EVALUATING A REACTIVE TEST-AND-TREAT PROGRAM FOR SUB-PATENT MALARIA IN MACHA, ZAMBIA: OPTIMAL STRATEGIES TO ACHIEVE ELIMINATION

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Abstract

Background: In Choma District, Southern Province, Zambia, malaria prevalence by rapid diagnostic test (RDT) declined from 8% in 2008 to 1% in 2013. As part of an effort to achieve elimination, the Zambian government implemented a reactive test-and-treat (RTAT) program in parts of Southern Province in 2013. Individuals with confirmed malaria by health workers are followed-up within two weeks of diagnosis. All individuals living in households within 140 meters of the index case are tested with an RDT and treated if positive. This study aimed to optimize the RTAT strategy by characterizing infected individuals missed by both the RDT and the current screening radius.

Methods: Health workers notified the study team of individuals with RDT confirmed malaria. For each study participant, a questionnaire was administered and a blood sample collected. To evaluate the optimal RTAT radius and assess the frequency of sub-patent, RDT negative infections, the radius was expanded to 250 meters and testing of dried blood spot samples by real-time polymerase chain reaction (PCR) was introduced. Spatial-temporal cluster detection was conducted to identify clusters of index households.

Results: From January 2015 to January 2016, 101 index cases were followed-up through the RTAT program. 2504 individuals residing in 394 households were screened. Excluding index cases, parasite prevalence was 2.5% by PCR (53 of 2225) and 1.2% by RDT (26 of 2108). 66% of PCR positive individuals tested negative by RDT. 24 households had a PCR+/RDT- individual. Nearly half of those infected resided within the index case household. No clustering of index house was identified.

Conclusion: The low number of secondary cases indicates a low efficiency of RTAT beyond the index case household in this setting, and the sensitivity of the RDT was too low to be an effective screening tool. Focal drug administration in which all individuals within index case households are treated may be a more efficient approach to achieving malaria elimination in southern Zambia.

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Chapter 1: Introduction

1.1 Malaria Epidemiology

Over the past two decades, there has been a large decline in the number of cases of malaria worldwide[1]. Between 2000 and 2013, the total number of malaria infections dropped from 227 million infections to 198 million infections; adjusting for population growth this represents a 30% drop in incident cases.[1] The number of infections amongst children (ages 2-10) has dropped by 46%.[1] This progress can be attributed to numerous factors including an increase in malaria control interventions such as indoor residual spraying (IRS) and insecticide treated nets (ITNs), and increased diagnostic testing.[2] Larger systemic progress, such as strengthened health systems and economic development, has also helped countries build malaria prevention programs and improve access to care.[2] Global funding for malaria control has also tripled since 2005, with more than half of funds directed towards developing drugs and vaccines.[1,3] Despite this progress, there were 214 million infections and nearly 500,000 deaths in 2015.[4] 90% of these deaths occurred in Africa and 70% were children under the age of 5.[4] Thus, malaria remains a pressing public health concern for many countries around the world.

Zambia is a malaria endemic country with a population of 15 million people.[5,6] In 2013 there were 4.9 million reported cases of malaria, the vast majority of which were *Plasmodium falciparum* infections.[6] To combat the number of infections, the Zambian

government has increased control programs in the past several years. This has included a scale-up of ITNs and IRS.[5] However, disease prevalence differs greatly depending on the region of the country. In an effort to combat malaria, the government created three epidemiological zones: areas with parasite prevalence below 1% (Zone 1), 1-14% (Zone 2) and above 14% (Zone 3).[5,7] Previous studies have shown that in Luapula Province in northern Zambia, parasite prevalence estimates can reach as high as 50%, while in Southern Province prevalence in 2013 was reported under 1%.[8,9] The high numbers in the north are likely due to several factors such as perennial transmission due to an active vector, *Anopheles funestus*, during the dry season, potential individual movement across the border to high risk areas, and a delay in the scale up of prevention efforts.[5,10,11] Thus, malaria control efforts must be focused to specific regions and tailored to the needs of the transmission setting.

This study focused within the region of Macha, a rural area located in Choma District within Southern Province. In this area, *P. falciparum* is the dominant parasite species and *An. arabiensis* is the primary vector.[12] Over the past decade, there has been a steep drop in malaria transmission in Macha with the prevalence declining from around 8% in 2008 to less than 1% in 2013.[13] Though this cannot be attributed to a single cause, several factors are thought to have contributed to the decline. These are: increased ITN use, a drought that eliminated a large proportion of the vector population (presumably *An.*

funestus), and increased treatment of cases with artemisinin therapy.[13–15] Due to the low disease prevalence, the Zambian government has increased efforts to eliminate malaria within the Macha catchment. However, in order to achieve this goal, there needs to be a better understanding of what is sustaining the remaining low levels of transmission. This will allow the government to focus efforts on the proper populations and implement effective interventions.

1.2 Malaria Diagnosis

Finding remaining cases of malaria in Macha is essential to achieve elimination; however, properly diagnosing people remains a challenge. Rapid diagnostic tests (RDTs) are a commonly used method for diagnosing infections in areas such as Macha that do not have access to laboratory facilities. These tests use a small amount of blood, do not require any laboratory processing, and can deliver a diagnosis almost immediately. RDTs utilize an immunochromotographic mechanism to detect various antigens of the parasite.[16] For *P. falciparum* infections, a commonly used RDT (the type used in this study) detects the presence of the parasite's histidine-rich protein II (HRP-II). Though these tests are easy to administer, their sensitivity is dependent on the parasite density of the individual being tested; as parasite density drops so does sensitivity.[17] A study from Thailand demonstrated that at low parasite densities (below 500 parasites/μL), the

sensitivity of *P. falciparum* RDTs was only 83%.[18] Thus, using RDTs to detect low-parasitemia infections is difficult. Though it should be noted that RDTs are recommended to confirm suspected clinical cases of malaria and not as a screening tool for low parasitemic, sub-patent infections[19]. Additionally, the HRP-II antigen can remain circulating in the blood for up to two weeks after a person has been treated for malaria, which can lead to a possible false positive test.[20] Using newer diagnostic methods such as polymerase-chain reaction (PCR), which detects the presence of parasite DNA, may help diagnose more individuals since it is a more sensitive test than an RDT.[21,22] Previous work in Zambia reported an RDT sensitivity of only 53% compared to PCR. However, PCR is more expensive than using RDTs and samples must be processed in a laboratory, eliminating the benefit of the point of care test. Therefore, the best method of diagnosing remaining low-parasitimia malaria cases in Macha remains to be determined.

Though PCR is able to detect more infections than RDTs, it has opened up new epidemiological questions regarding individuals with low-parasitemia infections. The role of these types of infections, in which individuals do not test positive via RDT but do have detectable DNA using PCR, in transmission remains unclear. Since many of these individuals do not develop clinical symptoms, they do not present at health clinics and may be overlooked by passive surveillance programs.[23] Previous work in areas with high transmission has shown that low-parasitemia infections can occur after multiple

exposures to the parasite as individuals build up immunity.[24] However, the role of these cases in low transmission areas is less well understood. Previous studies have found evidence that such sub-patent cases may sustain local transmission in low endemic areas.[25] A report compiled by the Malaria Eradication Research Agenda consulting group stated that transmission may be possible at any level of parasitemia.[26] Thus, targeting low-parasitemia infections should be considered as part of any malaria elimination campaign.[26]

Several groups have investigated the role of low-parasitemia infections using molecular methods. Many studies have focused on investigating the concentration of gametocytes, the sexual stage of the parasite, which are ingested by mosquitoes during a blood meal.[27] Since it is at this stage that the parasite is transmitted from humans to mosquitoes, it stands to reason that the higher the gametocyte density, the more likely a mosquito is to become infected. However, several studies have found that the association between gametocytes and infectiousness is not clear-cut. Low gametocyte counts do not ensure low infectiousness.[28–30] Thus, additional research, including both molecular and epidemiological approaches, is necessary to determine whether or not such cases can contribute to larger transmission chains.

1.3 Strategies for achieving elimination

There are several strategies that have been employed in order to reach elimination. These include: mass test and treat campaigns (MTAT), mass drug administration (MDA), and focal drug administration (FDA).[31] The first of these options, MTAT, requires testing all individuals within a given area using RDTs and immediately treating anyone who tests positive. This type of program has been used in several countries including Zambia, Burkina Faso, and Zanzibar.[32–34] However, as mentioned, using RDTs as the method of diagnosis is likely to miss many infected individuals with low-parasitemia. An alternative strategy to MTAT is to use an MDA approach, in which all individuals within a given region are given antimalarial treatment regardless of RDT status. This strategy avoids the problem of low sensitivity of the diagnostic test and can provide larger community-wide protection. MDA campaigns have been used to successfully stop transmission in several countries including Taiwan, China, and Cambodia.[31] A third option is an FDA approach; test all individuals within a small geographic area (such as a household or a neighborhood) using RDTs and provide treatment for anyone who tests positive.[35] This strategy is operationally easier than an MDA though often still relies on RDTs as the method of diagnosis. Each of these strategies may be useful for elimination of malaria though it is important to determine which, if any, is most appropriate for a given population.

Considering the potential reservoir of sub-patent, PCR+/RDT- infections, the Zambian government is considering implementing an MDA program within Southern Province. However, further understanding of the sub-patent reservoir is needed to determine whether or not an MDA is necessary. A current study in Southern Province, Zambia aims to investigate the difference between the MDA and FDA approach to prevent *P. falciparum* infections.[35] This is will also help determine which strategy, if any, will be most useful for achieving elimination in Macha.

1.4 Reactive Test and Treat

In 2011, the Zambian government implemented a national strategy aimed at eliminating malaria by 2020.[36] The strategy consisted of five steps that included elements such as scaling up use of ITNs, improving diagnosis of cases and mass drug administration amongst others.[36] The fourth step in this system (Step D) called for increased case identification. To accomplish this, the government began a reactive test and treat (RTAT) program to find cases, particularly those that may not otherwise present at health clinics.[37] The program, which began in 2013, identifies individuals who test positive for malaria at local health clinics as index cases. Community health workers then visit the index case's home and test each person in the household, as well as anyone living within a 140-meter radius of the index case. Each person is tested for malaria via

RDT.[37] Though the exact implementation differs, similar reactive case detection (RCD) strategies have been used in many countries within Africa and south east Asia including Senegal, Swaziland, Thailand and Malaysia.[38–40] Though RCD can be operationally difficult, it is a particularly useful strategy for countries moving towards elimination as it can help identify and treat remaining undiagnosed patients.[39]

The effectiveness of the Step D program in Zambia has never been formally evaluated; however, the program was expanded in January 2015 for research purposes. The new program, called Enhanced Step D (ESD), is not meant to serve as an intervention nor is it part of the national malaria control strategy. Rather, it is a research study conducted by the Southern Africa International Centers for Excellence in Malaria Research, which aims to further investigate malaria transmission in Macha. ESD extended the case detection radius from 140 meters to 250 meters in order to determine if 140 meters was a sufficient study radius. ESD also added quantitative PCR testing for each person; blood spots were collected and taken for testing back at the Macha Research Trust laboratory. Since PCR testing is more sensitive than RDT, it was added to ESD to identify individuals with low-parasitemia infections. The goal of expanding Step D, which remains ongoing, is to capture remaining cases, particularly low-parasitemia infections.

The objective of this study was to optimize the RTAT strategy in Macha by characterizing infected individuals missed by the initial RTAT program. This included individuals living within the extended 140m-250m screening radius as well as those with infections not detectable by RDT.

Chapter 2: Methods

2.1 Study population

This study was conducted in the region of Macha, within the catchment area of Macha Mission Hospital, in Choma District, Southern Province. Macha is a rural area located roughly 70 km from Choma, the nearest large town. Malaria transmission in Macha has historically been considered hyperendemic, though, as discussed, prevalence by RDT has dropped to under 1% over the past decade[41,42]. Macha experiences an increase in transmission during the rainy season (December - March), which is then followed by drop in transmission during a relatively cool dry season (April - July) and a hot dry season (August – November).[12,42] As stated, the primary vector in Macha is *An. arabiensis* and the vast majority of malaria cases are *P. falciparum* infections.[42] Artemether- lumefantrine (Coartem) was introduced to the area in 2004 as the first line anti-malarial therapy and an ITN distribution program was conducted in 2007, with additional distribution campaigns since.[42,43]

2.2 Reactive Case Detection

Data collection began in January 2015 and continued through January 2016. The first index case was reported on January 7th and followed up on January 12th. Analyses

for this study included only data collected between January 12th and January 27th, 2016. Children, with the consent of parents, were included within the study.

Study participants were recruited using an active surveillance process. Individuals diagnosed with malaria, by RDT, at a local health clinic were considered index cases. Health clinic staff reported these cases to Macha Research Trust (MRT) study team within seven days. The home address on record for the index case was geocoded to obtain GPS coordinates. Index houses were indicated on a topographical map of Macha using high-resolution satellite imagery in ArcGIS v.10 (ERSI, Redlands, California). Using the same satellite imagery, all houses within 250 meters of the index house were marked on a map and indicated as a secondary house. A map with the index house and all secondary houses was given to the members of the MRT study team, which then visited each house.

At each home, the study team used finger pricks to collect blood samples from each family member. RDTs were administered to each individual and used to detect the presence of *P. falciparum* HRP-II. Blood spots were also collected on a Protein Saver Card (Sigma-Aldrich, Piscataway, New Jersey) and taken back to the laboratory for *P. falciparum* quantitative PCR (qPCR) analysis. Hemoglobin level and body temperature were also recorded for each person. All individuals who tested positive via RDT (other than the original index case) were given a full course of Coartem to treat the infection.

Each participant was also orally administered a survey with a study team member recording answers electronically using an Android tablet. The questionnaire ascertained information regarding demographics, recent malaria symptoms, knowledge of malaria transmission, and prevention behavior (such as bed net use). Questionnaires were administered to guardians on behalf of children under the age of sixteen.

Though there were 109 reported index cases, only 101 were followed up and tested. Eight index cases either refused participation in the study or were not present at the time of the study.

2.3 Diagnostic assays

Finger pricks were used to obtain blood for rapid diagnosis and well as collected on Protein Saver cards (Sigma-Aldrich, Piscataway, New Jersey) to prepare dried blood spots (DBS). DBS were sealed in plastic bags, taken back to the MRT laboratory and stored at -20 degrees Celsius until used for qPCR testing.

Rapid Diagnostic Tests (Standard Diagnostics Inc., Gyeonggi-do, Republic of Korea) were administered to each study participant to detect the presence of *P. falciparum* HRP-II. Tests were read when all blood had cleared the test reading window and a control indicator band appeared, approximately within 20 minutes of loading the blood sample.

DBS were used to extract DNA and perform qPCR at the MRT laboratory. DNA was extracted using a previously described Chelex extraction protocol[42,44] Quantitative PCR was then conducted to detect the presence of the *P. falciparum pfcytb* gene. The limit of detection was 1 parasite/100 uL. The following gene specific primers were used:

Pfcytb forward: 5' CCT GAT AAT GCT ATC GTA 3'

Pfcytb reverse: 5' TAA TAC AAT TAC TAA ACC AGC 3'

For a full description of the Chelex extraction and the qPCR protocol see Laban et al, 2015.

All samples were also evaluated using gel electrophoresis and run on a 6% agarose gel in order to confirm the presence of *P. falciparum* DNA. Only samples with detectable DNA using both qPCR and gel electrophoresis were considered PCR positive.

2.4 Ecological Data

Ecological factors were selected for inclusion based on previous research in Zambia. Past work has shown that ecological factors including household elevation, slope of the land, aspect, and proximity to streams are all associated with malaria infection[12] . Ecological covariates were determined for all households with available longitude and latitude coordinates.

A QuickBird high-resolution satellite image of Macha obtained in 2011 was used to identify study households. GPS coordinates were imported into ArcGIS and used to determine the distance between index and secondary houses. A digital elevation model (DEM) of Macha was obtained from the Shuttle Radar Topography Mission (STRM) version 3. The DEM has a resolution of 90 meters and provides elevation values based on the reflective surface of the earth. The DEM was processed using Erdas Imagine 2011 and then imported into ArcGIS to obtain elevation values for each study household. The DEM was also used to obtain the slope and aspect for each household.

A stream network was created using the ArcHydro tool within ArcGIS. This works by using a location's elevation to determine water accumulation and flow direction. Streams are assigned an order classification based off of the Shrahler stream network definitions.[45] Classifications range from 1-5 based off drainage between streams. For example, the joining of two first order streams forms a second order stream, two second order streams that drain together form a third order stream.[45] Distance between each household and the nearest stream was also calculated.

2.5 Statistical analysis

We predominantly employed descriptive statistics due to the low number of non-index case infections. The primary outcomes of interest were 1) RDT positive test and 2)

a PCR+/RDT- result. Households were categorized according to the presence of at least one test positive individual (RDT+ and PCR+/RDT-). Index cases were excluded from the analysis.

To assess the utility of extending the ESD radius we enumerated the number of individuals who tested positive via RDT at each of the household distance designations: 0 meters (index houses), within 140 meters from the index, and 140-250 meters from the index. Similarly, we determined the number of households at each designation with an individual who tested RDT positive. We then evaluated both individual and household characteristics of RDT positive cases compared to non-infected individuals at each designation. Individual characteristics included: sex (binary), age (categorized into five groups), recent malaria symptoms (binary) and reported bed-net use (binary). Malaria symptoms were defined as the presence of fever with headache or chills. Household characteristics included: elevation (meters), slope (percent), aspect category (eastern/south-eastern, western/south-western, and other), and distance to the closest stream (quartiles).

The number of infections missed by RDTs was determined by counting PCR+/RDT- cases in each of the household distance categories. As with the RDT positive cases, we assessed individual and household characteristics of PCR+/RDT- cases compared to non-infected persons.

It was originally considered that logistic regression should be used to assess individual and household level factors associated with PCR+/RDT- infection. However, due to the low number of this type of infection, it was determined that the results of these analyses would not be meaningful. The results of these regression analyses are not presented.

All statistical analyses were performed using Stata version 13 (StataCorps LP, College Town, TX).

2.6 Cluster Detection

The presence of index case "hotspots" was evaluated through a space-time cluster detection analysis. This was conducted in SatScan v. 9.4 (SatScan, Boston, MA). This method analyzes potential clusters within specific time periods, comparing the number of observed cases in an area to the number that is expected assuming that no clustering exists. Thus, clusters are detected if an area has a higher number of cases in the time period compared to other areas at that time. This method therefore adjusts for both spatial and temporal changes and is able to detect clusters without needing location data for a non-infected control group.[46] Clusters are detected by using a moving cylinder approach in which a cylindrical study radius is placed at each household and expands until a pre-

specified percentage of the population is included. The height of the cylinder corresponds to the time period of potential clusters. Statistical significance is determined using a Monte Carlo approach, comparing maximum likelihood rankings from the data to those from random data.[46] For this analysis we used a time frame of one month and a cylinder radius of 25% of the population.

Chapter 3: Results

3.1 RTAT Results

In total, there were 101 index cases residing in 95 index households included in the study. A total of 2324 individuals were tested using RDTs and 2194 by PCR. Excluding index cases, malaria prevalence was 2.5% by PCR and 1.2% by RDT. 29.8% of non-index individuals lived within index houses, 23.4% in households within 140 meters from the index and 46.8% in households 140-250 meters from the index case household (Table 1). 31% of the PCR positive individuals were also RDT positive while 69% were RDT negative (Table 2). RDT data was not available for 2 PCR positive individuals.

Among the households, 26.7% were index households, 27.0% within 140 meters of the index and 46.3% fell between 140-250 meters (Table 3). 5.6% of households had at least one non-index case that tested positive via RDT and 10.1% had at least one non-index PCR positive test. 28 households had at least one PCR+/RDT- individual (Table 4).

Of the 25 RDT positive individuals, 13 lived in index houses, 4 lived within 140 meters, and 8 lived between 140 and 250 meters. On the household level, 55% of households with an RDT positive case were index houses, 18% were located within 140 meters, and 27% located within 250 meters (Figure 1).

On both an individual and household level, roughly half of PCR+/RDT- cases lived in index houses and half lived in houses 140-250 meters from the index case household (Figure 2). On the individual level, 43% of the PCR+/RDT- cases lived in index houses and 57% lived in secondary households. Two of the secondary cases lived in the 0-140 radius and 14 lived in the 140-250 radius. GPS data was not available for 4 secondary PCR+/RDT- cases. On the household scale, 50% of PCR+/RDT- households were index houses, 8% fell within 140 meters of the index, and 42% were between 140 – 250 meters.

Among the index cases, 21% of 85 individuals tested positive by PCR but not by RDT while 69% of 85 tested positive by RDT but negative using PCR. Four non-index individuals tested positive by RDT but negative by PCR.

3.2 Cluster Detection Results

The cluster detection revealed no significant spatial-temporal clusters of index households.

Chapter 4: Discussion and Conclusion

4.1 Discussion

One of the initial aims of this study was to determine if the ESD program could identify RDT-/PCR+ cases and investigate whether or not these cases are part of the same transmission event as index cases. The goal was to determine if the secondary cases exhibited evidence of spatial clustering around index cases, and to evaluate environmental risk factors associated with the secondary cases. However, due to the low number of PCR+/RDT- individuals identified, it was determined that the results of analyses were not meaningful. The finding that most of secondary asymptomatic cases were found further from the index households, in the 140-250 meter distance rather than within 140 meters, may indicate that these cases are not a result of local transmission from index cases. However, this hypothesis could not be formally tested. Though clustering of these cases or risk factors may exist, more PCR+/RDT- cases will need to be captured in order to fully investigate this question.

Given how few cases were found through ESD, a focal drug administration strategy in the index case household will likely be a more effective way to stop transmission. The low number of secondary cases, both PCR+/RDT- and RDT+, indicates that there is little utility in extending the ESD radius past the index house. Though several cases were found within the 140-250 meter radius, the ESD strategy is

operationally intensive and screening all individuals within the 250-meter radius is not an efficient use of resources.

The PCR results demonstrate that RDTs miss more than half of infected individuals. Within this study, the sensitivity of the RDTs was only 31% compared to qPCR diagnosis. Previous work in Macha found RDT sensitivity to be higher, approximately 54%, compared to qPCR.[44] However, this difference may be a due to the small number of cases found in each study rather than a true difference in sensitivity. The previous study also used a random sampling strategy rather than the RTAT, which may have affected sensitivity as well.[44] Both studies confirm that using RDTs as the only method of diagnosis will likely not be sufficient to stop transmission. Future efforts should aim to treat all individuals within index houses regardless of RDT status. An upcoming study of a focal drug administration to all residents living within 140 meters of an index case in Zambia will provide further evidence of whether or not this type of program can lower transmission.[35] However, the results of the present study indicate that few cases are likely to be found living within 140 meters of the index households.

The findings of the present study concur with evaluations of previous RTAT programs. RTAT programs in several sub-Saharan African countries have shown the strategy to be an inefficient methods for finding cases[47]. Studies conducted in Zambia, Senegal and Swaziland found that the number of secondary individuals that needed to be

tested in order to find one positive case ranged from 37 – 250.[38,39,48] These studies were all conducted in areas with low malaria prevalence, similar to Macha. In the present study, an average of 86 non-infected people were tested for each positive RDT case that was found, and 60 non-infected people for each PCR+/RDT- case. This provides further evidence that in low transmission settings, RTAT may not be the most efficient strategy for eliminating malaria.

The individuals who tested positive by RDT but negative by PCR are likely a result of a treated infection. The HRP-II protein, which is detected by the RDT as the method for determining infection, can persist in blood for several weeks after malaria treatment.[49] The high number of RDT+/PCR- index cases indicates that many of these individuals likely received treatment and cleared the parasite DNA prior to the study. Similarly, the four non-index individuals who were RDT+/PCR- may also have recently cleared infection. However, data on recent treatment for malaria infection was unavailable for most study participants and therefore could not be assessed.

Future studies will aim to use parasite genotyping to further study the genetic similarity of the parasite in the PCR+/RDT- infections compared to the index infections. A new project from our group will study genetic "barcodes", a group of small nucleotide polymorphisms collected from across the *Plasmodium* genome. Comparison of barcodes can differentiate between different populations of the parasite. Evidence that the barcodes

of secondary PCR+/RDT- infections are distinct from those of the index cases will support the hypothesis that the infections are epidemiologically unrelated.

There are several limitations to this study. Firstly, since we used a cross-sectional study design we were unable to obtain follow-up data on participants. PCR+/RDT- individuals may have recently been infected and not yet developed a high enough parasitemia to test positive by RDT. However, without follow-up it is unknown how many PCR+/RDT- cases would later test positive by RDT and how many would remain RDT negative. The MRT study team has already begun implementing follow-up visits after 30 days from the report of the index case. This will help distinguish between those with low-parasitemia infections and those who have not been infected for long enough to develop a high parasite density. Another limitation was missing data. 51 of the 398 households did not have GPS coordinate data and therefore could not be placed in a distance category. Lastly, only individuals with *P. falciparum* infections were detected in this study, though *P. malariae* infections have been found in Macha.[44] These infections are not detected using the HRP-II RDTs that were used in this study. The number of *P. malariae* infections in Macha has been found to be quite low and therefore likely did not dramatically alter the overall number of infections.[44] However, it is unknown how many individuals in the present study may have had *P. malariae* infections. The MRT study

team recently obtained RDTs that detect both *P. falciparum and P. malariae* infections in order to address this limitation.

4.2 Conclusion

The analysis of the Enhanced Step D program indicates low efficiency of the current RTAT strategy. Only half of infected individuals, using both RDTs and PCR as methods of diagnosis, were found in secondary households. Additionally, relying on RDTs to find secondary cases will not be sufficient given the low sensitivity of this assay. Therefore, a focal drug administration within index case households may prove to be a more useful strategy to achieve elimination in Macha.

Table 1: Baseline characteristics of all individuals by RDT status within index and neighboring households

	Index Case Household (excluding index case)		**Neighboring Households <140m**		**Neighboring Households 140-250m**	
	RDT Positive	**RDT Negative**	**RDT Positive**	**RDT Negative**	**RDT Positive**	**RDT Negative**
Total N = 1847	13 (2%%)	552 (98%)	4 (1%)	408 (99%)	8 (1%)	862 (99%)
Sex						
Female	5 (36%)	305 (55%)	3 (75%)	222 (57%)	4 (50%)	443 (52%)
Male	9 (64%)	250 (45%)	1 (25%)	165 (43%)	4 (50%)	420 (48%)
Age (years)						
Median (IQR)	7 (4-8)	12 (6-26)	11.5 (6-19)	13 (6-29)	13.5 (7-32)	11 (5-25)
0-5	6 (46%)	125 (23%)	0	92 (24%)	0	222 (26%)
6-10	5 (38%)	109 (20%)	1 (25%)	75 (19%)	3 (38%)	179 (21%)
11-20	0	151 (28%)	2 (50%)	82 (21%)	2 (25%)	199 (23%)
20-40	2 (15%)	954 (17%)	1 (25%)	74 (19%)	2 (25%)	170 (20%)
41+	0	68 (12%)	0	64 (17%)	1 (12%)	93 (11%)
Malaria Symptoms						
Yes	3 (23%)	80 (15%)	2 (50%)	43 (11%)	3 (38%)	104 (12%)
No	10 (77%)	454 (85%)	2 (50%)	355 (89%)	5 (62%)	730 (88%)
Sleep under a bet net						
Yes	6 (46%)	255 (47%)	1 (25%)	187 (52%)	6 (67%)	488 (57%)
No	7 (54%)	292 (53%)	3 (75%)	200 (48%)	2 (33%)	375 (43%)

Table 2: Baseline characteristics of individuals by PCR status within index and neighboring households

	Index Case Household (excluding index case)		**Neighboring Households <140 m**		**Neighboring Households 140-250 m**	
	PCR+/ RDT-	**PCR-/ RDT-**	**PCR+/ RDT-**	**PCR-/ RDT-**	**PCR+/ RDT-**	**PCR-/ RDT-**
Total N = 1697	14(3%)	536(97%)	2(1%)	367 (99%)	14 (2%)	764 (98%)
Sex						
Female	7(50%)	292(55%)	1	197 (57%)	5 (36%)	394 (52%)
Male	7(50%)	239(45%)	1	149 (43%)	9 (64%)	371 (48%)
Age (years)						
Median (IQR)	15 (11-20)	12 (6-26)	--	14 (6-29)	7.5 (4-15)	11 (5-25)
0-5	2 (14%)	122 (23%)	1	80 (23%)	5 (36%)	201 (27%)
6-10	1 (7%)	107 (20%)	0	64 (19%)	4 (29%)	155 (20%)
11-20	8 (57%)	143 (27%)	0	74 (21%)	2 (14%)	173 (23%)
20-40	1 (7%)	93 (18%)	0	71 (21%)	0	159 (21%)
41+	2 (14%)	66 (12%)	1	57 (16%)	3 (21%)	77 (10%)
Malaria Symptoms						
Yes	4 (31%)	76 (15%)	1	37 (10%)	5 (38%)	95 (13%)
No	9 (69%)	443 (85%)	1	321 (90%)	8 (62&)	643 (87%)
Sleep Under a bed net						
Yes	9 (64%)	245 (46%)	1	163 (47%)	10 (71%)	442 (58%)
No	5 (36%)	286 (54%)	1	183 (53%)	4(29%)	323 (42%)

Table 3: Baseline characteristics of index and neighboring households by RDT status.

	Index Case Household (excluding index case)		**Neighboring Households <140 m**		**Neighboring Households 140-250 m**	
	RDT+	**RDT-**	**RDT+**	**RDT-**	**RDT+**	**RDT-**
Total N = 319_	12 (14%)	73 (86%)	4 (4%)	82 (96%)	6 (4%)	142 (96%)
Elevation (IQR) - meters	1092 (1072-1126)	1093 (1065-1120)	1127 (1107 - 1151)	1114 (1085-11364	1077 (1052-1102)	1090 (104-1113)
Slope (IQR)(%)	2.33 (1.30 - 3.16)	2.04 (1.15 -3.41)	2.57 (1.65-4.15)	1.78 (0.99 – 2.75)	2.52 (0.56-4.07)	1.44 (0.99 2.75)
River Distance quartile (m)						
Median (IQR)	379 (237-599)	383 (192-646)	319 (205-581)	439 (269-654)	315 (275 - 348)	488 (287 - 671)
0-267	3 (25%)	26 (37%)	1 (25%)	21 (26%)	1 (17%)	31 (22%)
268 – 443	4 (33%)	13 (19%)	2 (50%)	20 (24%)	5 (83%)	32 (23%)
444 - 673	2 (17%)	13 (19%)	0	20 (24%)	0	39 (27%)
674+	3 (25%)	18 (26%)	1 (25%)	21 (26%)	0	40 (28%)
Aspect						
Eastern or south-eastern	3 (25%)	19 (27%)	1(25%)	22 (45%)	5 (83%)	44 (31%)
Western or North-western	2 (17%)	18 (25%)	1(25%)	23 (28%)	1 (27%)	24 (17%)
Other	7 (58%)	34 (48%)	2(50%)	37 (27%)	0	74 (52%)

Table 4: Baseline characteristics of index and neighboring households by PCR status.

	Index Case Household (excluding index case)		**Neighboring Households <140 m**		**Neighboring Households 140-250 m**	
	PCR+/ RDT-	**PCR-/ RDT-**	**PCR+/ RDT-**	**PCR-/ RDT-**	**PCR+/ RDT-**	**PCR-/ RDT-**
Total N = 319	12 (14%)	71 (86%)	2 (2%)	84 (98%)	10 (7%)	138 (93%)
Elevation (IQR) - meters	1091 (1039-1116)	1093 (1071-1121)	1157	1114 (1087 - 1134)	1077 (1061-1142)	1092 (1066-1113)
Slope (IQR)(%)	1.23 (0.63 – 1.92)	2.38 (1.15 – 3.41)	2.75	1.79 (1.15 – 2.76)	2.27 (1.12 – 4.07)	1.54 (0.99– 2.75)
River Distance quartile (m)						
Median (IQR)	347 (93-637)	382 (210-646)	1396	433 (270-634)	386 (276-758)	478 (287-662)
0-267m	5 (42%)	23 (33%)	0	22 (26%)	2 (20%)	30 (22%)
268 - 443	2 (17%)	15 (22%)	1	21 (25%)	3 (30%)	34 (25%)
444 - 673	2 (17%)	13 (19%)	0	20 (24%)	2 (20%)	37 (27%)
673+	3 (25%)	18 (26%)	1	21 (25%)	3 (30%)	37 (27%)
Aspect						
Eastern or south-eastern	2 (15%)	20 (29%)	1	22 (26%)	3 (30%)	46 (33%)
Western or North-western	5 (46%)	15 (21%)	0	24 (29%)	2 (20%)	23 (17%)
Other	5 (38%)	35 (50%)	1	38 (45%)	5 (50%)	69 (50%)

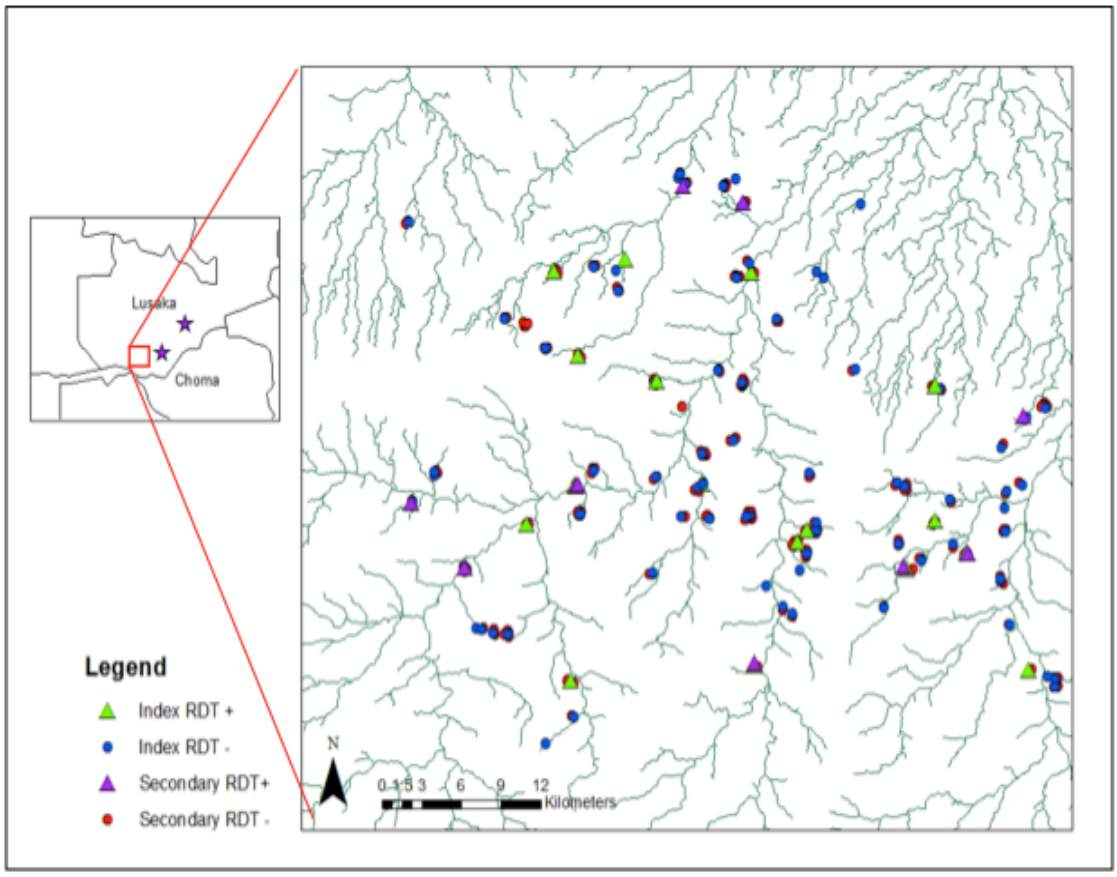

Figure 1: Map of households visited in the Enhanced Step D program by RDT status. 2324 total individuals were administered RDTs. 25 non-index individuals residing in 23 households tested positive.

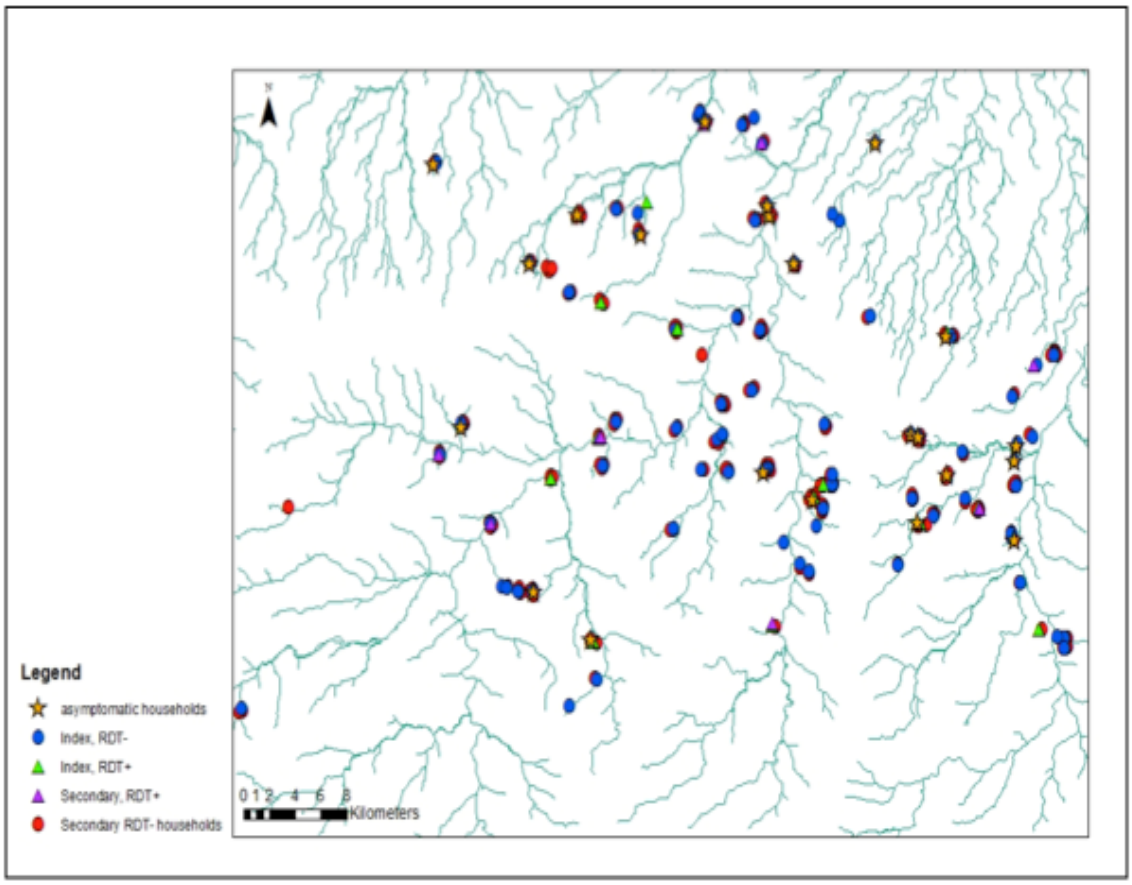

Figure 2: ESD Households by index and RDT status with PCR+/RDT- households highlighted. 2194 individuals were tested for malaria infection by PCR. 35 individuals residing in 28 households tested PCR+/RDT-.

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EDUCATION

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD May 2016
Master of Science
Department: Epidemiology, infectious disease track.
GPA 4.00/4.00

Wesleyan University, Middletown, CT May 2012
Bachelor of Arts
Major: Molecular Biology and Biochemistry, International Relations Certificate.
GPA 3.73/4.00

School for International Training, Durban, South Africa January-May 2011
One semester study abroad program focused on community health and social policy
GPA 3.89/4.00

HONORS AND AWARDS

Global Health Established Field Placement, Johns Hopkins School of Public Health
Masters Tuition Scholarship, Johns Hopkins School of Public Health
Dean's List, Wesleyan University
Howard Hughes Undergraduate Research Fellowship, Wesleyan University

RESEARCH EXPERIENCE

Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD
June 2015-Present
Conduct research on spatial patterns of malaria infection in southern Zambia using various molecular diagnostic tools. Spent two months in Zambia through the Global Health Established Field Placement at Johns Hopkins. Conducted immunological assays, field data collection, and statistical analyses on health center data.

Berman Institute of Bioethics, Johns Hopkins University, Baltimore, MD
September 2014-Present
Research Assistant for the Fogarty African Bioethics Training Program. Help conduct research and prepare manuscripts on bioethics programs at various African research institutions.

Laboratory of the Biology of Addictive Diseases, The Rockefeller University, New York, NY
June 2012-July 2014
Research Assistant for clinical and pharmacological studies focused on neurological pathways of drug addiction. Assisted nurses in hospital and prepared patient blood

samples, performed radioimmuno-assays, helped plan new studies, analyzed and presented data.

Department of Chemistry, Wesleyan University, Middletown, CT
September 2009-May 2012
Conducted research on gram-negative bacterial enzymes. Performed DNA extraction, cell transformation, polymerase chain reactions; collected, analyzed and presented data. Prepared weekly literature presentations and lab updates.

Naval Medical Research Center, Silver Spring, MD
June-August 2007, 2008
Assisted with research on haemostatic bandages. Observed swine surgeries, performed blood chemistries, entered and analyzed data. Wrote a research paper and presented poster at the end of the summer.

PUBLICATIONS AND PRESENTATIONS

Hyder A, **Deutsch-Feldman M**, Ali J, Sikateyo B, Kass N, Michelo C. Rapid Assessment of Institutional Research Ethics Capacity: A Case Study in Zambia. Under Review.

Deutsch-Feldman, M, Picetti R, Seip-Cammack, K, Zhou Y, Kreek K. Handling and Vehicle Injection Induced Stress Differentially Impact Adrenocorticotropic and Corticostrerone Levels in Sprague-Dawley Versus Lewis Rats. *J Am Assoc Lab Anim Sci.* 2015;54(1):35-39.

Zhang Y, **Deutsch-Feldman M**, Buonora M, et al. Self-Administration of Oxycodone by Adolescent and Adult Mice Differentially Affects Hypothalamic Mitochondrial Metabolism Gene Expression. *J Alcohol Drug Depend*. 2014;2(153).

Deutsch-Feldman, **M**, Zhang, Y, Buonora M, et al. Self-Administration of Oxycodone by Adolescent and Adult Mice Differentially Affects Hypothalmic Mitochondrial Metabolism Gene Expression. Oral presentation delivered at the College on Problems of Drug Dependence Conference (June, 2014)

Reed, B, Ducat, E, **Deutsch-Feldman, M** and Kreek, MJ. Vasopressin and CRF Regulation of Hypothalamic-Pituitary-Adrenal Axis Responsivity in Healthy Volunteers and Drug Free Former Cocaine Dependent Participants. Poster presentation delivered at the American College of Neuropsychopharmacology Conference (December, 2013).

Deutsch-Feldman M and Taylor E. Characterization of Heptosyltransferease I in Various Gram Negative Bacteria. Poster presentation for the Howard Hughes Summer Fellowship Program at Wesleyan University (August, 2010).

WORK EXPERIENCE

Teaching Assistant, *Department of Epidemiology*, Johns Hopkins School of Public Health August 2015-Present
Assist with Epidemiologic Methods II and Human Viral Infection courses. Duties include assisting with lab sections, grading exams and presentations, and answering student questions.

Teaching Assistant, *Department of Chemistry*, Wesleyan University
September 2010 - May 2012
Assisted organic chemistry professor by running a weekly review sessions, graded exams and tutored individual students

Management Team Intern, *South Africa-Washington Internship Program,* Washington DC
May – August 2011
Planned fundraisers, organized speakers, and performed office duties for a group of South African university students during a five week stay in Washington DC

Head Chef Campus Cooking Co-Op, *Department of Religion*, Wesleyan University
September 2009 - May 2012
Organized and cooked weekly Friday night dinner for Wesleyan community, around 50 people per week

VOLUNTEER ACTIVITIES

Masters Representative, *Department of Epidemiology*, Johns Hopkins School of Public Health
June 2015-Present
Liaison between Epidemiology Department masters students and faculty. Coordinate quarterly meetings and answer student questions regarding the masters program.

Co-Founder, *Women's Health Student Group*, Johns Hopkins School of Public Health
December 2014-Present
Created a student group focused on women's health and gender studies within the field of public health. The group hosts journal clubs, movie screenings and round-table discussions.

Volunteer, *Housing Works Bookstore Cafe,* New York, NY
April 2013-June 2014
Volunteer barista at a local bookstore-cafe run by the Housing Works non-profit organization. All proceeds support programs to aid those affected by homelessness and HIV/AIDS.

Co-Founder, *Wesleyan Forum for International Development,* Wesleyan University
September 2011- May 2012
One of four founding members. Organized a one-day conference focused on international development involving speakers, workshops and panel discussions. Raised money and publicized event around campus.

SKILLS

Languages: Conversational Hebrew and French
Computer: Proficient in Microsoft Office (Word, PowerPoint, Excel). Working knowledge of Stata, ArcGIS. Basic knowledge of R.