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Understanding the characteristics of individuals requiring a proxy response for mass drug administration coverage surveys and the potential for recall bias

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2012

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Abstract

Understanding the characteristics of individuals requiring a proxy response for mass drug administration coverage surveys and the potential for recall bias

By Rini Jose

The success of mass drug administration (MDA) for neglected tropical diseases is dependent upon achieving adequate drug coverage, which is validated through household coverage surveys. Coverage surveys rely on respondent recall and often permit proxy responses, whereby another household member is allowed to respond on behalf of an absent individual. This study used data from coverage surveys for lymphatic filariasis in Malawi, Burkina Faso, and Uganda to determine the demographic characteristics of individuals for whom a proxy response was required and the extent to which a proxy response was associated with reported drug coverage. According to our results, teenagers and young adults (11 – 25 years) were more likely to be absent during the coverage survey and require a proxy response, compared with older adults. Similarly, males were more likely to require a proxy response than females. Adults who were eligible to receive MDA for lymphatic filariasis (i.e. everyone, excluding women who are pregnant or in the first week of breastfeeding and the severely ill) were more likely to be absent and require a proxy response than individuals who were ineligible for MDA. A multivariate analysis found that individuals for whom a proxy response was provided had 1.5199 times the odds of being recorded as having swallowed the drugs compared to self-reporting individuals, controlling for age and sex (95% CI (1.0308, 2.2409)). This finding is surprising, given that individuals who are unavailable at the time of a coverage survey may also have been unavailable at the time of MDA, and suggests that proxy respondents may be inflating drug coverage. This finding could be explained in part by the fact that self-reporting individuals are more likely to have been ineligible to receive MDA and thus are expected to have lower coverage; however this does not account for the entire increase in odds. This study highlights the possibility for recall bias in proxy responses to MDA coverage and suggests that further research in necessary to determine the best method for obtaining information on drug coverage when individuals are absent.

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Table of Contents

Chapter I. Literature Review

Introduction:

Neglected Tropical Diseases (NTDs) are a group of seventeen communicable diseases prevalent among the world's poorest populations in approximately 149 countries, affecting more than one billion people (1). These illnesses, when left untreated, can lead to dire health and socio-economic consequences for affected families and individuals. Among these profound consequences, NTDs can lead to impaired childhood growth and development, hindered economic prosperity, and risk of life-long morbidity (2-4). As a group, NTDs are estimated to account for more years lost to ill-health, disability, or early death (measured as disability-adjusted life years) than malaria, causing significant disability and resulting in large-scale lost productivity and discrimination (5).

Of the thirteen NTDs recognized by the World Health Organization (WHO), there are seven that the WHO have included in their roadmap for implementation (including lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiases, and trachoma). Through mass drug administration, the WHO hopes to effectively control and even eradicate these illnesses (6). These diseases are treated with regular distributions of single-dose chemotherapy medication to an entire at-risk population with the idea that successive, adequate coverage of mass drug administration (MDA) can reduce the prevalence of infection and in some cases, lead to elimination (7). Therefore, MDA coverage must be maintained and maximized in order to determine the success of NTD control and elimination programs (7).

Mass Drug Administration as a Treatment for Neglected Tropical Diseases:

Mass drug administration is currently used in over 80 countries worldwide to both control and eradicate neglected tropical diseases. Mass drug administration is used as a preventative chemotherapy measure at the population level for seven neglected tropical diseases, usually conducted annually, during which drug distributors disperse medications en masse to the target population of interest (8). All members of the population are included in the MDA except where contraindicated due to young age, pregnancy, or present illness (8). The World Health Organization is one of the many international bodies that help monitor and evaluate the effectiveness of this protocol, particularly through measurements of nationwide drug coverage.

The measurement of drug coverage is essential to the effectiveness of the MDA because it is a core indicator of success of the program (8). This is because the success of the MDA to disrupt the transmission of NTDs and consequently reach the elimination and control goals is dependent upon achieving adequate drug coverage (7). Drug coverage is defined as the proportion of individuals who have ingested a drug or combination of drugs (1). World Health Organization (WHO) guidelines mandate reporting of coverage as part of monitoring and evaluation activities (9). Some NTD eradication programs rely exclusively on reported drug coverage, calculated based on the number of doses distributed as recorded in drug registers during the MDA divided by the estimated size of the population (7). This method can be flawed, however, because this fails to acknowledge some drug distributors who may have financial or other incentives to over-report coverage (9). Similarly, these estimates for overall drug coverage also rely on estimates of population size, such as potentially outdated or inaccurate census data

(10). Although most countries routinely calculate vaccination coverage using administrative data, results can be unreliable, particularly when the target population size is poorly characterized or when reporting is incomplete (11).

One way to validate administrative coverage data is to measure drug coverage through population-based surveys (7). In population-based surveys, drug coverage is calculated by dividing the total number of individuals reporting to have taken the drugs by the total number of individuals sampled in the survey (7). Therefore, population-based surveys are independent of the issues associated with incomplete reporting or unreliable data and are thus generally considered the "gold standard" for assessing coverage (11). Although coverage surveys are recommended by the WHO to accomplish program monitoring and are recommended by drug donation programs, they often fail to be implemented because it is perceived that the cost is prohibitively high in these settings, due to constrained financial and human resources (9). One such study that attempted to validate drug coverage surveys found that while school-distribution led to significant discrepancies between reported and surveyed coverage, all other surveys of drug coverage found that the true coverage fell within recommended WHO guidelines for an adequate MDA (7). This research suggests that drug coverage surveys are important tools to effectively monitor MDA programs because their results can potentially paint a more realistic picture of drug adherence, as well as lead to improved drug delivery strategies and better targeting of non-compliant groups, which can reduce the number of treatment rounds required to interrupt transmission of NTDs (7).

One major criticism, however, with the population-based drug coverage survey approach to assess adherence to the MDA program is the issue of recall bias. Recall bias

is the ability to correctly recall whether, in this case, an individual has actually ingested a medication or not and therefore affects an individuals' ability to correctly respond to survey questions (7). This potential issue is further complicated when we consider proxy responses. Proxy responses are responses that individuals can give on behalf of others, if they are unable to be reached when the surveys are administered. Many researchers employ proxy responses for ease of measurements and convenience. In many cases proxy responses involve women answering for their spouses or children (8). The purpose of this literature review is to assess the validity of proxy responses and the extent of recall bias among drug coverage surveys.

Validation of Proxy Responses and Recall Bias:

There are few published data regarding the validity of proxy responses and recall bias among drug coverage surveys, and even among the literature these findings do not always result in a clear consensus. A majority of studies assessing proxy responses against medical records, however, do suggest that proxy responses have high concordance with administrative records and could be valid estimates of drug coverage. For example, in one study which assessed accuracy in household coverage surveys following a mass drug administration, researchers concluded there were high levels of concordance even after a year. In this study, researchers used community-based surveys to verify coverage and test recall accuracy at one month, six months, and twelve months after integrated mass drug administrations in Togo (8). To ensure accuracy of recording, drug distributions were observed during the MDA. Coverage was defined as the percentage of persons taking at least one of the medications and information obtained from the population varied in number (8).

Concordance between treatment registers and survey responses for just one pill was >95% at one month and >86% at twelve months, and researchers hypothesized the drop in percentage was due to difficulty matching survey respondents with year old treatment register rather than inaccurate responses (8). Similarly, respondents were generally able to distinguish between pills that were similar in appearance, resulting in recall that was over 80% concordance (8). Ultimately, coverage estimates based on survey responses were highly consistent (between 88% and 91%) and concordance for any ingestion of MDA was >86% in all surveys (8).

These results are relatively consistent with another study of recall bias which tested the accuracy of mothers' estimates of immunization coverage. In some countries, vaccination status for individuals is typically determined based on documentation of vaccination dates on household-retained vaccination cards and can sometimes be supplemented by parental recall (11). Typically, in developing countries, estimates of immunization coverage are made on a "card plus history" basis, meaning information from vaccination cards is combined with information from mothers' reports for children whose vaccination cards are unavailable (12). In these countries, immunization cards, in combination with parental recall, are considered to be the most accurate estimates of drug coverage available (13).

Researchers in this study determined that comparisons of the vaccination status initially (based only on maternal recall) and a year later (using immunization cards) indicated very high concordance, approximately between 83% and 98% of the time mothers' reports were confirmed, depending on the vaccine in question and the child's age (12). Similarly, mothers of children who had not been vaccinated were more likely to

give consistent responses than were mothers of vaccinated children (12). The number of incorrect “non-vaccinated” responses was also greater than the number of incorrect “vaccinated” responses, suggesting that “card plus history” vaccination coverage slightly underestimates true coverage estimates (12). This further bolsters the idea that proxy responses and recall bias among drug coverage studies have relatively high reliability and concordance with the true estimates of coverage.

A similar study, conducted in Costa Rica, measured maternal recall error of child vaccination status by comparing information on vaccination cards to maternal recall (14). In this study, vaccination cards were used as the “accurate count” of vaccinations and recall error was measured as the difference between the number of remembered vaccinations and the accurate count (14). The researchers determined that the distribution of the number of doses from the vaccination cards and from the maternal recall were similar; suggesting that in the absence of vaccination cards, maternal recall can be used as a valid estimate of coverage (14). They also concluded, however, that maternal recall should not be used to determine an individual child’s vaccination status because of significant differences in accurate recall with respect to a child’s age, and the vaccine in question (14).

Similar results were also obtained in a study conducted in rural Nigeria to assess vaccination coverage using both a survey administered to mothers and information from vaccination cards (15). Ultimately the researchers determined an overall vaccination coverage of 61%, where coverage was higher among children who had a vaccination card than in those assessed by maternal history (15). Based on these results, researchers

concluded that it may be possible to rely on maternal proxies alone to determine relatively accurate levels of vaccination coverage (15).

Several studies also suggest high levels of concordance between parental responses and immunization data from the National Immunization Survey administered in the United States. In two studies that assessed the accuracy of parental reports of children's HPV vaccine status when compared to the NIS-Teen data, both studies suggest that parental recall may have reasonable reliability for assessing vaccination status (16, 17). Although both studies suggest recall bias varies with respect to race, income, and parental education level; the researchers concluded that these variations in demographic characteristics resulted in an underreporting of vaccine coverage (16, 17). Similarly, these studies proposed that accuracy was best when mothers were reporting for their children; suggesting that adult proxies have sufficient levels of recall when reporting for HPV vaccination status (17). These studies did however identify some cases of recall bias as well as social desirability bias (the tendency of survey respondents to give answers that they think are more socially acceptable) although the researchers still suggested adult proxies report reasonably accurate measures of coverage (16).

Ultimately, almost all of the studies examined concluded that coverage estimates using parental recall indicated high concordance with vaccination cards or medical records. Furthermore, several studies also noted discrepancies among proxy coverage estimates with respect to the age of the individual, medication in question, and other demographic characteristics (13). One such study, using household-retained vaccination cards and parental recall actually indicated that household-retained vaccination cards were an inconsistent source for information in estimating overall vaccination coverage

and that instead estimates based on recall were closer to estimates of coverage from medical records (13). Results from this study also suggest that routine immunization is comprised of a series of events spanning a period of several months rather than a single, memorable event and is therefore more susceptible to misclassification bias (13). In contrast, most integrated mass drug administration programs consist of a single, large scale effort annually and involve several healthcare workers and researchers who travel to sometimes incredibly rural areas to deliver treatment. These results suggest high levels of concordance between administrative reports of coverage and proxy recall and further support the idea that proxy recall may not only be less subject to misclassification bias but also can act as reliable estimates of drug coverage for entire populations.

Chapter II: Manuscript

Title: Understanding the characteristics of individuals requiring a proxy response for mass drug administration coverage surveys and the potential for recall bias

Authors: Rini Jose, Katherine Gass

Abstract:

The success of mass drug administration (MDA) for neglected tropical diseases is dependent upon achieving adequate drug coverage, which is validated through household coverage surveys. Coverage surveys rely on respondent recall and often permit proxy responses, whereby another household member is allowed to respond on behalf of an absent individual. This study used data from coverage surveys for lymphatic filariasis in Malawi, Burkina Faso, and Uganda to determine the demographic characteristics of individuals for whom a proxy response was required and the extent to which a proxy response was associated with reported drug coverage. According to our results, teenagers and young adults (11 – 25 years) were more likely to be absent during the coverage survey and require a proxy response, compared with older adults. Similarly, males were more likely to require a proxy response than females. Adults who were eligible to receive MDA for lymphatic filariasis (i.e. everyone, excluding women who are pregnant or in the first week of breastfeeding and the severely ill) were more likely to be absent and require a proxy response than individuals who were ineligible for MDA. A multivariate analysis found that individuals for whom a proxy response was provided had 1.5199 times the odds of being recorded as having swallowed the drugs compared to self-reporting individuals, controlling for age and sex (95% CI (1.0308, 2.2409)). This finding is surprising, given that individuals who are unavailable at the time of a coverage survey

may also have been unavailable at the time of MDA, and suggests that proxy respondents may be inflating drug coverage. This finding could be explained in part by the fact that self-reporting individuals are more likely to have been ineligible to receive MDA and thus are expected to have lower coverage; however this does not account for the entire increase in odds. This study highlights the possibility for recall bias in proxy responses to MDA coverage and suggests that further research in necessary to determine the best method for obtaining information on drug coverage when individuals are absent.

Introduction:

Neglected Tropical Diseases (NTDs) are a group of seventeen communicable diseases prevalent among the world's poorest populations in approximately 149 countries, affecting more than one billion people (1). These illnesses, when left untreated, can lead to dire health and socio-economic consequences for families and individuals living in the countries where they exist including impaired childhood growth and development, hindered economic prosperity, and the risk of life-long morbidity (2-4). Of the thirteen WHO-recognized NTDs, there are seven that through mass drug administration, the WHO hopes to effectively control and even eradicate (6). These diseases are treated with regular distribution of single-dose chemotherapy to an entire at-risk population with the idea that successive, adequate coverage of mass drug administration (MDA) can reduce the prevalence of infection and in some cases, lead to elimination (7). Therefore, MDA coverage must be maintained and maximized in order to achieve successful NTD control and elimination programs (7).

The World Health Organization is one of the many international bodies that help monitor and evaluate the effectiveness of this protocol, particularly through measurements of nationwide drug coverage. The measurement of drug coverage is essential to the effectiveness of the MDA because it is a core indicator of success of the program (8). Of the several methods to measure drug coverage, population-based surveys are the most widely used and generally result in the most valid estimates of true coverage. Population-based surveys are independent of the issues associated with incomplete reporting or unreliable data and are thus generally considered the "gold standard" for assessing coverage (11). One major criticism, however, with the population-based drug coverage survey approach to assess compliance with the MDA program is the issue of recall bias.

Recall bias is the ability to correctly recall whether, in this case, an individual has actually ingested a medication or not and therefore affects an individuals' ability to correctly respond to survey questions (7). This potential issue is further complicated when we consider proxy responses. Proxy responses are responses that individuals can give on behalf of others, if they are unable to be reached when the surveys are administered and in many cases can involve women answering for their spouses or children (11). Many researchers employ proxy responses for ease of measurements and convenience. However, proxy responses and recall bias within drug coverage surveys have rarely been formally tested, particularly following mass drug administration programs (8). To assess the quality of proxy responses compared to self-reported drug coverage estimates, a population-based survey was conducted following MDA for lymphatic filariasis in Burkina Faso and Malawi and an integrated MDA for lymphatic

filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis and trachoma in Uganda.

Methods:

Data for the study was collected following MDA program implementation in Burkina Faso, Uganda, and Malawi separately. The original purpose of the multi-country study was to compare coverage survey methodologies in the three countries by conducting three independent coverage surveys in each country – using three different survey methodologies. This present study is a secondary analysis of the original data, with the objective to determine what demographic characteristics affect the probability of a proxy response and to elucidate the relationship between proxy responses and drug coverage estimates.

In-Country Team Members

In each country, survey data was collected by two surveyors: one record keeper, in-charge of recording the time of arrival and the survey responses in a hand-held electronic device; and one interviewer in charge of interviewing the respondents and showing examples of medication offered during the MDA. At least one person in each pair was familiar with the study area and spoke the local language. One person at the country level was designated as the study evaluator, and another the country-level principal investigator. The study evaluator was responsible for overseeing the feasibility of surveys, as well as protocol adherence.

Study Area and Sampling Design

In each country three separate survey methodologies were employed: the Expanded Programme on Immunizations cluster survey methodology (EPI), probability proportionate to estimated size sampling using segmentation and enumeration to select households (PSS) and lot quality assurance sampling – this latter method was dropped from the current analysis due to a lack of household-level data. In both the EPI and PSS methodologies, thirty census enumeration areas (EAs), or clusters, were selected from amongst all the EAs in each district using probability proportional to estimated size sampling. For the EPI approach, within each selected EA, households were selected randomly, by spinning a bottle. Team members enumerated all households from the starting point to the periphery of the enumeration area, and randomly selected a number to determine which household would be the first selected for interview. For the PSS approach, a segment of approximately 50 households was first selected within each EA and a fixed fraction of the households from within each segment were included in the study. In both the EPI and PSS methods all household members were interviewed for the coverage surveys. .

In Malawi and Burkina Faso each method was conducted independently in a separate district. Districts within the same country were chosen to have similar characteristics, with regards to NTD endemicity, population density and geography. In Uganda all three survey methods were conducted as independent surveys in the *same* district, with the surveys conducted sequentially starting with PSS, followed by LQAS and then the EPI method. In Malawi and Burkina Faso coverage of albendazole and ivermectin was assessed with a single question (e.g. “did you swallow the albendazole and ivermectin offered during the recent MDA?”). The Ugandan survey, in contrast, was

an integrated assessment of multiple drugs (albendazole, ivermectin, praziquantel, and azithromycin). Each individual was asked separate questions for having ingested each drug.

Eligibility and Exclusion Criteria

Ideally, all individuals who were living in the household during the time of the last MDA are enumerated. This includes individuals who may have been eligible (e.g. pregnant women), those who may not currently reside in the household, or those who were not present at the time of the survey. Respondents were excluded from the present analysis if they were unsure of their drug coverage status or if the individual was 10 years old or younger.

Measures

The main outcome variable considered was considered drug coverage status, which was defined as "yes" (having ingested the drug) or "no" (not ingesting the drug). The main predictor variable was proxy response status, which was defined as "yes" (someone else responded on behalf of the individual) or "no" (self-report). If individuals were proxy respondents, the characteristics (i.e. sex, age, etc.) recorded in the coverage survey were those of the individual they were responding for, rather than the respondent themselves. Covariates considered in the analysis were demographic characteristics such as age of respondent (continuous, but later categorized as 25 or above years of age or less than 25 years of age), sex of respondent (female or male), and eligibility for MDA (yes or no). Geographic characteristics including district, household number and enumeration area were also considered.

Data Analysis

Data cleaning and analysis was performed using SAS version 9.4 (Cary, NC). Univariate analysis was performed using SAS PROC FREQ to assess the relationship between drug coverage status or proxy response status and covariates of interest. A predictive model was fit using SAS PROC LOGISTIC to determine demographic characteristics associated with proxy response status. Multivariate analysis was performed using SAS PROC GLIMMIX to determine associations between drug coverage status and proxy response status, controlling for demographic characteristics and evaluating interaction terms of interest. Interaction terms were evaluated using likelihood ratio testing and backwards elimination procedures. Model fit statistics including Pearson's correlations, R^2 correlations, AIC statistics, Receiver Operating Curves and corresponding areas under the curve were considered when selecting the best models. Random intercepts were evaluated using the COVTEST option in SAS PROC GLIMMIX to evaluate independence, and significance of random effects. Collinearity was evaluated by assessing collinearity diagnostics including condition indexes and variance decomposition proportions (VDP's). Results were reported at the p=0.05 level of significance.

Results:

Demographic Characteristics

The total sample was composed of 12,338 responses, of which 4,311 (34.9%) responses were proxy responses, and 8,027 (65.1%) responses were self-reported [Table 1]. In addition, 529 responses were missing both the main predictor variable, proxy

response status, and the main outcome variable, drug coverage status, due to absence or refusal of consent to participate in the survey [Table 1 and 2]. Approximately 96.9% (11,411 respondents) were eligible for MDA medications, meaning they were eligible to receive medications, and responded with either a yes or no when asked about their drug coverage status [Table 1 and 2]. Among all responses; 1,942 (15.7 %) respondents were asked about albendazole, 1,953 (15.8%) were asked about ivermectin, 4,598 (37.3%) were asked about both ivermectin and albendazole combined, 1,912 (15.5%) were asked about praziquantel, and 1,933 (15.7%) were asked about azithromycin [Table 1 and 2].

Considering the same individuals in Uganda were asked about multiple medications, further analyses were restricted to coverage of albendazole only or ivermectin and albendazole combined (to avoid over-counting individuals), resulting in a total of 6,540 respondents [Table 1 and 2]. Of these respondents, 26.2% (1,942) were from Uganda, 34.1 % (2,229) were from Malawi, and 36.2% (2,369) were from Burkina Faso [Table 1 and 2]. More than half of the respondents were female, 3,530 (54.0%) [Table 1 and 2]. Similarly, the average age of respondent ranged from 11 years to 106 years; but for ease of analysis respondent age was dichotomized at the approximate median age of 25 years [Table 1 and 2]. The median respondent age for the total sample was 26 years, with an interquartile range of 24 years [Table 1 and 2].

Among individuals who reported receiving drugs, approximately 2,780 (39.9%) were proxy responses, compared to 4,195 (60.1%) who were self-reporters [Table 1]. These observations were similar among individuals who did not receive drugs, resulting in 28.6% (1,531) proxy responses and 61.6% (3,303) self-reporters [Table 1]. 529 individuals were missing drug coverage status and proxy response status due to an

absence or refusal of consent during the coverage survey [Table 1 and 2]. Among those individuals who did not receive any medication, 78.3% (1,227) were eligible to receive medications [Table 1]. The median age of individuals who received drugs was 25 years old, similar to the median age of individuals who did not receive drugs at 26 years old [Table 1]. The χ^2 test of association was highly significant at $\alpha = 0.05$, with an associated p-value of less than 0.0001 for the association between drug coverage status and: proxy response status, eligibility, drug package, and country [Table 1]. The χ^2 test of association was not significant at $\alpha = 0.05$, between drug coverage status and sex and between drug coverage status and dichotomized age [Table 1].

Among self-reporting respondents, 4,195 (52.3%) received medication, compared to 3,303 (41.2%) who did not receive any medication [Table 2]. Among proxy respondents, however, approximately 64.5% (2,780) received medications, compared to 35.5% (1, 531) who did not receive any medications [Table 2]. Similarly, although individuals who self-reported had a median age of 28 years old, proxy responses had a median age of 22 years old [Table 2]. The χ^2 test of association was highly significant at $\alpha = 0.05$, with an associated p-value of less than 0.0001 between drug coverage, eligibility, dichotomized age, drug package, country, and sex with drug coverage status [Table 2].

Multivariate Model Describing Proxy Response Status

A multivariate model to describe proxy response status was fit, where dichotomized age, sex, eligibility to participate in the MDA, district of respondent, and product terms between age and gender, age and eligibility, and gender and eligibility

variables were all under consideration. A likelihood ratio test was used to determine the significance of interaction terms, which resulted in a 7.81 test statistic under χ^2 distribution with three degrees of freedom. Based on these results, we failed to reject the null and conducted backwards elimination model selection procedures. Backwards elimination resulting in dropping all product terms but the dichotomized age by sex interaction term. The final model selected as the best model has statistically significant parameter estimates for all variables included in the model [Table 3]. The final models' goodness of fit was assessed using deviance statistics and Pearson's statistics, but both p-values were highly statistically significant ($p < 0.0001$) indicating poor fit. A Receiver Operating Curve was fit to determine how well the multivariate model was able to determine proxy responses from self-reporting individuals, using the covariates of interest. Using this test, the area under the curve was calculated to be 0.7130, indicating fair deterministic capabilities.

According to the model, the odds of having a proxy response comparing eligible individuals to ineligible individuals were statistically significant for women younger than 25 years old and men for both age groups [Table 4]. For example, the odds of having a proxy response among men eligible for MDA aged 25 years or older is 3.238 times the odds of having a proxy response among men who are ineligible for MDA aged 25 years or older (95% Confidence Interval: 2.1062, 0.5982) [Table 4]. The odds of having a proxy response among men eligible for MDA aged younger than 25 years old is 5.0381 times the odds of having a proxy response among men who are ineligible for MDA aged 25 years or older (95% Confidence Interval: 3.2807, 7.7367) [Table 4]. The odds of having a proxy response among individuals varied by district as well, with statistically

significant odds ratios comparing individuals living in Diebougou (Burkina Faso) to individuals living in Amuru (Uganda) across all age and sex categories [Table 4]. This final multivariate model, on average, described the odds of having a proxy response as higher among individuals aged less than 25 years old compared to women 25 years old or older [Table 4]. This relationship was preserved among men, as well, where the odds of having a proxy response among men were higher among individuals aged less than 25 years old compared to men 25 years old or older [Table 4]. Conversely, the odds of having a proxy response among individuals aged 25 years old or older was higher among men compared to women [Table 4]. This relationship was also observed among individuals less than 25 years old [Table 4].

Unadjusted Associations between Drug Coverage Status and Covariates of Interest

Unadjusted odds ratios between drug coverage status and covariates of interest were determined with their associated 95% confidence intervals, and are shown in Table 5. The odds of receiving medications among proxy respondents was 1.773 (95% CI: (1.562, 2.012)) times the odds of receiving medications among self-respondents. The odds ratios comparing the odds of receiving medications among individuals older than 25 years old and the odds of receiving medications among individuals less than 25 years old (1.058, 95%CI: (0.941, 1.190)) and comparing the odds of receiving medications among men and the odds of receiving medications among women (0.969, 95% CI: (0.862, 1.089)) were both non-significant at the 0.05 significance level [Table 5]. In contrast, the odds ratios comparing the odds of receiving drugs at various districts to the odds of receiving drugs in the Amuru district, Uganda were all significant at the 0.05 significance

level [Table 5]. These district-level variables were further considered in the multivariate model as random intercepts.

Hierarchically-nested Multivariate Model with Drug Coverage Status Outcome

A hierarchically-nested multivariate model with drug coverage status as the outcome was fit, with district, enumeration area (EA), proxy response status, dichotomized age, sex, and interaction terms with proxy response by gender and proxy response by dichotomized age were all under consideration. Both district and EA were considered as random intercepts in the model. Initially, tests of collinearity was run to determine if any collinearity issues were present prior to model selection. Using cut-points of greater than 30 for conditional indexes and variance decomposition proportions of greater than 0.5 to indicate collinearity, no collinearity issues were present. A SAS CONTRAST statement was used to determine the significance of interaction terms, which resulted in a 0.31 test statistic under χ^2 distribution with two degrees of freedom. Based on this result, we failed to reject the null and conducted backwards elimination model selection procedures. Through backwards elimination, both interaction terms were dropped from the model. Using PROC GLIMMIX, a multivariate model was fit using the EMPIRICAL option to retain conservative estimates assuming the variance-covariance matrix specified within the procedure was not correct.

The COVTEST option in PROC GLIMMIX was used to assess independence of the covariates and the significance of random effects. Both tests yielded highly statistically significant results, indicating that the model is not independent and the random effects accounted for in the model are statistically significant. Therefore, the final

multivariate model fit describing the outcome drug coverage status involved proxy response status, dichotomized age and gender as the explanatory variables and had statistically significant variables for random intercepts by EA within districts.

Final Model: $Y_{ij} = \beta_0 + \beta_1(\text{Proxy\_Response})$

$+ \beta_2(\text{Binary\_Age})$

$+ \beta_3(\text{Sex})$

$+ b_{0i}$

$+ e_{ij}$

According to the above final model, the odds of receiving drugs among proxy respondents within this drug coverage survey was 1.5199 (95% CI: (1.0308, 2.2409)) times the odds of receiving drugs among self-reporters, controlling for age and sex [Table 5]. Neither the odds of receiving medications across dichotomized age categories nor the odds of receiving medications across sex categories were statistically significant [Table 5]. Similarly, although the odds of receiving medications among proxy respondents compared to the odds of receiving medications among self-respondents is constant across all of the EAs considered, each EA has a different starting likelihood of drug coverage, represented by the statistically significant random intercepts included in the final multivariate model.

A sensitivity analysis was conducted by fitting the same multivariate model as above, after removing ineligible individuals from the data. According to these results, the odds of receiving drugs among proxy respondents within this drug coverage survey was 1.3364 (95% CI: (0.9051, 1.9731)) times the odds of receiving drugs among self-

reporters, controlling for age and sex. These results are similar to the results using both eligible and ineligible individuals, however once ineligible individuals were removed, the association between proxy response and drug coverage was no longer statistically significant at $\alpha = 0.05$ significance level.

Discussion:

Proxy responses can often pose problems to survey designers because, although proxy responses are convenient – they reduce non-response rates and, in some cases, reduce the cost of data collection – previous research has not produced conclusive evidence to suggest that proxy responses are accurate in their ability to approximate self-reporting (18). The intent of this study was to evaluate the extent to which proxy response status affects reported drug coverage among persons receiving preventative chemotherapy through MDA in Uganda, Burkina Faso, and Malawi. A secondary aim was to assess demographic characteristics that describe proxy response status. We found that age, gender, eligibility for MDA, and residential district all affect the likelihood that an individual will have a proxy response in a coverage survey [Table 4]. According to our results, on average, individuals older than 25 years are less likely to have proxies, but males and individuals that are eligible for MDA are more likely to require proxy responses. This could be because males are more likely to work outside the home, due to social and cultural constructs in the countries studied (19-21).

According to the previous body of literature, men are more likely to work outside the home, and similarly are more likely to pursue education for longer periods of time than women (19-21). Research also suggests that although there is a general rise in school

enrollment across Africa, in most places there is a persistent gender gap present such that men are more likely to be in school than their female counterparts (19, 21). It has been suggested that these discrepancies exist because parents are more likely to invest in a sons' education than a daughters' (21). The gender gap in education level and employability in the study area may contribute to the differences observed in this studies' results. If men are more likely to pursue higher education or be employed outside the home, they will then be more likely to be unable to be contacted when interviewers conduct surveys and therefore would necessitate proxy respondents. It is also possible that individuals who were not available to be asked directly during the survey may not have been available for the actual distribution of the medication, although further research is necessary to clarify these relationships.

The results presented here also suggest that individuals reporting on behalf of others (proxy respondents) might be more likely to report receiving drugs than self-reporters. These results are in contrast with some previous published literature, which suggest that proxy respondents actually underestimate true medication coverage (12). This could be due to social desirability bias among proxy respondents, who feel pressured to report individuals receiving drugs rather than not receiving them (18). Social desirability bias, i.e. reporting that an individual took medications when they did not, could have resulted in higher drug coverage estimates among proxy responses than among self-reporters. Similar studies assessing NTD control measures in other countries suggest that social desirability bias may be particularly salient in communities such as these because study respondents are incredibly vulnerable, and may have felt that responding negatively to MDA programs or to receiving drugs in general could have

impacted their future treatment or employment (22). Unfortunately, the results presented here do not have a "gold standard" against which to compare, therefore proxy responses may actually accurately represent medication adherence in these populations. Further studies on MDA and proxy responses are necessary to support these associations, with emphasis on concordance studies.

These results also indicate that the odds of proxy response among individuals eligible for receiving medication was, on average, higher than the than the odds of proxy responses among individuals who were not eligible for receiving medication [Table 4]. This relationship was statistically significant among women less than 25 years old, and men of both age groups [Table 4]. Eligibility in this study was defined such that individuals who reported receiving or not receiving medications were considered eligible, and those that reported ineligible drug coverage were considered ineligible. Women are considered ineligible for medication if they are pregnant, in the first week of breastfeeding, or are severely ill. Men are only considered ineligible if they are severely ill at the time of MDA.

According to our results, eligible individuals are more likely to have a proxy response rather than self-reported drug coverage. Given that individuals, particularly men, may not be available to self-report receiving medication due to school or work outside the home, these results may explain in part why proxy respondents report higher levels of coverage – they are more likely to be eligible to have taken the MDA medications (19-21). Conversely, it is possible that if these individuals were not available to report receiving medications during the drug coverage surveys and thus needed a proxy to respond on their behalf, it could be expected that proxy respondents would

report lower levels of drug coverage, which is not what was observed in our results [Table 2]. However, these results were limited to include only questions about albendazole separately and albendazole and ivermectin together; therefore further research assessing all of the preventative chemotherapy medications distributed in these areas might yield different results. Ultimately, our results necessitate further studies assessing proxy responses and drug coverage estimates in MDA settings to better elucidate these relationships. Furthermore, our results highlight some of the difficulties of conducting field studies in resource-poor settings, and suggest several potential improvements for future studies of proxy response accuracy.

Strengths and Limitations

This study has several notable strengths and limitations. First and foremost, it is one of the first studies to assess proxy reporting in the setting of MDA for NTDs. This study also benefits from a large sample size and increased statistical power. Similarly, the data included three separate countries, which provided an opportunity to assess proxy responses and drug coverage estimates in three separate locations with differing NTD endemicity and drug distribution mechanisms. Several limitations exist, including the lack of data collected among the individuals the proxy respondents were assessing, which could have provided valuable assessments on validity and concordance on drug coverage estimates among this population. Furthermore, the questions asked to individuals differed across countries, so there was a lack of available data to assess attitudes or incorporate household-level correlation into models. Similarities in data collection methods or questions asked by interviewers could have better allowed for amalgamated data to be assessed across countries.

It is important to note that coverage surveys (including population-based surveys in general) are useful only to the extent that the survey population is representative of the general population of interest (8). This study was conducted among three countries in Africa (Burkina Faso, Uganda and Malawi) and utilized probability sampling procedures and is therefore likely to be representative of these countries. Whether these results are representative of other areas in Africa or even of other areas of the world is hard to say, but important to keep in mind when planning future surveys (8). In addition, due to available data, surveys administered in Uganda assessed each drug included in the MDA (albendazole, praziquantel, ivermectin, and azithromycin) separately, so individuals from Uganda included in analyses were limited to reporting albendazole separately which improved ease of analysis but decreased sample size as well as geographic locations (districts and enumeration areas) studied.

Despite its limitations, this study provides several important insights. First and foremost, age, sex, and eligibility to receive preventative chemotherapy medications are strongly associated with whether or not a proxy response is used. Similarly, proxy responses are highly associated with greater odds of reporting ingesting medication following an MDA program. Further studies that emphasize concordance between self-reported drug coverage and proxy-reported coverage could be important to determine the reliability of proxy-reported coverage in MDA programs. Perhaps future studies may also consider contacting respondents that are absent at the time of a MDA program through alternate means (including cellphones or email) before relying on a proxy response, given the ubiquity of this technology in study areas. Ultimately, reducing the prevalence of NTDs worldwide is contingent upon the success of a MDA program, which hinges upon

achieving high coverage of MDA. Coverage surveys are a good tool for validating if high coverage has been achieved and often rely on both self-reported and proxy responses to measure drug coverage. Determining the reliability of proxy responses could be a significant contribution in the control and eventual eradication of NTDs across the globe.

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Tables

Table 1. Characteristics of Respondents of a Multi-Country Neglected Tropical Disease Preventative Chemotherapy Drug Coverage Survey by Drug Coverage Status[a]

	All Responses (n=12338)		Did Not Receive Drugs (n=4834)		Received Drug(s) (n=6975)		Chi-square Test of Association
	No.	%	No.	%	No.	%	χ2 (p-value)
Proxy Response Status[b]							170.58 (p < 0.0001)
Yes	4,311	34.9	1,531	28.6	2,780	39.9	
No	8,027	65.1	3,303	61.6	4,195	60.1	
Eligible							548.07 (p < 0.0001)
Yes	11,411	96.9	1,227	78.3	4,973	100.0	
No	368	3.1	207	13.2	0	0.0	
Missing	529	4.3	133	8.5	0	0.0	
Age, years[c,d]	26	24.0	25	20.0	26	24.0	0.90 (p = 0.3426)
Drug[a,e,f]							3997.49 (p < 0.0001)
Albendazole	1,942	15.7	985	50.7	825	42.5	
Ivermectin	1,953	15.8	720	36.9	1,101	56.4	
Ivermectin and Albendazole	4,598	37.3	449	9.8	4,148	90.2	
Praziquantel	1,912	15.5	1,299	67.9	481	25.2	
Zithromax	1,933	15.7	1,381	71.4	420	21.7	
Country[f]							1719.11 (p < 0.0001)
Burkina Faso	2,369	100.0	123	5.2	2,245	94.8	
Malawi	2,229	100.0	326	14.6	1,903	85.4	
Uganda	1,942	100.0	985	50.7	825	42.5	
Sex							0.28 (p = 0.5969)

Female	3,530	54.0	801	55.9	2,681	53.9
Male	3,010	46.0	633	44.1	2,292	46.1

[a]529 responses are missing drug coverage due to absence or refusal of consent
[b]529 responses are missing proxy response status

[c]Median (IQR)

[d]Chi-squared test of association reflects binary age, where 1 indicates ages 25 years old and above and 0 indicates ages less than 25 years old

[e]Individuals in Uganda were asked about albendazole, ivermectin, praziquantel and zithromax separately.

[f]Row percentages reported, stratified by drug coverage

Table 2. Characteristics of Respondents of a Multi-Country Neglected Tropical Disease Preventative Chemotherapy Drug Coverage Survey by Proxy Response Status[a]

	All Responses (n=12338)		Self-Report (n=8027)		Proxy Response (n=4311)		Chi-square Test of Association
	No.	%	No.	%	No.	%	χ2 (p-value)
Drug Coverage[b]							170.58 (p < 0.0001)
Yes	6,975	59.1	4,195	52.3	2,780	64.5	
No	4,834	40.9	3,303	41.2	1,531	35.5	
Eligible							76.18 (p < 0.0001)
Yes	11,411	96.9	3,747	92.4	2,453	98.8	
No	368	3.1	176	4.3	31	1.3	
Missing	529	4.3	133	3.3	0	0.0	
Age, years[c,d]	26	24.0	28	23.0	22	21.0	77.82 (p < 0.0001)
Drug[e,f]							105.95 (p < 0.0001)
Albendazole	1,942	15.7	1,328	68.4	614	31.6	
Ivermectin	1,953	15.8	1,332	68.2	621	31.8	
Ivermectin and Albendazole	4,598	37.3	2,728	59.3	1,870	40.7	
Praziquantel	1,912	15.5	1,314	68.7	598	31.3	
Zithromax	1,933	15.7	1,325	68.5	608	31.5	
Country[f]							246.35 (p < 0.0001)
Burkina Faso	2,369	100.0	1,171	49.4	1,198	50.6	
Malawi	2,229	100.0	1,557	69.9	672	30.1	
Uganda	1,942	100.0	1,328	68.4	614	31.6	
Sex							148.09 (p < 0.0001)
Female	3,530	54.0	2,430	59.9	1,100	44.3	
Male	3,010	46.0	1,626	40.1	1,384	55.7	

[a]529 individuals are missing proxy response status due to absence or refusal of consent

[b]529 individuals are missing drug coverage

[c]Median (IQR)

[d]Chi-squared test of association reflects binary age, where 1 indicates ages 25 years old and above and 0 indicates ages less than 25 years old
[e]Individuals in Uganda were asked about albendazole, ivermectin, praziquantel
and zithromax separately.
[f]Row percentages reported, stratified by
proxy response status

Table 3. Multivariate Model Describing Proxy Response Using Covariates of Interest Taken From a Multi-Country Neglected Tropical Disease Preventative Chemotherapy Drug Coverage Survey[a]

Variable Considered	Parameter Estimate	Standard Error	p-value
Intercept	-1.4210	0.2114	$p < 0.0001$
Age, years			
25 years or older	-0.6710	0.0802	$p < 0.0001$
Less than 25 years old	ref		
Sex			
Male	0.5659	0.0798	$p < 0.0001$
Female	ref		
Eligible			
Yes	1.0512	0.2122	$p < 0.0001$
No	ref		
District			
Batie	-0.2529	0.058	$p < 0.0001$
Diebougou	1.3035	0.0585	$p < 0.0001$
Machinga	-0.6523	0.0611	$p < 0.0001$
Zomba	-0.1476	0.0588	$p = 0.0121$
Amuru	ref		
Age*Sex[b]	0.2289	0.1126	$p = 0.0420$

[a]132 missing proxy response status due to lack of consent

[b]This term represents the interaction between categorized age and sex, where the associated odds ratio represents the odds of proxy response for a 25 year or older man

Table 4. Multivariate Model Describing Proxy Response Using Covariates of Interest Taken From a Multi-Country Neglected Tropical Disease Preventative Chemotherapy Drug Coverage Survey[a]

Variable Considered	Age < 25 years old, Sex = Male	95% Confidence Interval	Age ≥ 25 years old, Sex = Male	95% Confidence Interval
Eligible				
Yes	5.0381	(3.2807, 7.7367) *	3.238	(2.1062, 4.9780) *
No	ref		ref	
District[b]				
Batie	1.7569	(1.4048, 2.1973) *	1.1292	(0.9059, 1.4076)
Diebougou	8.3316	(6.6054, 10.5090) *	5.3548	(4.2817, 6.6969) *
Machinga	1.1784	(0.9317, 1.4904)	0.7574	(0.6021, 0.9527) *
Zomba	1.9520	(1.5491, 2.4599) *	1.2546	(1.0006, 1.5730) *
Amuru	ref		ref	

Variable Considered	Age < 25 years old, Sex = Female	95% Confidence Interval	Age ≥ 25 years old, Sex = Female	95% Confidence Interval
Eligible				
Yes	2.861	(1.8873, 4.3368) *	1.4625	(0.9427, 2.2689)
No	ref		ref	
District[b]				
Batie	0.9977	(0.8465, 1.1760)	0.5100	(0.4097, 0.6349) *
Diebougou	4.7313	(4.0085, 5.5844) *	2.4186	(1.9539, 2.9938) *
Machinga	0.6692	(0.5641, 0.7939) *	0.3421	(0.2708, 0.4321) *
Zomba	1.1085	(0.9388, 1.3089)	0.5667	(0.4520, 0.7104) *
Amuru	ref		ref	

[a]132 missing proxy response status due to lack of consent

[b]Odds ratios describing proxy response using district level variables were estimated using indicator/dummy variables, rather than effects coding used for parameter estimates

*Statistically significant at the $\alpha = 0.05$ level.

Table 5. Unadjusted and Adjusted Odds Ratios Between Covariates of Interest and Outcome of Drug Coverage Status, Taken From Respondents of a Multi-Country Neglected Tropical Disease Preventative Chemotherapy Drug Coverage Survey[a]

	Received Drugs (n=6975)		Received Drugs	
	unadjOR	**95% Confidence Interval**	**adjOR**	**95% Confidence Interval**
Proxy Response Status				
Yes	1.773	(1.562, 2.012)	1.5199	(1.0308, 2.2409)
No	ref		ref	
Age, years[b]				
25 years or older	1.058	(0.941, 1.190)	0.8150	(0.5799, 1.1456)
Less than 25 years old	ref		ref	
Sex				
Male	0.969	(0.862, 1.089)	0.9317	(0.6817, 1.2549)
Female	ref		ref	
Country[b]				
Burkina Faso	10.259	(8.385, 12.551)		
Malawi	2.299	(2.002, 2.639)		
Uganda	ref			
District[b]				
Batie	31.011	(22.822, 42.138)		
Diebougou	23.803	(18.195, 31.139)		
Machinga	8.073	(6.667, 9.775)		
Zomba	7.966	(6.547, 9.694)		
Amuru	ref			

[a]132 missing drug coverage status due to lack of consent

[b]Country and district were included in the final model by including a random intercept term that adjusted for the hierarchy of EA within District

Chapter III: Summary, Public Health Implications, Possible Future Directions

Summary

The intent of this study was to evaluate the extent proxy response status affects drug coverage status among persons receiving preventative chemotherapy treatments following an MDA program in Uganda, Burkina Faso, and Malawi. A secondary aim was to assess demographic characteristics that describe proxy response status. The results presented in this study indicate that age, gender, eligibility for MDA, and residential district all affect the likelihood an individual's response in drug coverage surveys will be through a proxy respondent. Using a model intended to describe characteristics associated with proxy response status, we found that men and individuals eligible for MDA are more likely to require a proxy respondent. These findings could be due to several factors, like the gender gap among men and women in the workplace as well as education level that contributes to the social and contextual context of the study area.

According to the previous body of literature, men are more likely to work outside the home, and similarly are more likely to pursue education for longer periods of time than women (19-21). Research also suggests that although there is a general rise in school enrollment across Africa, in most places there is a persistent gender gap present such that men are more likely to be in school than their female counterparts (19, 21). It has been suggested that these discrepancies exist because parents are more likely to invest in a sons' education than a daughter (21). The gender gap in education level and employability in the study area may contribute to the differences observed in this studies' results. If men are more likely to pursue higher education or be employed outside the

home, they will then be more likely to be unable to be contacted when interviewers conduct surveys and therefore would necessitate proxy respondents.

The results presented here also suggest that individuals reporting on behalf of others (proxy respondents) might be more likely to report receiving drugs than self-reporters. These results are in contrast with some previous published literature, which suggest that proxy respondents actually underestimate true medication coverage (12). This could be due to social desirability bias among proxy respondents, who feel pressured to report individuals receiving drugs rather than not receiving them (18). Social desirability bias, i.e. reporting that an individual took medications when they did not, could have resulted in higher drug coverage estimates among proxy responses than among self-reporters. Similar studies assessing NTD control measures in other countries suggest that social desirability bias may be particularly salient in communities such as these because study respondents are incredibly vulnerable, and may have felt that responding negatively to MDA programs or to receiving drugs in general could have impacted their future treatment or employment (22).

Public Health Implications

Ultimately, reducing the prevalence of NTDs worldwide is contingent upon the success of a MDA program, which can often include proxy respondents and self-reports as measures of medication coverage. Determining the reliability of these measures could be a significant contribution in the control and eventual eradication of NTDs across the globe. Although the present study is unable to directly measure the validity of proxy responses in drug coverage surveys following an integrated MDA, our

results do have valuable contributions to the body of literature surrounding NTDs. Most importantly, proxy responses are more likely to respond that individuals have received the medications in question compared to self-reporters. This is particularly important because it could be an indication that proxy respondents are susceptible to social desirability and are therefore, report that individuals have received medications when they may not have. More research is necessary to truly determine the reliability of a proxy response, however, as it is possible that these individuals are reporting accurately in terms of overall drug coverage estimates.

Our research has suggested that age, sex, and eligibility to receive preventative chemotherapy medications are strongly associated with whether or not a proxy response is used. Similarly, proxy responses are associated with greater odds of ingesting medication during the MDA, even after controlling for the sex and age of the respondent. It is possible that since these individuals were not available to be asked directly during the drug coverage survey if they received medication, they may not have been available for the actual distribution of the medication, although further research is necessary to clarify these relationships. This is also a significant contribution to the field of public health because of the importance of drug coverage surveys as a measurement tool. Drug coverage surveys are administered after MDA programs as a method of measuring their success, and therefore are integral to controlling and eradicating NTDs worldwide. This research has been able to reveal some truths behind MDA and its effectiveness, but more research is necessary before we can truly understand the role MDA plays in the eradication of NTDs.

Possible Future Directions

Future studies should seek to address the validity of proxy respondents compared to self-reported drug coverage. These studies should also determine the relationship of a proxy respondent to the individual as research suggests that demographic characteristics could also prevent meaningful differences in the quality of proxy responses across categories like education, income, and age (13, 16, 17). Perhaps future studies may also consider contacting respondents that are absent at the time of a MDA program through alternate means (including cellphones or email) before relying on a proxy response. Although there is a body of literature describing concordance between self-report and proxy response, very few studies address these issues in a MDA setting, which could be beneficial for future policies and to adequately measure the effectiveness of preventative chemotherapy medications in controlling and eradicating neglected tropical diseases.