

Persons ‘never treated’ in mass drug administration for lymphatic filariasis: identifying programmatic and research needs from a series of research review meetings 2020–2021

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As neglected tropical disease programs rely on participation in rounds of mass drug administration (MDA), there is concern that individuals who have never been treated could contribute to ongoing transmission, posing a barrier to elimination. Previous research has suggested that the size and characteristics of the never-treated population may be important but have not been sufficiently explored. To address this critical knowledge gap, four meetings were held from December 2020 to May 2021 to compile expert knowledge on never treatment in lymphatic filariasis (LF) MDA programs. The meetings explored four questions: the number and proportion of people never treated, their sociodemographic characteristics, their infection status and the reasons why they were not treated. Meeting discussions noted key issues requiring further exploration, including how to standardize measurement of the never treated, adapt and use existing tools to capture never-treated data and ensure representation of never-treated people in data collection. Recognizing that patterns of never treatment are situation specific, participants noted measurement should be quick, inexpensive and focused on local solutions. Furthermore, programs should use existing data to generate mathematical models to understand what levels of never treatment may compromise LF elimination goals or trigger programmatic action.

Keywords: adherence, compliance, elimination, equity, filariasis, mass drug administration.

Introduction

In 2020, the World Health Organization (WHO) introduced the 2021–2030 Neglected Tropical Disease (NTD) Roadmap, which outlines disease-specific goals for 20 NTDs.¹ Preventive

chemotherapy for NTDs, often delivered through mass drug administration (MDA), treats people in endemic areas regardless of their infection status and is a core intervention used by several NTD programs to achieve disease control or elimination.^{1,2}

Published NTD models demonstrate that the likelihood of reaching elimination through MDA is associated with higher coverage,³ less clustering of persons missing treatment⁴ and fewer persons never treated.⁵

NTDs are defined by their burden on the poorest and most marginalized populations. The plan to end poverty, laid out in the 2030 Agenda for Sustainable Development, includes as a measurable target, 'ending neglected tropical disease epidemics by 2030' (target 3.3), alongside 'achieving universal health coverage (UHC) with access to quality services and medicines for all' (target 3.8).⁶ The first WHO/World Bank report on tracking UHC ties these two targets together when it states that measuring preventive chemotherapy treatment coverage for NTDs is 'key to ensuring that the diseases of the least well-off are being prioritized from the very beginning of the path towards UHC'.⁷

The WHO has issued guidelines for measuring treatment coverage through routine administrative reporting, post-MDA coverage evaluation surveys and rapid estimates done by supervisors during MDA.^{8–10} To date, these have focused on measuring the percentage of the target and at-risk populations treated in the last MDA. Programs targeting lymphatic filariasis (LF)—a mosquito-borne parasitic disease—use reported annual MDA coverage to determine readiness to conduct impact surveys, which in turn determine whether MDA can be stopped. However, there is little focus on identifying persons never treated, their potential role in driving continued transmission and understanding their sociodemographics, geographic distribution, infection status and reason(s) for not being treated, among other factors.

As elimination programs increasingly reach the endgame and prepare for the post-elimination phase, there is concern that people who have never been treated could contribute to continued transmission, posing a barrier to elimination. Previous research has suggested that the size and distribution of the population never treated with MDA may be an important issue—as ongoing transmission in a large population could threaten achievement of elimination targets—and one that has not been sufficiently addressed within the research community.^{11–15}

To address this critical knowledge gap, a series of expert meetings was held and included participation from a variety of organizations represented by the authors of this article, among others. This article summarizes the information shared and proposes next steps, including defining metrics, expanding routine data collection and an operational research agenda. While we focus on LF, lessons from this NTD are applicable to other diseases and public health areas.

Research links meeting series

The Coalition for Operational Research on Neglected Tropical Diseases and the Improving Community Health Outcomes through Research, Dialogue and Systems Strengthening (iCHORDS) community of practice hosted a series of four virtual meetings from December 2020 to May 2021 designed to explore and compile expert knowledge on persons never treated in LF MDA programs. Invited participants had previous research experience in this area and/or were exploring this through

routine programmatic monitoring and evaluation. The meetings explored four questions: the number and proportion of people never treated, their sociodemographic characteristics, their infection status and the reasons why they were not treated.

The first three meetings were held with 30 experts from LF national programs, the WHO, research institutions, implementing partners and donors. A smaller group met to discuss and propose more appropriate and inclusive terminology. All meeting information was then packaged, shared and discussed in a public webinar with 174 participants from 47 countries. This article presents the consolidated proceedings of these meetings and proposed next steps.

Terminology

In the literature, the phenomena of frequently not swallowing or never swallowing MDA medicines across any round has multiple terms, including systematic non-compliance, persistent non-compliance, systematic non-adherence and semi-systematic non-compliance (Table 1). These terms have generally referred to those intentionally refusing (e.g. due to fear or lack of perceived need) and those not given the opportunity to take the treatment (e.g. due to ineligibility, lack of knowledge of the MDA or never having been offered MDA). Conversely, some literature captures the inverse of never taken by noting which people have ever swallowed MDA tablets.¹⁶

In the broader health literature, compliance is usually defined as the act of an individual conforming to professional recommendations with regards to prescribed dosage, timing and frequency of an intervention²⁴ or the extent to which a patient acts in accordance with the prescribed interval and dose of a regimen.²⁵ Many in the NTD community have indicated that the term 'compliance' is neither adequate nor appropriate to illustrate swallowing LF tablets during MDA because it assumes the individual has no agency in the decision and risks oversimplifying the complex programmatic and individual reasons a person may not take medicines. The medical literature has also used the terms 'medicine persistence' and 'concordance' to describe compliance. Medicine persistence illustrates the duration of time from initiation to discontinuation of therapy,²⁵ while concordance infers that the prescriber and patient must come to an agreement about the regimen the patient will take.²⁶ An alternative term, 'adherence', describes the extent to which a person's behaviour corresponds with the agreed recommendations from a healthcare provider.²⁷ None of these terms adequately describe whether an individual receives treatment and do not specify either intentional refusals and/or unintentional reasons for missing treatment.

After soliciting additional input from stakeholders, the term 'never treated' was suggested to capture those individuals who self-report that they have never ingested tablets during any round of LF MDA. 'Never treated' does not put the onus for taking LF tablets solely on either the program or the recipient. In addition, it has the benefit of being easily understood and translated into various languages. The use of 'treatment' is consistent with nomenclature used in the WHO NTD 2030 Roadmap, which lists a target of 90% reduction in the number of people requiring treatment for NTDs.¹ The WHO's Joint Application Package (JAP)

Table 1. Previous definitions of systematic non-compliance

Definitions used	Country (reference)
Individuals who systematically do not adhere to treatment, over a number of treatment rounds	Non-specific ¹⁷
Individual who never attended any rounds of MDA/people who are never treated in any rounds of MDA	Non-specific/modelling paper ³
People who persistently refuse or do not ingest the antifilarial medications over the course of an MDA program	Indonesia ^{18,19}
People who have never participated in an MDA	Haiti ²⁰
People who miss all rounds of MDA	Egypt ¹¹
The proportion of people who never took the medicines during the three distributions of MDA	Haiti ²¹
Individuals receive treatment in every round but never swallow the tablets (persistent non-compliers)	India ²²
Proportion of the population who repeatedly miss or refuse MDA	WHO-WER ²³

uses similar terminology in its register to capture ‘reasons for non-treatment’ at the peripheral level.²⁸ In this article we will use the terminology ‘never treated’ to represent those individuals who either self-report never treatment or who have been identified through registers to have not taken any LF tablets during any MDA rounds.

What we already know

Proportion of persons never treated

Experts shared experiences that showed wide variation of results (within and between countries) in the proportion of people who reported having never been treated in LF MDA. This is illustrated in the summary of results from published studies that were presented in the meeting series (Table 2). These data were collected using a variety of methods, with different sample sizes and from different populations (different ages, and while some included only those eligible for treatment in the denominator, others included all respondents). These differences pose challenges for comparing results across settings and underpin the need for standardized terminology and metrics.

Characteristics of persons never treated

Noting the small number of published studies presented that included characteristics of persons never treated,^{12,15} experts also shared information from ongoing work and unpublished research and from national NTD program routine data. Based on published studies and unpublished data, they hypothesized that there may be higher proportions of persons never treated among hard-to-reach populations (including those living in very remote areas, migrants and urban centres), those with limited awareness about LF and MDA and those who did not know if others in their household took the LF medicines. Trends such as systematic differences among world regions and by MDA drug regimen emerged. Meeting participants reported different associations of never treated by age group and sex. For example, in some settings, more men than women were never treated, perhaps due to not being home because of their occupation, while in other settings it was women who were more often never treated, possibly related to repeated

pregnancies across MDA rounds and thus not being eligible to receive treatment.

Reasons for never treatment

Experts had limited information to share on why people were never treated in MDA, as most of the data pertained to why people were not treated during the most recent round of MDA offered. Reported reasons for not being treated during the last MDA round included ineligibility, absence, fear of side effects and the perception of not being at risk; these have been documented in previous literature reviews for LF and other NTDs.^{19,34,35} While these reasons are commonly accepted, they require more investigation, e.g. absence could imply not being home at the time of day the drug distributor came, intentional avoidance or travel out of the district for the duration of the MDA campaign. Similarly, fear of side effects could imply the desire to take tablets after eating or at night, reluctance due to a lack of follow-up care for side effects or fear of death from the medicines due to rumours. These reasons will vary culturally across contexts and may also be directly linked to the effectiveness of the social mobilization campaign. Variations in how questions were asked and how data were analysed resulted in reasons being grouped differently, making comparing results across studies difficult.

Experts discussed the challenges in capturing explanations as to why people were never treated. These reasons would likely vary for the same person from year to year and open to recall bias and the relative importance of each reason would be difficult to determine.

Association between never treated and infection status

Having groups of never-treated people, regardless of who they are and why they were not treated, is of concern if they are infected and therefore at personal risk of clinical disease and potentially contributing to ongoing transmission. In Egypt, after completing five rounds of MDA, with overall coverage >85%, it was found that 7.4% of the study population was never treated in any of the five rounds of MDA. Infection rates, as measured by microfilaraemia and antigenaemia tests, were statistically significantly higher in the groups who reported taking zero

Table 2. Proportion of people never treated in LF MDA, from published literature

Country	Study year	Location	Tool	Age group (years)	Sample size	Previous MDA rounds, n	Never treated, %
American Samoa ²⁹	2007	Urban and rural	Randomly selected household survey	≥2	1881	7	6
American Samoa ³⁰	2014	Urban and rural	Worksite study	≥15	496	7	31
American Samoa ³¹	2016	Urban and rural	30 randomly selected villages	≥8	2507	7	58
Samoa ³²	2018	Urban and rural	Population-based survey with 35 clusters	≥2	4420	8–10, 9–11	14 (pre-2018); 3 (including 2018)
Fiji ³³	2019	Rural	Community-based study	>14	300	>10	15
Myanmar ¹⁶	2015	Peri-urban and rural	Population-based household survey	>1	1014	6	19
India ³³	2019	Peri-urban	Community-based study	>14	397	12	85
India ²²	1994–2000	Rural	Prospective study in 10 villages	Individuals >15 kg	18 415	6	3.5–4 of those eligible in all rounds
Indonesia ¹²	2013–2014	Urban and rural	Community-based study	>15	806	5	19 (rural) and 24 (urban)
Egypt ¹¹	2000–2006	Rural	Coverage evaluation survey	>5	1064	5	7
Haiti ³³	2019	Peri-urban	Community-based study	>14	407	8	25
Haiti ²⁰	2008	Peri-urban	Population-based household survey	>5	455	7	24
Guyana ¹⁵	2021	Peri-urban	Community-based pre-MDA study	>18	451	3	21

or one round of treatment compared with those who took two or more.³⁶ Similar results were found in one American Samoa study where 6% of persons were never treated and those who had ever been treated in MDA had a lower odds of infection compared with those never treated in multiple regression analysis (odds ratio [OR] 0.39, $p=0.04$).²⁹ However, these results were not replicated in two other American Samoa studies with higher percentages (31% and 58%) of persons reporting to have been never treated.^{30,31} A study in Samoa found higher antigen prevalence (5.8%) among participants who reported never taking MDA compared with those who reported taking MDA at least once (4.9%), but the difference was not statistically significant.³² In Myanmar, significantly higher infection rates among the never treated in a univariate analysis did not hold when other factors were controlled for in a multiple regression analysis.³⁷

Suggestions to strengthen measurement of never treatment

Create standard indicators on frequency of treatment

Contributing to this general lack of information on never-treated persons—number, characteristics, why they were never treated

and their role in contributing to continued transmission—is the lack of a standardized indicator and measurement in routinely collected programmatic data or in research studies (Table 3). During analysis, some researchers grouped ‘treated zero or once’ versus ‘treated twice or more’, while others grouped ‘never treated’ versus ‘treated once or more’. Researchers have also used variations of survey questions to understand who has never been treated. One of the most common questions used was ‘including this year, how many times have you taken the medicines for LF?’ with possible responses of ‘never’, ‘one time’, ‘two or more times’. This indicator has been validated through use in population-based surveys, in acceptability studies as well as in some national programmatic data collection.^{12,15,33}

Because studies have shown that two or more rounds of annual diethylcarbamazine plus albendazole or twice a year albendazole clears filarial infections significantly faster than zero or one round^{11,38} and that just one round of triple drug therapy almost totally clears microfilaraemia,³⁹ experts recommended reporting results for both ‘never treated’ and ‘treated once’ in addition to treatment in two or more rounds. Further recommendations for measurement included disaggregating data by age and sex. This will not account for the potential to routinely miss certain people in surveys and so considerations for weighting or adjusting the timing of surveys also should be considered.

Table 3. Summary of methodological issues and suggested approaches

Issue	Description	Suggestions
Measuring ‘never treated’ (NT)	There is no standardized indicator used within programmatic data and research for measuring NT	Use NT indicator: How many times have you taken the medicines for LF? with responses of never, one time or two or more times. Use age and sex standardization of the NT indicator. Further validate the proposed indicator against treatment registers, where available.
Adapting design and use of existing tools	Tools that are widely used rarely measure the NT indicator and often miss the opportunity to collect and use more information on persons not treated, including their infection status.	Include NT indicator in pre-TAS, coverage evaluation survey and SCT. Standardize recording and analysis of answers to increase understanding on who is not being treated, why and their potential impact on transmission.
Ensuring representation of the NT in data collection	Concern that current tools to measure coverage and infection prevalence are missing persons not treated.	Explore ways to adjust data collection tools to be more inclusive.

Modify existing tools

There are different quantitative and qualitative tools that LF programs use routinely to assess disease prevalence, MDA coverage and implementation methods (Table 3). Meeting participants identified opportunities to modify the design, use and analysis of these existing tools to increase knowledge on who is not treated, including the never treated. Participants reported from experience that it is feasible to add questions on the frequency of past treatment to pre-transmission assessment surveys (TASs), coverage evaluation surveys and the Supervisor’s Coverage Tool (SCT). Pre-TASs have the advantage of linking infection status with never-treatment data; however, it collects data from two or three high-risk sites within a district so is not representative of the entire district. Participants also agreed that a standardized list of options to record reasons for non-treatment is needed to allow for comparing and synthesizing data collected across studies and countries. For example, currently the term ‘ineligible’ does not differentiate between those contraindicated for treatment and those who are misidentified as ineligible, but that distinction is important in planning programmatic responses. Similarly, there would also be value in providing options that provide more nuance to answers like ‘absent’ or ‘side effects’. Clear categorization of these responses is needed to better link reasons for never being treated with potential solutions. At a minimum, results should be disaggregated by people who were never treated due to issues with program reach (unintentional) or due to individual refusal (intentional). Qualitative research may also need to be used and current operational research is under way to explore potential approaches and methods.

Other adjustments currently being piloted by programs and research studies include oversampling specific populations of interest (e.g. migrants, youth, males) and collecting information on other variables that would elicit programmatically actionable information, such as levels of trust in drug distributors, health behaviour influencers in the community

and migration patterns. Suggested modifications also include adding diagnostic tests to enable linking treatment history to infection status and collecting georeferenced data to conduct geospatial analysis that visually represents associations between multiple variables.

Ensuring the never treated are not missing from other data collection

One concern expressed by several participants is that there may be selection bias inherent in the design of existing tools that needs to be explored and, if necessary, addressed. The same people missed in surveys designed to estimate coverage and infection prevalence may also be missed by MDA, potentially impacting the coverage and infection prevalence estimates produced. For example, in a study in American Samoa, 97.5% respondents were of the majority Samoan ethnic group, although census data showed that 15% of the population in the area were from non-Samoan ethnic groups.³⁰ The use of proxy responders, permitting a household member to respond on behalf of someone who was not home at the time of the survey or could not answer for themselves, was also questioned. A recent analysis of NTD coverage surveys in three countries hypothesized that proxy responses may lead to an inflation of surveyed drug coverage.⁴⁰ Thus it was recommended that analyses of never treatment exclude proxy responses. Overall, ensuring never treated are not missing from data collection requires further exploration—both programmatically by adjusting the time of day or week or year that both MDA and the surveys are conducted and with operational research.

Adapting to reach those who have never been treated

Ultimately data collected on persons never treated needs to be used to adapt strategies for distributing the medicines. These

strategies will need to be specific to the local context and will likely vary according to geography, such as urban versus rural setting, and population groups involved, such as undocumented migrants, transient labour forces or other marginalized groups. In previous research, data collected on people who were never treated was useful for tailoring and refining MDA strategies to improve reach and strengthen equity in groups where coverage had been previously low.^{12,33} This may include social mobilization approaches that are adapted using gender-specific messages and young people as behaviour change agents (personal communication arose from some of the experts). Motivating drug distributors to identify individuals who have never been treated during the MDA was proposed as a response to never treatment in Indonesia.¹² In Myanmar, recommendations were made to change the timing of treatment to align with when people are at home and ensuring resources were available for mop-up.³⁷ Finally, other public health programs, such as immunization campaigns, may be helpful to LF programs in sharing techniques they have used to reach those never treated, such as when to use fixed locations versus house-to-house distribution, extending personal invitations to participate from health workers and strategic use of media.

Conclusions and next steps

The expert review presented here has confirmed there is a lack of evidence and understanding about the never treated and their impact on LF elimination programs. Little is known about the proportion of persons never treated, their infection status, their demographic profiles, reasons for not being treated and effective programmatic responses. There is mounting evidence that people never taking drugs (or taking them only once) are slower at clearing infection, but little is published on the impact of groups who have never taken LF treatment on ongoing transmission. If persons never treated are found to be high infection reservoirs, tackling this challenge will be critical to reaching NTD elimination targets.

We recognize that patterns of never treatment are context specific—often down to the village level. Measuring the issue of never treated therefore needs to be quick and inexpensive, with an aim to adapt solutions to local contexts. Given the 2030 elimination goals for LF, the need is urgent. Meeting participants noted that this can be done most feasibly and efficiently by modifying existing programmatic tools that are already in wide-scale use. Synthesis of data and learning across settings is also important to identify common challenges and solutions that can be tried in different settings. Standardization of questions and indicators will be crucial for cross-site analysis. Furthermore, as data are collected on those who are never treated, these data need to be utilized to improve mathematical models that help determine what levels of never-treatment risk elimination goals should trigger programmatic action. Specific opportunities for further analysis and operational research proposed have been captured in [Boxes 1 and 2](#), some of which are related to more general coverage issues and some of which are specific to never treatment. To move this agenda forward, a core group of meeting participants volunteered to develop data collection and analysis standard operating procedures to be shared widely on the iCHORDS website (www.ichords.org) for use and real-time

feedback by national programs, implementing partners and researchers.

Box 1. Secondary data analysis

- Analyse data from MDA registers that include age, sex and reasons for non-treatment, recognizing this does not capture non-treatment due to lack of access.
 - Explore differences between once-only treatment and never treated, the reasons and how these are affected by age and sex.
- Triangulate coverage evaluation survey (CES) data with MDA treatment registers to determine if recall bias is an issue in CES responses.
- Expand modelling to allow users to include never-treat data.
 - What is the relationship between reported and modelled treatment coverage and the proportion of people never treated? Can we estimate a never-treated proportion from treatment coverage?
 - For modelling based on these data, consider what assumptions would be required for how many people have had 1, 2 or 3 treatments or would be covered in subsequent rounds and evaluate if this is important or whether the dynamics are driven by the never-treated proportion.
- Publish aggregate coverage evaluation survey data analyses that re-analyse existing data based on standard categorizations and exclude those who would have been too young to participate in any MDA.

Box 2. Operational research priorities

- Measure who was never treated.
 - Analyse whether never-treated people are more likely to be infected, especially in low-prevalence areas, including links to baseline infection intensity.
 - Develop profiles of persons never treated and reasons for not being treated.
 - Develop a stand-alone set of questions to collect data on never treatment, reasons why and proposed solutions.
- Measure reasons why people were never treated.
 - Measure the percentage of never treatment due to intentional (refusal) versus unintentional (access) issues.
 - Determine whether the reasons why people were never treated are similar to the reasons why people were treated once.
- Determine the impact of never treatment.
 - Determine whether people who were never treated are a reservoir of infection.
 - Determine the transmission potential of never-treated populations through modelling.

- Determine the impact of missing different population groups on infection prevalence, e.g. are those who perceive themselves to be ineligible more likely to be infected than those who refuse treatment for other reasons?
- Through modelling, determine the appropriate level of never treatment in various groups that should trigger action.
- Define responses to never being treated.
 - Develop and test cost-effective intervention strategies targeted to reasons for never being treated.
 - Explore how much coverage might increase from various programmatic responses to the different elements of why people are never treated.
 - Determine if never treatment is a proxy for primary healthcare access.
 - Explore whether identifying and engaging people who have never been treated can have catalysing effects on health.

Evidence regarding populations who are never treated, their infection status and why they have not taken treatment will strengthen programmatic responses to the broader issue of low MDA treatment coverage. New knowledge generated from these next steps will improve access to MDA and ultimately increase coverage towards more universal healthcare.

Attendees of the research review meetings

Presenters: Molly Brady (RTI International), Patricia Graves (James Cook University), Deirdre Hollingsworth (University of Oxford), Louise Kelly-Hope (Liverpool School of Tropical Medicine), Alison Krentel (University of Ottawa and the Bruyere Research Institute), Bhupendra Tripathi (Bill & Melinda Gates Foundation India Country Office), Diana Stukel (FHI 360) and Gary Weil (DOLF Project, Washington University at St Louis).

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