Conclusions/Significance

Our results demonstrate the high potential for misclassification when the average prevalence of lymphatic filariasis in the combined areas differs with regards to the TAS threshold. Of particular concern is the risk of ªpassingº larger EUs that include focal areas where prevalence is high enough to be potentially self-sustaining. Our results reaffirm the approach that Haiti took in forming smaller EUs. Where baseline or monitoring data show a high or heterogeneous prevalence, programs should leverage alternative strategies like mini-TAS in smaller EUs, or consider gathering additional data through spot check sites to advise EU formation.

Author summary

Lymphatic filariasis is a disease caused by roundworms that may lead to disability, psychological problems, stigma, and lowered quality of life. One of the key strategies to control and eliminate lymphatic filariasis is mass drug administration (MDA), or repeated treatment of all at-risk people living in affected areas with an annual dose of medicine. To determine whether MDA can be stopped in a particular area, a transmission assessment survey (TAS) is conducted whereby a sample of children are tested for filarial antigen and proportion with a positive result is compared against a target threshold. Existing guidelines for delimiting the geographic areas to conduct TAS permit large evaluation units. In 2015, TASs were conducted in Haiti using more stringent criteria for forming evaluation units, resulting in much smaller geographic areas for evaluation. Using simulations, the authors found that, had Haiti followed the existing guidelines and assessed larger geographic areas, many of the areas might have been misclassified and MDA stopped prematurely in some settings. This research suggests that caution is needed when forming evaluation units for TAS, especially if the prevalence of lymphatic filariasis is not uniform.

Introduction

Lymphatic filariasis (LF) is a vector-borne disease caused by nematodes, or roundworms, that reside in lymphatic vessels and can lead to debilitating disability, as well as stigma, psychological problems, and lowered quality of life [1,2]. The cornerstone of the global LF program is prevention through Mass Drug Administration (MDA). The primary objective of MDA is to lower the level of microfilaraemia in infected people so that, even after MDA is stopped, transmission cannot continue [3]. The World Health Organization recommends annual MDA to all those living in areas at risk until transmission is no longer deemed to be ongoing. Of the 72 countries considered endemic for lymphatic filariasis, 50 are considered to require MDA, of which only three have yet to start MDA; 17 countries have been validated as having eliminated LF as a public health problem [4].

There are costs associated with implementing MDA; consequently, to maximize the use of scarce public health resources, it is important for programs to know when MDA can be stopped with minimal risk of recrudescence. A 2011 study of communes in Haiti that received MDA found the cost of MDA distribution in the first year of the national strategic plan in just nine out of 55 communes to be $264,970. Extending this cost to all of the communes in program amounts to about $1,214,102 for just one year, not including the cost of albendazole [5].

In 2011, the World Health Organization (WHO) developed guidelines for determining when MDA can be stopped [3]. The geographic area across on which a decision to stop MDA will be based is called an evaluation unit (EU), and is often made up of a combination of MDA implementation units (IUs). An EU should not exceed two million people [3]. An EU should be comprised of epidemiologically homogeneous areas that have received at least five rounds of MDA, with at least 65% of the population swallowing the drugs each round, and the prevalence of circulating filarial antigen (CFA) in all sentinel and spot-check sites in an EU must be less than 2% [3]. If all of these conditions are satisfied, a Transmission Assessment Survey (TAS) is carried out to determine whether MDA should be stopped [3].

The target population for TAS is children 6 to 7 years old. In areas where over 75% of children are enrolled in primary schools, school-based surveys can be used for TAS, whereas community-based surveys are required in areas with lower school enrollment [3]. The tests and critical thresholds used to determine if an EU can safely stop treatment differ based on the type of LF and its vector. In areas where *Wuchereria bancrofti* is the endemic parasite, and the mosquito vector is *Culex* or *Anopheles*, decision rule and critical cut-off are set to determine if the upper one-sided 95% confidence limit around the CFA prevalence is less than 2% in order for the EU to `pass' the TAS and safely stop MDA.

TAS is an example of a modified Lot Quality Assurance Sampling method, with schools or communities serving as the primary sampling unit (PSU). When the total number of PSUs in the EU is small (e.g., <40), PSUs are selected via systematic sampling, while cluster sampling is used in larger EUs. The TAS guidelines provide a table, which takes into account the total population of 6 to 7 year olds in the EU, the sampling methodology, and anticipated design effect, to determine the recommended sample size and critical cutoff value for the survey [3]. Upon completion of the survey, the observed number of positive tests is compared to a critical cutoff, designed to measure the target threshold with known error. In the case of the TAS, the critical cutoff is designed to measure a threshold of 2% (1% where *Aedes* is the vector), with <5% chance of Type I error (falsely rejecting the null hypothesis that the prevalence is above the target threshold) and maintaining power of at least 75% when the true prevalence is less than half the threshold. Practically, if the observed number of positive cases in a TAS is greater than the critical cutoff, the EU `fails' and continues MDA for at least two more rounds; if the observed number of positive cases is less than or equal to the cutoff, the EU is considered to `pass,' and can stop MDA [3].

Haiti is one of four countries in the Americas endemic for LF, bearing 90% of LF disease burden in the region. The species endemic to Haiti is *Wuchereria bancrofti* and the primary vector is the *Culex quinquefasciatus* mosquito [6]. In 2001, the CFA prevalence among children aged 6 to 11 was between 0 and 45%, with over 88% of all communes showing prevalence greater than 1% and thus qualifying for MDA according to WHO guidance [3]. In 2000, with support from the Ministry of Public Health and the Population (MSPP), the National Program to Eliminate LF (NPELF) was started. Despite hurricanes, a devastating earthquake, and a cholera outbreak, by 2012, NPELF was able to implement MDA nationwide, reaching more than eight million people, with estimated coverage of 71% [7]. By 2019, 122 of the 140 communes in Haiti passed at least one TAS and no longer required MDA [8].

Despite the tremendous success of the TAS at enabling over a thousand EUs to stop MDA for the global LF program, some evidence suggests that the TAS, as it is currently designed, may not be an effective tool for stopping MDA in all settings [9]. The focality of LF infection, which increases as transmission is driven towards elimination, calls the liberal size allowance (up to two million population) for EUs into question. For example, the epidemiology and geographic distribution of LF is likely to be very different for people living in a densely populated area with homogeneous vector distribution, as opposed to those living in a sparsely populated

area with varying altitudes, humidity, and vector distribution. As the heterogeneity of transmission

this manner, nine unique combinations of adjacent EUs (hereby referred to as `combo-EUs') were formed. Each of these new combo-EUs represented an alternative EU that the NPELF could have designated as the basis for its stopping MDA decision, as the combo-EUs would satisfy the TAS eligibility guidelines specified by WHO. Homogeneity criterion was not considered in forming combo-EUs, as baseline prevalence estimates were several years old, and becomes some other countries and TAS disregard homogeneity criterion when forming EUs. Target populations for each combo-EU were determined by combining the target populations for each component EU contained in the combo-EU. The total number of schools in the combo-EU was taken to be the sum of schools in each component EU. The expected absentee rate for each individual evaluation unit varied from 10% to 15%; since each of the combo-EUs contained at least one EU with an expected absentee rate of 15%, all of the combo-EUs were assigned the expected absentee rate of 15%. Because the target population of each of the combo-EUs exceeded 1000 and the number of schools in each combination exceeded 40, cluster sampling was assumed, as recommended by the WHO TAS guidelines. The WHO TAS table was used to obtain the necessary TAS sample size for the combo-EUs [3]. The average number of students per school was estimated by dividing the total target population of the combo-EU by the number of schools in the combo-EU. Finally, the target TAS sample size was divided by this average number of students to obtain the number of schools that needed to be sampled for each combo-EU, with a minimum of 30 schools required. If the sample size was not reached, additional children were sampled from a list of backup schools, selected proportionately from the EUs comprising the combo-EU.

Passing or failing decision

In this study it was assumed that the programmatic decision for a combo-EU was to `pass' the TAS if all component EUs passed the TAS (i.e., with the number of positive tests less than or equal to the critical cutoff), allowing MDA to be stopped. Whereas if any of the component EUs failed, the programmatic decision for the combo-EU was to fail, a conservative decision to avoid prematurely stopping MDA in areas with ongoing transmission.

A TAS in each combo-EU was treated as a stratified cluster survey, with component EUs acting as strata and schools as clusters. Sampling weights were assigned to each child with a positive or negative ICT, with the weights for children in EU *j* defined as follows:

$$w_j \hat{} \frac{N_j}{n_j} \quad \ldots 1\dagger$$

where N_j is the target population in EU *j* and n_j is the number of children with a valid (positive or negative) ICT in the sample in EU *j*. The expected prevalence for the combo-EU was then obtained as a weighted average of each component EU's prevalence.

To assess the TAS critical cutoff, an upper one-sided 95% confidence interval was calculated for each expected prevalence accounting for the stratified cluster sampling using R package *survey*. If the confidence interval around the expected prevalence in the combo-EU contained or exceeded the TAS threshold of 2%, then the expected decision for the combo-EU was to fail; otherwise, the expected decision for the combo-EU was to pass.

Bootstrapping

To understand the distribution of TAS results that one might expect had larger EUs been formed, bootstrapping, that is sampling with replacement from the observed data, was used to estimate the number of ICT positives if TAS were conducted in each combo-EU. In the first step, the estimated number of schools required to meet the TAS sample size for a combo-EU

was sampled with replacement from among all the schools in the observed TAS datasets for each of the component EUs. School selection was stratified by EU and schools were bootstrapped independently from each EU, with the number of selected schools proportional to the total number of schools in the EU. For those component EUs that were originally sampled systematically, rather than through cluster sampling, additional bootstrapping of children within the school was performed in order to obtain the necessary sample size. In these schools, the number of children selected was equal to the average number of children per school in the

target grades in schools in the EUs ranging from 707 children 6±7 years to 35,357. Four of these EUs had low baseline prevalence of infection (0.1±4.9% ICT positivity), one had medium baseline prevalence (5.0±9.9% ICT positivity), and nine had high baseline prevalence of infection (10.0% and over ICT positivity) based on estimates from 2001 [16]. The number of schools in the EUs ranged from 17 to 721 and the average number of students in target grades per school ranged from 29 to 64.

The number of schools visited per EU as part of the TAS spanned from 16 in EU #7 to 53 schools in EU #3. Four of the EUs had <40 schools and required systematic sampling,from

Table 2. Characteristics of combination Evaluation Units, formed from adjoining Evaluation Units.

Evaluation Unit Combination	Component Evaluation Units	Observed Decision	Target sample size	# Schools to be sampled	Programmatic decision	Expected true prevalence (upper 1-sided Confidence Interval)	Expected transmission assessment conclusion
A	12	Fail	1540	41	Fail	1.03%	

not be informative. This left nine combo-EUs for the simulations; a description of these combo-EUs is presented in Table 2.

As seen in Table 2, the expected TAS decision, based on the expected prevalence of positive ICT results from the weighted average of the component EUs, differed from the programmatic decision for five out of the nine combo-EUs. That is, although the programmatic decision for the combo-EU was to fail if at least one of its component EUs had failed the TAS, in five of the combo-EUs that had at least one component EU that failed the TAS, the upper one-sided 95% CI around the expected prevalence was less than 2%, indicating a passing result. Thus, for these combo-EUs, there was a discordance between the desired and expected decisions.

Combo-EU Bootstrapping

The results from the bootstrapping to obtain the distribution of likely TAS results for each combo-EU are shown in Table 3. When the combo-EUs were comprised of EUs with the same

observed TAS

Mini-TAS

The results of mini-TAS simulations are presented in Table 4. The vast majority of the mini-TAS bootstrap replicates passed the TAS. In seven of the thirteen EUs, all of the bootstrap replicates would pass in the mini-TAS, which is intuitive because the total number of positive ICTs in the full TAS sample was at or below the

combo-EU if any of the comprising EUs should fail TAS. It should be noted that the two EUs that failed TAS (EU #11 and EU #12) had below average target

likelihood that appropriate stop-MDA decisions are made and enable programs to reach their elimination goals as efficiently as possible.

Supporting information

S1 Fig. Spatial distribution of positive Immunochromatographic card test results in Haiti Transmission. The administrative division shapefile that served as a base map is available at https://data.humdata.org/dataset/777e8b06-337f-4295-80bc-ca1515244215/resource/9b57a285-e12f-4d1a-b167-676d96a2b4af/download/hti_adm_cnigs_20181129.zip; the shapefile with Evaluation Unit number as an attribute is available for download https://doi.org/10.15139/S3/JUUSHC. Assessment Survey data.
(TIF)

S1 Table. Decision rules and sample size for mini-Transmission Assessment Surveys. Table adapted from [13].
(PDF)

S2 Table. Comparison of observed 2015 Haiti Transmission Assessment Survey results in 13 Evaluation Units and simulated results using bootstrapping.
(PDF)

S3 Table. Distribution of positive Immunochromatographic card test results within Evaluation Units.
(PDF)

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Author Contributions

Conceptualization: Natalya Kostandova, Amy Kirby, Katherine Gass.

Formal analysis: Natalya Kostandova.

Investigation: Luccene Desir, Abdel Direny, Alaine Knipes, Jean Frantz Lemoine,

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