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Simulating the Impacts of Augmenting Intensive Vector Control with Mass Drug Administration or Test-and-Treat Strategies on the Malaria Infectious Reservoir

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Abstract. Highly effective vector control can reduce malaria burden significantly, but individuals with parasitemia provide a potential reservoir for onward transmission. We performed an empirical, non-parametric simulation based on cohort data from Tororo District, Uganda—an area with historically high but recently reduced malaria transmission—to estimate the effects of mass drug administration (MDA) and test-and-treat on parasite prevalence. We estimate that a single round of MDA would have accelerated declines in parasite prevalence dramatically over 2 years (cumulative parasite prevalence ratio [PPR], 0.34). This decline was mostly during the first year of administration (PPR, 0.23) and waned by 23 months (PPR, 0.74). Test-and-treat using a highly sensitive diagnostic had nearly the same effect as MDA at 1 year (PPR, 0.27) and required many fewer treatments. The impact of test-and-treat using a standard diagnostic was modest (PPR, 0.58 at 1 year). Our analysis suggests that in areas experiencing a dramatic reduction in malaria prevalence, MDA or test-and-treat with a highly sensitive diagnostic may be an effective way of reducing or eliminating the infectious reservoir temporarily. However, for sustained benefits, repeated rounds of the intervention or additional interventions are required.

INTRODUCTION

A number of malaria endemic areas have recently benefited from substantial declines in malaria burden as a result of successful vector control, raising the possibility of eventual elimination in these areas.[1] One dramatic example is in the Tororo District in eastern Uganda, a historically high-transmission area (estimated entomological inoculation rate of 302 infective bites/person/year in 2011)[2] that has experienced significant reductions over just a few years (estimated entomological inoculation rate of 0.43 infective bites/person/year in 2019).[3] This success has been attributed to the rollout of vector control interventions in the district starting in 2013, including indoor residual spraying (IRS) and long-lasting insecticide-treated nets (LLINs). However, despite a marked decline in transmission intensity, a significant proportion of the population remains parasitemic, with most infections being asymptomatic. These asymptomatic infections provide a potential reservoir to fuel onward transmission, posing challenges to control and elimination efforts because they may lead to malaria resurgence when interventions are withdrawn.[4] To sustain gains from vector control interventions and move from control to elimination status, additional strategies targeting the parasite reservoir need to be explored. One such strategy is the use of antimalarial drugs to reduce the human reservoir of infection.

Drug interventions for transmission reduction may be administered through a number of strategies, including mass drug administration (MDA) and treatment based on proactive case detection (test-and-treat). MDA, the provision of a therapeutic dose of an effective antimalarial drug to the entire target population regardless of infection status or symptoms, was a component of many malaria elimination programs during the mid-20th–century eradication era.[5,6] This strategy fell out of favor as a result of declining efficacy, fears of sustainability, and accelerating drug resistance,[7] but MDA has recently received renewed interest.[8,9] Recent studies have shown MDA to be safe and effective in decreasing malaria prevalence and incidence.[10–13] As a result, MDA is currently recommended by the WHO as a potential strategy for the elimination of *Plasmodium falciparum* malaria in areas approaching interruption of transmission, given the prerequisites of good access to case management, effective vector control and surveillance, and limited potential for reintroduction.[14] The related test-and-treat strategy relies on screening of target individuals (e.g., specific households or an entire community) for parasitemia, with treatment of those who are positive.[15] Models have shown that, when combined with other interventions, test-and-treat may accelerate reduction in transmission intensity to pre-elimination levels, especially when a highly sensitive diagnostic tool and a highly effective antimalarial are used.[16] In addition, studies have highlighted the benefits of test-and-treat strategies in communities where the intervention has been rolled out, including 1) the identification of malaria infections in the communities for further management, 2) reductions in parasite prevalence, and 3) declines in malaria incidence. However, these studies have shown no impact of the intervention on malaria transmission.[17,18]

According to the WHO *Global Technical Strategy for Malaria 2016–2030*, in areas such as Tororo, where the number of malaria cases has been reduced to low levels, malaria program priorities and activities may need to be adjusted to ensure that every infection is detected and eliminated to interrupt local transmission.[14] Both MDA and test-and-treat may help to achieve this goal; however, most recent evaluations of these interventions have been in areas with historically moderate to low transmission intensity rather than areas with recently high transmission.[10,13,19,20] The few studies that have evaluated the interventions in high-transmission settings showed limited impact on clinical outcomes, and findings were not statistically significant.[10]

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Most importantly, no study has evaluated the intervention in areas of declining transmission. We developed an empirical simulation leveraging detailed longitudinal data on infectious status from a recently completed cohort study. Empirical simulation is a nonparametric method based on the same concept as a bootstrap and other subsampling methods that makes simple assumptions to construct a counterfactual. Using this technique, we estimated the impact of augmenting intensive vector control with MDA or test-and-treat on the *P. falciparum* reservoir in a historically high-transmission setting that has experienced a significant reduction in malaria burden as a result of the rollout of effective control interventions.

MATERIALS AND METHODS

Design and setting. This simulation analysis used data collected from a cohort study conducted in Nagongera subcounty, Tororo District, between October 2017 and October 2019. Prior to 2013, malaria control in Tororo was limited to the distribution of LLINs through antenatal care services, promotion of intermittent preventive treatment during pregnancy, and malaria case management with artemether–lumefantrine. In November 2013, universal distribution of free LLINs was conducted as part of a national campaign, and a similar campaign was repeated in May 2017. IRS with the carbamate bendiocarb was first initiated in December 2014 and January 2015, with additional rounds administered in June and July 2015 and November and December 2015. In June and July 2016, IRS was administered with the organophosphate Pirimiphos-methyl (Actellic®50EC), with repeated rounds in June and July 2017, June and July 2018, and March and April 2019. By the end of the cohort study, the district had received seven rounds of IRS. The simulation was conducted in October 2017, and although this is during the short rainfall season in Uganda (with monthly rainfall estimated at 100 mm at the study site in October 2017), malaria transmission was low at the time of the simulation.[21]

Study population, enrollment, and follow-up. Details of the cohort have been published elsewhere.[3] Briefly, in October 2017, all permanent residents from 80 randomly selected houses in Nagongera subcounty were screened and enrolled in the cohort study if they met the following criteria: 1) the selected household was considered their primary residence, 2) they agreed to go to the study clinic for any febrile illness, 3) they agreed to avoid antimalarial medications outside the study, and 4) they provided written informed consent. The cohort was dynamic, such that over the course of the study, any permanent residents that joined the household were screened for enrollment. Participants were monitored through October 2019 (~2 years) unless they withdrew prematurely. Reasons for withdrawal included 1) permanent movement out of Nagongera subcounty, 2) inability to locate the participant for more than 120 days, 3) withdrawal of informed consent, or 4) inability to comply with the study schedule and procedures. Cohort participants were evaluated every 4 weeks. Evaluations included a standardized history and collection of blood by finger prick/heel stick (if younger than 6 months of age) or venipuncture (if 6 months or older) for thick blood smear, hemoglobin measurement (every 12 weeks), and storage for future molecular studies. Study subjects who missed their scheduled routine visits were visited at home and requested to come to the study clinic as soon as possible. Cohort study participants were also encouraged to come to a dedicated study clinic open 7 days per week for all their medical care.

The study was approved by the Makerere University School of Medicine Research and Ethics Committee, the University of California Research and Ethic Committee, and the Uganda National Council for Science and Technology.

Laboratory evaluations. Quantitative PCR (qPCR) data were obtained at the time of enrollment and at each routine visit (every 4 weeks). DNA was extracted from 200 μL whole blood, and extraction products were tested for the presence and quantity of *P. falciparum* DNA via a highly sensitive qPCR assay targeting the multicopy conserved var gene acidic terminal sequence, with a lower limit of detection of 0.05 parasite/μL.[3,22]

Estimating the potential impact of interventions. We performed a nonparametric simulation in which empiric longitudinal data on parasite status collected from the cohort were used to simulate the impacts of additional interventions. We simulated 80% coverage of a random subset of the population with all interventions, and 60% coverage for MDA as well. For the MDA simulations, we assumed 80% (or 60%) of the target population was treated and cured. For the test-and-treat simulations, we assumed 80% was tested, and observed parasitemia was used to determine the test outcome. We assumed that individuals with parasite densities at or more than the limit of detection on the day of the intervention would have tested positive, and if the test would have been positive, the infection was treated and cured. Diagnostic test sensitivity was assumed to be 1 parasite/μL for a highly sensitive assay and 100 parasites/μL for a standard assay. We report the results of the simulation as a parasite prevalence ratio (PPR)— the prevalence at a single point in time in a simulation compared with the baseline—and cumulatively (cPPR). cPPR was defined as the ratio of the parasite prevalence in the group with MDA versus no MDA over the 2 years of follow-up.

To perform the simulations as described, it was necessary to make assumptions regarding what constitutes a persistent infection versus a new infection, informed by the relatively low incidence of malaria and largely stable and low parasite densities observed in individuals. For sequential visits, asymptomatic parasitemia was considered to be caused by the same persistent infection(s), so the simulated treatment would affect the entire course of infection. A qPCR-negative visit flanked by two positive visits was assumed to be part of the same continuous infection (i.e., assuming that a single "skip" was a false negative). A symptomatic malaria episode with a parasite density of more than 1,000 parasites/μL after two or more sequential visits with asymptomatic parasitemia was assumed to be a new infection. Parasite density was interpolated linearly for the entire course of a persistent infection, such that the density could be estimated for any given day of infection. Parasite densities for time points with negative qPCR assumed to be false negatives (as defined earlier) were assigned a value of 0.001 parasite/μL.

To estimate community (indirect) effects of the interventions, we assumed that observed new infections experienced the same relative reductions as parasite prevalence over the preceding 35 days (estimated duration of a

human–mosquito–human transmission cycle). For example, if a new infection first appeared in a participant on a given day and the estimated prevalence 35 days prior in the intervention scenario was 50% of the baseline prevalence, that infection (along with its entire trajectory) would be prevented in the simulation with 50% probability. The community effect was propagated forward from the time of intervention throughout the 2 years of observation using a time step of each day of observation. Using this process, for each day of observation, the proportion of individuals infected under the given intervention or without the intervention was estimated. Age-stratified results, where presented, were obtained from simulations performed on the whole community, with outcomes evaluated in the age stratum indicated.

Given the stochastic nature of the sampling of the population for the intervention as well as the forward propagation of the community effect, estimates were obtained from the median of 100 replicates. Inference was obtained for each simulated intervention using the 0.025 and 0.975 quantiles of prevalence, and relative prevalence obtained from 1,000 bootstrap replicates, with resampling occurring at the level of the participant.

RESULTS

Characteristics of the study population. Details of the primary study enrollment and follow-up have been published elsewhere.[3] Briefly, 413 households selected randomly from an enumeration survey were screened for eligibility to join the cohort in October 2017, of which 80 were enrolled (Figure 1). All household members were enrolled in this dynamic cohort, of which 12% were enrolled after the initial screening period and 12% were withdrawn by the end of the 2-year follow-up. At enrollment, 72 (90%) reported having received IRS within the last 12 months. Of the 531 total participants enrolled, 177 (33%) were younger than 5 years, 193 (36%) were between 5 and 15 years, and 161 (31%) were older than 15 years (Table 1). The 531 participants had a total of 14,702 visits to the study clinic, with 13.6% representing unscheduled (sick) visits.

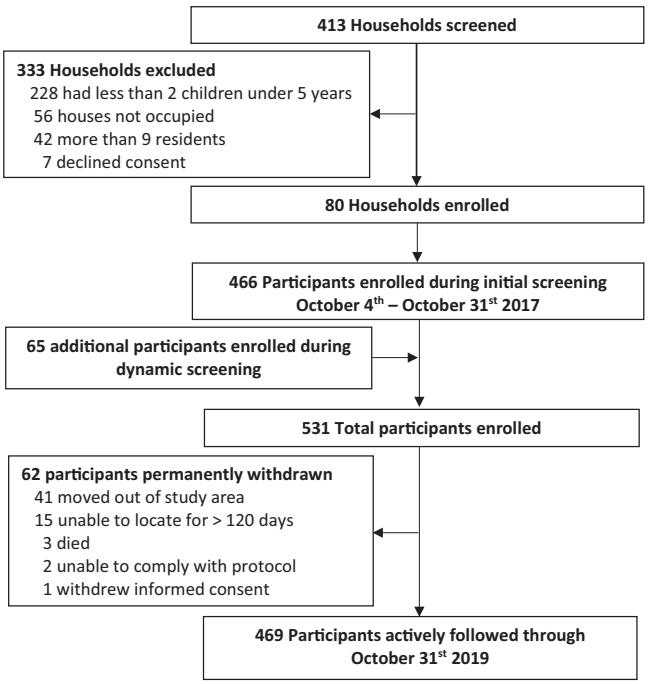

FIGURE 1. Flow diagram of the cohort participant recruitment and follow-up.

Tororo experienced a dramatic reduction in malaria transmission since IRS was initiated late in 2014, with a change in the prevalence of parasitemia (based on PCR readings) from 67.5% before the implementation of IRS to 6.8% after 5 years of sustained IRS in children 0.5 to 10 years.[3] During the cohort follow-up, the overall prevalence of parasitemia for all age groups was 10.4%. The majority of these infections were submicroscopic in all age groups, and the proportion that was submicroscopic increased with age. The prevalence of any parasitemia was greatest in school-age children (14%) and lowest in those younger than 5 years (4%). An overall decline in parasite prevalence was observed in all age groups over the 2 years of observation (Figure 2). Only 38 episodes of symptomatic malaria were diagnosed during follow-up, giving an overall incidence of 0.04 episodes/person/year, with an incidence less in adults than in children (Table 1).

Simulation of intervention scenarios. We estimated that a single round of simulated MDA at 80% coverage would have reduced prevalence from 11.9% with no intervention to 3.9% after MDA (cPPR, 0.34; 95% CI, 0.22–0.55). One effect of the simulated MDA was to blunt the increase in prevalence that was observed just prior to IRS in June 2018 as a result of the estimated effect on community transmission of reducing the parasite reservoir (Figure 3, Supplemental Figure 1A). MDA had the greatest estimated efficacy averaged over the first year of follow-up (PPR at 12 months, 0.23; 95% CI, 0.10–0.39), but most of the impact had waned by 23 months (PPR at 23 months, 0.74; 95% CI, 0.56–0.86) (Figure 3, Table 2). The estimated impact of MDA on the PPR was similar across age groups, but absolute impact varied given differences in baseline prevalence. The largest absolute benefit was observed in children 5 to 15 years (16.1% if no intervention versus 4.9% with intervention; cPPR, 0.31; 95% CI, 0.17–0.56)—the group with the greatest baseline prevalence. Older participants had a smaller absolute impact, and a reduction of only 3% in prevalence was estimated for children younger than 5 years. A single round of MDA simulated at a lower coverage of 60% produced similar patterns over time, but with lower efficacy than 80% coverage (Supplemental Figure 1B).

We estimated that a single round of test-and-treat (80% coverage) with a highly sensitive malaria diagnostic (able to detect parasite densities to 1 parasite/μL) would have had nearly the same efficacy as MDA, with the cPPR estimated at 0.41 and a 95% CI of 0.26 to 0.63 (PPR, 0.27; 95% CI, 0.11–0.43 at 12 months; and PPR, 0.74; 95% CI, 0.59–0.89 at 23 months). However, this intervention would have decreased the percentage of the community receiving antimalarials from 80% to 10%—an 8-fold decrease in the number of antimalarials delivered compared with MDA. Results stratified by age group and across time were similar to what was observed with MDA in all respects (Figure 3, Table 2).

Unfortunately, most point-of-care diagnostics do not have the sensitivity to detect 1 parasite/μl. We therefore also estimated the effect of a test-and-treat campaign using a standard diagnostic (such as a rapid diagnostic test [RDT] or

TABLE 1
Characteristics of the study population

Characteristic	Total	Age group, years < 5	5–15	> 15
Individual characteristics at enrollment				
No. of participants enrolled	531	177	193	161
Male gender, *n* (%)	253 (47.7)	80 (45.2)	108 (56.0)	65 (40.4)
Age at enrollment, years; mean (SD	15.9 (16.5)	2.6 (1.4)	9.5 (2.9)	38.0 (12.2)
Characteristics of study participants during the 2 years of follow-up				
Total no. of visits	14,702	4,112	5,910	4,680
Type of visit, *n* (%)	–	–	–	–
Unscheduled	2,006 (13.6)	760 (18.5)	603 (10.2)	643 (13.7)
Scheduled*	12,696 (86.4)	3,352 (81.5)	5,307 (89.8)	4,037 (86.3)
Parasitemia during scheduled visit, *n* (%)	–	–	–	–
Microscopic only	244 (1.9)	40 (1.2)	173 (3.3)	31 (0.8)
Microscopic + submicroscopic	1,314 (10.4)	134 (4.0)	743 (14.0)	437 (10.8)
Fever reported, *n* (%)	–	–	–	–
During scheduled visit	77 (0.6)	39 (1.2)	33 (0.6)	5 (0.1)
During unscheduled visit	530 (26.4)	311 (40.9)	143 (23.7)	76 (11.8)
No. of symptomatic malaria episodes	–	–	–	–
During scheduled visits	5	2	3	0
During unscheduled visit	33	10	17	6
Person-years of follow-up	955	250	400	304
Incidence of malaria per person-year	0.040	0.048	0.050	0.020

* Includes all enrollment visits and routine visits done every 28 days.

microscopy), assuming a limit of detection of 100 parasites/μL. With this approach the temporal trends were similar to what was observed with MDA, and the percentage of the community receiving antimalarials would have been reduced from 80% to 6.3%. However, the efficacy of test-and-treat with a standard diagnostic cumulatively over the 23 months (cPPR, 0.67; 95% CI, 0.47–0.97), and even at 1 year (PPR, 0.58; 95% CI, 0.40–0.76) was modest (Figure 3, Table 2). Unlike the other simulated interventions, test-and-treat with a standard diagnostic had differences in the relative as well as the absolute reductions in prevalence by age group. Adults, who had the lowest parasite densities, were estimated to have a limited benefit, as many infections would have been missed, whereas children age 5 to 15 years, who had the greatest baseline prevalence and mostly detectable parasites, would have the greatest reductions. It is important to note that by the 23-month time point the prevalence ratio estimates for the three interventions were quite similar (Table 2).

DISCUSSION

We used nonparametric simulation to determine the potential effect of community distribution of antimalarials on the *P. falciparum* parasite reservoir in an area of

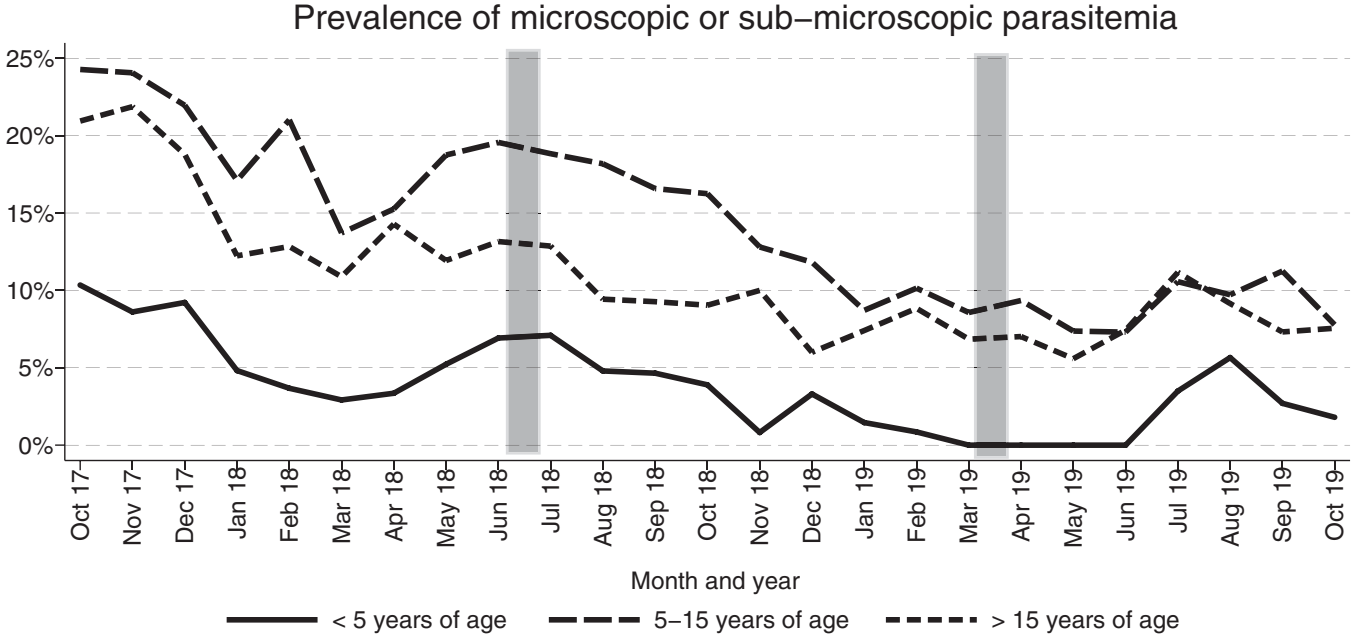

FIGURE 2. Prevalence of microscopic and submicroscopic parasitemia in the study cohort over the 2 years of follow-up. Gray bars are rounds of indoor residual spraying.

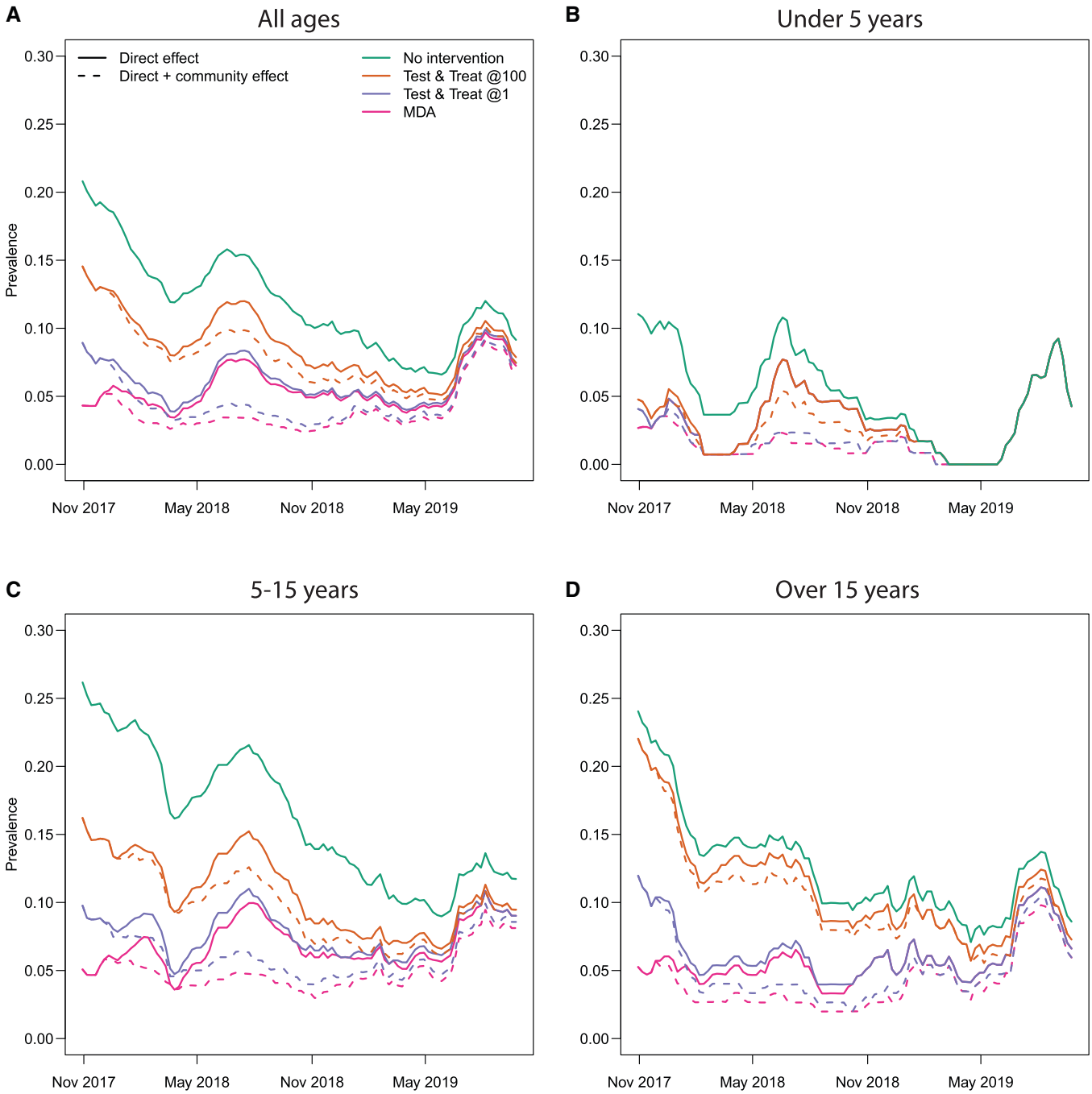

FIGURE 3. Predicted impact of different malaria control interventions with and without accounting for the community effect, stratified by age. Estimated community and direct effect of mass drug administration (MDA) or test-and-treat with a standard or highly sensitive diagnostic (**A**) regardless of age group, (**B**) in children younger than 5 years, (**C**) in children 5 to 15 years, (**D**), and in participants older than 15 years. Test & treat @100 = test-and-treat with a standard diagnostic; Test & treat @1 = test-and-treat with a highly sensitive malaria diagnostic. This figure appears in color at www.ajtmh.org.

sub-Saharan Africa with recently reduced transmission using 2 years of longitudinal data from a detailed cohort study. We observed that 1) MDA would have had a dramatic initial effect, with most of the impact waning by 18 to 24 months; 2) test-and-treat with a highly sensitive diagnostic would have had nearly same effect as MDA and required many fewer treatments; and 3) test-and-treat with a standard diagnostic would have had a very limited impact overall, and almost no impact in adults, in whom the vast majority of parasitemia would have remained undetected and untreated. These results suggest that regular rounds of either MDA or test-and-treat with a highly sensitive diagnostic may be effective tools for sustaining control in previously high-transmission settings where transmission has recently been driven down by effective vector control.

Drug administration interventions for transmission reduction are rapidly gaining favor as effective malaria control tools, especially in low-transmission settings;[13,23–28]

TABLE 2
Modeled impact of a single round of mass drug administration or test-and-treat on the parasite reservoir

Age group, years	Time point, months	No intervention,* % positive	Intervention					
			MDA		Test-and-treat at 1 parasite/μL		Test-and-treat at 100 parasites/μL	
			% Positive	PPR (95% CI)	% Positive	PPR (95% CI)	% Positive	PPR (95% CI)
All	0	20.5	–	–	–	–	–	–
	6	12.8	2.8	0.22 (0.10– 0.35)	3.5	0.27 (0.15–0.41)	8.0	0.62 (0.49–0.77)
	12	10.2	2.3	0.23 (0.10–0.39)	2.8	0.27 (0.11–0.43)	5.9	0.58 (0.40–0.76)
	18	7.1	3.5	0.48 (0.32–0.68)	3.9	0.55 (0.35–0.73)	5.2	0.73 (0.54–0.88)
	23	8.3	5.9	0.74 (0.56–0.86)	6.1	0.74 (0.59–0.89)	6.6	0.79 (0.66–0.93)
	Cumulative†	11.9	3.9	0.34 (0.22–0.55)	4.8	0.41 (0.26–0.63)	7.9	0.67 (0.47–0.97)
< 5	0	10.4	–	–	–	–	–	–
	6	4.5	0.8	0.17 (0.0–0.60)	0.8	0.17 (0–0.67)	1.5	0.33 (0.0–0.67)
	12	3.3	0.8	0.25 (0.0–0.77)	0.8	0.25 (0–1)	1.6	0.5 (0.0–1.0)
	18	0	0.0	N/A	0.0	N/A	0	N/A
	23	3.0	3.0	1.00 (1.00–1.00)	3.0	1.00 (1.00–1.00)	3.0	1.0 (1.00–1.00)
	Cumulative†	4.9	1.9	0.33 (0.09–1.21)	2.1	0.45 (0.14–1.42)	2.8	0.56 (0.19–1.62)
5–15	0	26.5	–	–	–	–	–	–
	6	17.8	3.9	0.22 (0.09–0.39)	5.0	0.28 (0.11–0.47)	10.0	0.56 (0.39–0.77)
	12	14.5	3.5	0.24 (0.07–0.43)	4.0	0.28 (0.10–0.48)	7.5	0.51 (0.29–0.73)
	18	10.2	5.3	0.52 (0.28–0.75)	5.8	0.57 (0.31–0.80)	7.3	0.71 (0.50–0.92)
	23	10.8	7.6	0.70 (0.50–0.88)	8.1	0.75 (0.54–0.91)	8.5	0.79 (0.61–0.95)
	Cumulative†	16.1	4.9	0.31 (0.17–0.56)	6.1	0.38 (0.22–0.66)	9.7	0.59 (0.37–0.94)
> 15	0	23.5	–	–	–	–	–	–
	6	14.1	2.7	0.19 (0.05–0.41)	3.4	0.24 (0.09–0.50)	11.4	0.81 (0.62–0.96)
	12	10.0	2.0	0.20 (0.0–0.47)	2.7	0.27 (0.00–0.50)	8.0	0.80 (0.50–1.00)
	18	8.3	4.1	0.50 (0.17–0.80)	4.1	0.50 (0.17–0.80)	6.2	0.75 (0.47–1.00)
	23	7.9	5.3	0.67 (0.38–0.95)	5.3	0.67 (0.38–0.93)	6.6	0.83 (0.56–1.00)
	Cumulative†	12.5	4.2	0.36 (0.17–0.79)	5.0	0.41 (0.19–0.86)	10.3	0.82 (0.45–1.47)

MDA = mass drug administration; N/A = not applicable; PPR = parasite prevalence ratio.
* Reference group.
† Cumulative estimates over the 23 months of follow-up.

however, their role has been limited to scenarios where there is seasonal transmission (seasonal malaria chemoprevention),[25] in pregnant women and infants,[14] and in elimination scenarios with implementation of vector control and MDA.[14] Using antimalarial drugs for malaria control is attractive because it can be used to target asymptomatic infections that would not be detected routinely and managed at health facilities. Our analysis shows that MDA or test-and-treat with a highly sensitive diagnostic may reduce the parasite reservoir effectively in areas where transmission has recently declined, even if, historically, it was very high. In addition, we show that the impact of a single course of therapy may be sustained for as long as 1 year after therapy, but that repeated dosing or alternative interventions may be required thereafter. Our simulation scenarios assumed a high (80%) coverage of the interventions, and treatment with a fully effective antimalarial to achieve this impact.

MDA was a key tool in malaria control and elimination in many countries, including Uganda, during the mid-20th century,[29] although concerns regarding its efficacy, sustainability, and operational feasibility, and fear of accelerating drug resistance led to a scale-down of its use. However, the role of MDA as a malaria control/elimination tool has been revisited, and recent studies have shown that MDA reduces the parasite reservoir and other measures of transmission, making it an important tool for malaria elimination.[7,9,13,19] Indeed, MDA is currently recommended by the WHO as a potential strategy for the elimination of *P. falciparum* in areas approaching interruption of transmission, given the prerequisites of good access to case management, effective vector control and surveillance, and limited potential for reintroduction.[14] In our analysis, in an area with declining transmission and effective vector control, we demonstrate that MDA may be an effective strategy to augment vector-based control and elimination efforts. We also demonstrate that test-and-treat with a highly sensitive diagnostic would likely be as effective as MDA and would require treatment of a much smaller percentage of the population. Considering these results, the choice of using MDA or test-and-treat with a highly sensitive diagnostic would depend on other factors, such as acceptability, cost, risk of drug resistance, and logistics of implementation. It is important to note that the utility of either intervention was predicted to be short-lived and not sustainable without repeated rounds or additional interventions.

Considering logistics, rolling out of MDA will be easier than implementing test-and-treat because it does not require testing. On the other hand, MDA requires treatment of whole populations. Mass treatment of populations increases 1) the number at risk of side effects, 2) drug costs, and 3) potential risk of selection of drug resistance.[30] Fortunately, most antimalarials recommended for MDA are safe and have not been linked directly to the emergence of antimalarial resistance, although some have been shown to increase significantly the selection pressure on parasite populations.[31] On the other hand, the test-and-treat strategy requires treatment of fewer members of the population, but was only as effective as MDA when a highly sensitive diagnostic was used. Unfortunately, highly sensitive malaria diagnostics are fairly expensive and not routinely available in resource-limited settings. An alternative is to use a less sensitive but more feasible diagnostic, such as a standard RDT, but our analysis showed limited effects of test-and-treat when a less sensitive diagnostic was used.

One strategy to reduce the costs associated with community interventions is targeting them to specific populations that would benefit maximally from the interventions and/or are most accessible logistically. We estimated the impact of the interventions in different age groups and observed that the maximum absolute reduction in prevalence was achieved in school-age children. This is not surprising, given that this group had the greatest prevalence of infection.[3] Targeting school-age children may be particularly attractive given that this age group is readily accessible through schools, malaria interventions could be integrated with ongoing school-based programs such as deworming, and, in our population, school-children were more infectious than adults.[4] Indeed, these findings further support our recent findings from membrane feeding assays that show that individuals with asymptomatic infections are important drivers of malaria transmission, and school-age children contributed to more than half of all mosquito infections.[32] It is important to note, however, that using drug interventions (including MDA or test-and-treat) for transmission reduction and sustained malaria control, whether targeted or to entire populations, is most likely to be effective in areas with good and prompt access to diagnosis and treatment, high coverage of effective vector control interventions, and strong surveillance mechanisms.[13,33,34]

This study was not without limitations. First, our analysis of the community effects of the interventions did not account for potential differences in transmissibility of different age groups, which might provide additional rationale for targeting school-age children, who appear to contribute disproportionately to transmission.[4] Second, we did not account for malaria importation, using instead a simple estimate of the community effect. Third, our study cannot be considered representative of typical rural African settings because participants received greater quality medical care in a more timely manner than is typically available. Fourth, these results were highly dependent on the ratio between prevalence and incidence. In other words, results are dependent on what proportion of infections over a given year are old versus new. In places where there is greater incidence, the impact of this type of intervention will be lower. Last, we did not conduct a cost-effectiveness analysis in this study, and so the relative costs of different approaches—an important consideration—were not compared formally.

In conclusion, we demonstrate that in a historically high-transmission area experiencing a dramatic reduction in the malaria burden after the implementation of highly effective vector control interventions, rollout of MDA or test-and-treat with a highly sensitive diagnostic (i.e., more sensitive than currently available standard or high-sensitivity RDTs) may be effective in further reducing the residual infectious reservoir. However, repeated rounds of the intervention or additional interventions is likely to be required to sustain the benefits achieved and accelerate progress to elimination.

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