance.
Water purification, -70°C storage, back-up generator.	Fully equipped for research purposes, no PCR. Only used when funded by research entity; not used for general clinical purposes. Otherwise remains closed, with maintenance staff to clean and up-keep.	**Research Lab**	Unsure; probably similar to referral lab.	Random sampling surveys, focal screening and treatment (FSAT), confirmation.
Back-up generator, tap water.	Basic clinical analysis, microscope for TB/malaria, centrifuge, cold storage. Older pipettes are functional but not recently calibrated.	**District Hospital**	Lab technicians with two-year degree.	Passive case detection.
Inconsistent power, sink, no back-up generator.	Microscopy and rapid diagnostic test (RDT). RDTs used when power is out or when lab technician is backlogged.	**Primary Health Care Center**	Lab technicians with two-year degree.	Passive case detection.
Inconsistent power, sink, no back-up generator.	Microscopy and RDT. RDTs used when power is out or when lab technician is backlogged.	**Primary Health Care Unit-Plus**	Lab technicians with two-year degree.	Passive case detection.
Inconsistent power, tap outside the clinic.	RDT only.	**Primary Health Care Unit**	Clinician with four-year degree.	Passive case detection.
Ranges, rainwater catches. In rural area, no power.	RDT only. Dried blood spots taken for research.	**Community**	Malaria-specific health officers: District Malaria Surveillance Officers (DMSOs) (two-week training on RDTs), clinicians.	Reactive case detection (RACD), random sampling surveys, FSAT.
No power, water basin (possibly from nearby water source).	RDT only.	**Home**	DMSO (two-week training).	RACD, random sampling surveys, FSAT.