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Integrating NTD Mapping Protocols: Can Surveys for Trachoma and Urinary Schistosomiasis Be Done Simultaneously?

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Abstract.

We determined whether the school-based “disease mapping” methodology used to assess urinary schistosomiasis (SCH) is useful for determining trachoma interventions and whether the district-based approach recommended for trachoma is useful for SCH control programs. We conducted two separate integrated surveys in eight districts of central Nigeria: school based and district based. A total of 17,189 children were examined for trachoma and 16,238 children were examined for hematuria from 363 schools and 2,149 households. School surveys identified 67 communities warranting praziquantel drug treatment of SCH and 142 trachoma-endemic communities warranting trachoma control activities. In district-level estimates, we identified 24 communities for praziquantel treatment and 0 for trachoma intervention. Integrating trachoma into SCH school-based surveys, and SCH into trachoma surveys, was quick and easy, but in this setting, school-based surveys were more useful for identifying communities where intervention is warranted.

INTRODUCTION

The scope and scale of control programs for the newly labeled “Neglected Tropical Diseases” (NTDs) has greatly increased in recent years, whereas resources allocated to them lag far behind that available for malaria, HIV/AIDs, and tuberculosis.¹ In an effort to decrease costs and simultaneously increase populations under NTD intervention coverage, the integration of NTD programs has been aggressively promoted. The argument for integration is based on co-endemicity of the NTDs within countries coupled with similar control activities—most prominently the application of mass drug administration (MDA). However, there is little empiric evidence that integrating previously vertical NTD programs is actually feasible and/or results in cost saving.

Integration of NTD programs for intestinal helminthiasis, lymphatic filariasis, onchocerciasis, schistosomiasis, and trachoma is ongoing within the Ministries of Health in Plateau and Nasarawa States, Nigeria, to test the hypothesis that integration can reduce fixed costs while benefiting more people. One area of integrated program implementation is mapping disease prevalence through surveys. Surveying for one disease provides an opportunity to survey for another; however, different sampling frames are currently used for each NTD. We aimed to assess the feasibility of integrating the two survey methodologies advocated by the WHO for trachoma and urinary schistosomiasis (SCH).

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Indicators for SCH.

Hematuria (blood in the urine) is the most common manifestation of urinary SCH and serves as a useful and rapid assessment proxy for parasitologic testing.⁷⁻⁹ Hematuria was assessed using a rapid reagent strip test, Uripath (Plasmatec Laboratory Products, Bridport, Dorset, UK), that changes color when there is blood in urine. We considered a reagent strip result of +1 or more as a positive indicator for hematuria.

Indicators for trachoma.

Clinical signs of trachoma were assessed using the WHO Simplified Grading System.¹⁰ Examiners recorded the presence or absence of all trachoma grades in both eyes of survey participants using a $\times 2.5$ binocular loupe and adequate light. Findings from the worst eye were reported.

School-based surveys.

We followed the standard mapping protocol for SCH adopted by Plateau and Nasarawa State Ministries of Health adapted from WHO. Because of the dispersed nature of water sources in the two states, one government primary school was selected for inclusion per community in all communities within each LGA. In the rare case where there was more than one school, the survey was conducted in a single school selected using a computer-generated random number. Private schools were excluded. A random sample of children 10–14 years of age were asked to voluntarily provide a urine sample, and children < 10 years of age were examined by an ophthalmic nurse or ophthalmologist for trachoma signs.

Children were systematically sampled in each school. To allow for error or refusal, a minimum of 32 school children in both age groups were selected and asked to participate in this survey. Boys and girls were called to assembly and divided into two age groups; 10–14 and < 10 years. A total count was taken for each group. Field teams applied the total count to a pre-prepared table to identify the sampling fraction required to provide a sample of at least 32 children and a maximum of 47 children. The variation in the number examined resulted from the use of sampling fractions that were easy to use in systematic sampling, such as $\frac{1}{2}$, $\frac{1}{3}$, $\frac{1}{4}$, etc. Once the sampling interval was determined, a random starting point between the first child in line and the sampling interval was selected using a pre-prepared random number from Microsoft Excel. In the situation that < 48 children in the desired age groups were attending school, all children were asked to participate.

District-based surveys.

We followed the standard mapping protocol for Trachoma adopted by Plateau and Nasarawa State Ministries of Health adapted from WHO. We estimated that a total sample size of 1,646 people of all ages and sexes per LGA was required for a precision of $\pm 10\%$ with an estimated TF prevalence in children 1–9 years of 50% and design effect of 4; a precision of $\pm 1.5\%$ with an estimated prevalence of 2.5% TT in adults > 14 years and design effect of 2; and a precision of $\pm 10\%$ with an estimated 50% prevalence of urinary schistosomiasis in children 6–15 years old and design effect of 2.5. For all indicators, we selected an α of 0.05. To estimate the average number of persons in the different age groups, we used data from the Nigeria 2003 Demographic and Health Survey and multiplied the percentage of the total population in these groups by an average household size of six persons based on previous trachoma mapping surveys. We assumed a non-response rate of 10%. The sample size of 1,646 was achieved by selecting 20 clusters of 16 households per LGA.

A multi-stage sampling design was used. In the first stage, clusters were selected by taking a systematic sample of 20 census enumeration areas (EAs) from the list of all EAs in the LGA without regard to the

EA population size. EAs were the smallest geographic unit for which population data was available and, according to the census bureau, have an approximate population of 300–500. EAs were typically smaller than a village, but in some rural areas, the EA was the entire village. The Bureau of the Census provided maps of the selected EAs. After walking the boundaries of the EA, survey teams divided the area into segments of ~16 households and recorded the number of segments. The village chief randomly selected one segment by lottery. All households in the selected segment were surveyed. No selection was conducted within the household; all household residents were examined for trachoma and all school children 6–15 years of age were asked to provide a urine sample for hematuria testing. One follow-up visit was made to any household with missing residents on the day of the survey.

Data management and quality control.

Eight laboratory technicians, 10 ophthalmic nurses, and 16 recorders were trained to conduct the integrated surveys. Laboratory technicians familiar with reagent strip tests were re-trained to perform the urine analysis, and ophthalmic nurses experienced from previous trachoma mapping surveys were re-trained in the WHO grading system. All persons were trained to take systematic samples of children in school, perform segmentation of EAs, randomly select a segment using the lottery method, and record findings on standardized forms. Training included a formal inter-observer reliability test of trachoma grading against a standardized set of 50 slides presented on a computer and two field exams of 50 children each. For WHO grade TF, the nurses' agreement with gold standard ranged from 75% to 90%, with the corresponding κ statistic ranging from 0.35 to 0.73. Ophthalmic nurses selected as examiners for the survey scored > 80% and a κ statistic of 0.6 and above for grade TF. Teams practiced segmentation, household selection, examination, and recording results in EAs not included in the sample.

Data were double-entered and validated. Variables collected included community of residence; age; sex; reported school attendance among children; availability for examination; presence or absence of ocular and nasal discharge; presence or absence of each individual trachoma grade; and negative (0), +1, +2, or +3 hematuria.

LGA-level prevalence estimates from both the school and household surveys were weighted according to the selection probabilities. Additionally, confidence intervals (CIs) for all LGA estimates were adjusted to account for correlation among the data caused by clustering using SAS SURVEYFREQ procedures (SAS version 9.1; SAS Institute, Cary, NC).^{11,12} Also, we tested the null hypothesis that prevalence estimates for each LGA derived from both integrated methodologies were not different by using a two-tailed Z-test with $\alpha = 0.05$.

Ethical considerations.

Standard Ministry of Health procedures for mapping the two diseases were followed. Additionally, this study was approved by the Emory University Institutional Review Board under protocols eIRB-2373 and 079-2006. Informed verbal consent and assent was received before any survey activity according to the principles of the Declaration of Helsinki. A child with a reagent strip positive for hematuria was considered infected and was offered free immediate treatment with praziquantel (40 mg/kg based on height according to WHO guidelines). Communities qualifying for either mass or school age SCH treatment were scheduled for treatment according to Ministry of Health guidelines. All children presenting signs of TF or trachomatous inflammation intense (Grade TI) were offered free tetracycline eye ointment and instructed to apply it twice daily for 6 weeks. Persons identified with TT were recorded, counseled, and referred for free consultation and surgery with a trained TT surgeon.

RESULTS

School-based surveys for SCH and trachoma.

The median school population for children 10–14 years of age was 60 students (inter-quartile range [IQR], 39–107; range, 16–745). For children under 10 years of age, the median population in schools was 61 (IQR, 39–103 students; range, 17–583).

A total of 13,045 children (52.5% boys) < 10 years of age were examined for trachoma from a total of 363 schools in the eight LGAs. The median age of children examined for trachoma in the schools was 7 years (IQR, 6–8 years; range, 3–9 years). The overall prevalence of TF in school children under 10 years of age was 4.6% (95% CI, 4.0–5.1%). Overall, the prevalence of TF in boys was 4.0% (95% CI, 3.4–4.7%) and 5.2% (95% CI, 4.4–6.1%) in girls. There was no significant difference in the likelihood of having TF between boys and girls (odds ratio [OR] = 1.2; 95% CI, 1.0–1.4). No TT cases were found among the examined children.

A total of 12,660 children (55.6% boys) between 10 and 14 years of age were examined for urinary SCH from a total of 363 schools in the eight LGAs. The median age of children examined for schistosomiasis was 12 years (IQR, 11–13 years; range, 8–15 years). The overall prevalence of hematuria was 5.5% (95% CI, 4.3–6.8%). Overall, the prevalence of hematuria in boys was 7.1% (95% CI, 5.5–8.8%) and 3.5% (95% CI, 2.5–4.5%) in girls. Boys were nearly twice as likely to have hematuria as girls (OR = 1.8; 95% CI, 1.6–2.2; $P < 0.01$).

The number of communities warranting public health interventions to control trachoma and SCH are quantified for each LGA in Table 1. We found endemic trachoma exceeding the intervention threshold of 5% TF in children 1–9 years of age in 142 (39%) of the total 363 communities assessed through schools, of which 53 (14.6%) exceeded the 10% threshold used at the district level to trigger mass district-wide intervention. Communities surrounding these 53 schools warranted activities to control trachoma including mass distribution of antibiotic. An additional 89 schools (142 less 53) warranted strategies to promote facial hygiene and the promotion of water and sanitation hardware. For SCH, the survey found that 16% of communities (surrounding the 59 schools having hematuria prevalence $\geq 10\%$) warranted praziquantel treatment of school-aged children, and eight communities (2.2%) warranted mass praziquantel treatment of the total population (hematuria prevalence $\geq 50\%$).

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TABLE 1

Communities warranting intervention to control trachoma and urinary SCH determined by integrated school-based surveys using the SCH protocol*

District-based surveys for SCH and trachoma.

Table 2 lists, by LGA, the results of district-based household surveys. In the LGA-level cluster surveys, a total of 14,571 persons were registered from 2,149 households in the eight LGAs. The overall mean household size was 6.4 persons (range by LGA, 5.9–7.9). Overall, reported school attendance among young children (those < 6 years of age) was 64.5% (range by LGA, 52.2–76.2%) and 93.7% among children 6–15 years of age (range by LGA, 87.2–97.8%). Reported attendance among boys 6–15 years of age was 95.3% and was 91.9% among girls of the same age.

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TABLE 2

Integrated district-based survey results by LGA using the trachoma protocol

A total of 11,192 persons were examined for trachoma for an overall response of 76.8%. The main reason for non-response was not being present at the time of the household visit. Among 4,754 children in the survey 1–9 years of age, 4,144 (87.2%) were examined for trachoma. Overall prevalence of TF, in children 1–9 years of age, was 3.4% (95% CI, 2.7–4.2%; LGA range, 1.7–5.2%; Table 2). In children 1–5 years of age, TF prevalence was 3.6% (95% CI, 2.6–4.6%). Among children 6–9 years of age, the prevalence of TF was 3.2% (95% CI, 2.2–4.2%). The prevalence of TF in boys 1–9 years of age was 2.7% (95% CI, 1.8–3.6%) and was 4.2% (95% CI, 3.2–5.2%) in girls of the same age. Girls were more likely to have TF than boys (OR = 1.6; 95% CI, 1.2–2.3; $P < 0.01$). In all, only 25 cases of trichiasis were identified for an overall prevalence of 0.22% (95% CI, 0.12–0.32%) and 0.37% (95% CI, 0.20–0.54%) in adults > 14 years of age. Not all 25 TT cases were in adults; 5 cases were recorded in those < 15 years of age. The sex distribution of TT cases was 17 in women and 8 in men, which was not statistically significant (OR = 1.8; 95% CI, 0.76–4.1).

Among 4,617 children 6–15 years of age eligible for assessment of hematuria, urine from 3,578 children was examined for a response of 77.5%. There was no difference in the sex distribution of children registered and those examined. The prevalence of hematuria in children ages 6–15 years was 4.5 (95% CI, 2.9–6.0%; range by LGA, 0.73–11.4%; Table 2). Hematuria prevalence in boys was 6.8% (95% CI, 4.3–9.3%) and was 1.8% (95% CI, 0.9–2.8%) in girls. Boys were more likely to have hematuria than girls (OR = 2.9; 95% CI, 2.0–4.2; $P < 0.01$).

Comparison of integrated survey results.

LGA-level estimates of trachoma in children < 10 years of age and hematuria in children 10–14 years of age derived from both district-based and school-based surveys are presented by LGA in Table 3. For comparison, estimates of trachoma were limited to children 3–9 years of age; the age range of examined children in school surveys. For trachoma, the differences between the estimates of TF were not significantly different between the district-based and the school-based surveys for any LGA. Prevalence estimates for TF were < 10% regardless of the methodology used to derive the LGA-level estimate, and no district-wide interventions would be indicated. LGA-level estimates of hematuria derived from trachoma survey methods were different from school-based LGA-level estimates in Jos North ($Z = 2.69$; $P = 0.007$), Jos South ($Z = 4.50$; $P < 0.0001$), Keffi ($Z = 2.66$; $P = 0.008$), and Lafia ($Z = 2.54$; $P = 0.011$) and were not different in the other four LGAs. Both school and district survey methods gave similar results in calling for LGA-wide praziquantel intervention (school-aged children based on a hematuria prevalence of $\geq 10\%$) in Keffi.

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TABLE 3

LGA-level estimates of trachoma and urinary SCH derived from both integrated protocols

Table 4 shows the theoretical programmatic decisions made to target areas for intervention based on interpretation of results obtained from each integrated survey methodology. The integrated survey using the SCH school-based methodology identified 142 communities warranting interventions to control trachoma and 67 communities warranting distribution of PZQ to control SCH. No district-wide trachoma interventions would be warranted. Similarly, using the recommended trachoma district-based survey methodology, no district-wide trachoma interventions are warranted. Three districts, where the rounded point estimate for prevalence of TF was between 5% and 10%, warranted further investigation of all communities to identify trachoma and implement interventions. Theoretically, those additional assessments would identify 81 communities for trachoma interventions, so that 61 (42.9%) of communities that warranted trachoma intervention would have been missed in districts where the district prevalence of TF in children 1–9 years was < 5%. Praziquantel treatment to school children would be targeted only to all communities in Keffi if current community-based treatment thresholds were applied to district-level estimates of hematuria. Basing SCH interventions solely on the integrated trachoma district-based surveys would have missed 57 communities qualified for praziquantel treatment, including all 8 of the hyperendemic ($\geq 50\%$ hematuria prevalence) communities. By treating all 24 communities assessed in Keffi with praziquantel, 14 communities would be treated that actually did not warrant treatment (Table 1).

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TABLE 4

Theoretical programmatic decisions based on results of each integrated mapping methodology

DISCUSSION

In this study, we showed that trachoma and urinary SCH surveys can be done simultaneously using integrated methods. In this setting, combining trachoma examination with urinary SCH surveys in schools gave similar district-based findings. An advantage was that school surveys became the community-by-community approach to assessment advocated where prevalence of TF is < 10% and all trachoma-endemic communities were identified. The practicality of this approach may be limited to areas where school attendance is high, because of the assumption that prevalence estimates from a random sample of school children represent the true prevalence in the surrounding community. Additionally, there was an indication of a slight sex bias in school attendance based on our school survey results. Such differences in attendance could bias disease estimates and affect intervention decisions. Also, the majority of children assessed for trachoma in schools were between the ages of 6 and 9 years. Trachoma studies in hyperendemic areas have shown higher chlamydial loads among preschool-aged than school-aged children,¹³ and increasing age has been associated with a reduced odds of active trachoma.¹⁴ In this study, there was no significant difference in TF prevalence between children 1–5 and 6–9 years of age, which meant implementation decisions between school-based and district-based surveys were the same.

Integrating urine analysis to the district-based household cluster survey methodology used by the global trachoma program was also possible. However, in only four LGAs, a sample of households in 20 clusters provided similar LGA level prevalence estimates of hematuria as LGA-level estimates derived from surveying all schools. Despite the difference between LGA-level estimates in Keffi, both indicate prevalence above the community threshold warranting praziquantel treatment of all school-aged children. Applying treatment thresholds designed for communities to district-level estimates qualified only Keffi

for mass treatment and would have overlooked 57 communities in other LGAs warranting praziquantel. Similarly, the district-level estimates we obtained from the standard trachoma survey were not useful for stratifying SCH communities into those that should have school-aged children treated from those needing community-level interventions. These findings support the current, recommended approach to mapping SCH community by community. However, guidelines for the use of praziquantel to control SCH have become more inclusive in recent years, recommending that all school children receive praziquantel at least twice in their primary school years.⁶ Perhaps models could be developed that would identify district-level thresholds that would maximize coverage of affected areas and potentially reach communities affected by intestinal SCH often overlooked by mapping only for urinary SCH.¹⁵ With a concurrent increased availability of praziquantel, country programs could consider conducting much smaller district-based surveys and targeting resources to provide treatment to more school children with the understanding that many communities may be misclassified if intervention decisions are based on LGA-level estimates.

One limitation of our integrated methodologies was sample size. Trachoma district-based cluster surveys resulted in a limited sample size of 10- to 14-year-old children, leading to imprecise estimates of hematuria prevalence. For the SCH school-based methodology, we aimed to maintain the current methods used by the Ministry of Health in the two states. Therefore, we modified slightly the sample size from 30 children to 32–47 children. The classification of each community was based on the point estimate of prevalence among the pupils examined. Small sampling fractions of 10- to 14-year-old school children result in less precise prevalence estimates than large sampling fractions and increase the likelihood that the community of which the school is part will be misclassified. The higher the actual prevalence of disease in the community, the greater chance we would have had in determining that the true prevalence was greater than the intervention thresholds. Where the disease was hypoendemic, we may have missed communities that actually qualified for interventions. This is an inherent risk associated with the tradition of using small sample sizes to make community-specific decisions based on point estimates alone. However, our sampling fraction in the majority of schools was one third or greater, and school attendance rates were high, possibly improving our estimate of true prevalence in the community.

Trachoma was hypoendemic in all of the surveyed LGAs compared with results from other states within the country^{16–18} and the other LGAs within the same states according to unpublished surveys. Based on LGA-level estimates derived from both survey methodologies, none of the LGAs qualify for district-wide intervention to control trachoma. However, the findings of the school-based assessment indicated that some communities had a prevalence that exceeded the 10% TF threshold and warranted intervention activities to eliminate trachoma as a public health problem. Trachoma, similar to SCH, is a focal disease, and these findings argue for the need for community assessment where district level prevalence is below the intervention threshold. Schools surveys provide an easy method of identifying hot spots of trachoma in hypoendemic areas where school enrollment is high.

School surveys in this setting were highly useful and may become a crucial tool as programs need to focus interventions to achieve elimination and to monitor prevalence to ensure the achievement of elimination is sustained. However, school-based surveys for trachoma do not provide estimates of TT necessary for planning surgical interventions. The correlation between TT prevalence in adults and TF prevalence in children is not consistent between settings, and the TF prevalence in children cannot be used to reliably predict the need for surgical services. Therefore, school-based community surveys should not replace the current population-based district level surveys but be used as a supplement in districts where TF falls below 10%.

Integrated mapping was feasible. However, the specific disease indicators obtained by integrated methods must be practical for making programmatic decisions. In this exercise, district-level estimates for urinary SCH derived using an add-on assessment for hematuria within the recommended trachoma sampling

methodology were not useful given current community-based thresholds for intervention. In contrast, community-level estimates of trachoma obtained using the SCH mapping method identified a remarkable number of communities warranting trachoma intervention that were missed with the standard district-based trachoma design. Given that NTD interventions cannot start without baseline mapping data, the benefits of including more than one disease indicator warrant further study.

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