Effect of weekly fever-screening and treatment and monthly RDT testing and treatment on the infectious reservoir of malaria parasites in Burkina Faso: a cluster-randomised trial

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Summary

Background The majority of *Plasmodium* spp infections in endemic countries are asymptomatic and a source of onward transmission to mosquitoes. We aimed to examine whether *Plasmodium falciparum* transmission and malaria burden could be reduced by improving early detection and treatment of infections with active screening approaches.

Methods In this 18-month cluster randomised study in Sapone, Burkina Faso, households were enrolled and randomly assigned (1:1:1) to one of three groups: group 1 (control) received standard of care only, group 2 received active weekly, at home, fever screening by a community health worker regardless of symptoms, participants with a fever received a rapid diagnostic test (RDT) and treatment if RDT positive, and group 3 received active weekly fever screening (as in group 2) plus a monthly RDT regardless of symptoms, and treatment if RDT positive. Eligible households had a minimum of three eligible residents, one in each age group (<5 years, 5–15 years, and >15 years). The primary outcome was parasite prevalence by quantitative PCR (qPCR) in the end-of-study cross-sectional survey. Secondary outcomes included parasite and gametocyte prevalence and density in all three end-of-season cross-sectional surveys, incidence of infection, and the transmissibility of infections to mosquitoes. This trial was registered at ClinicalTrials.gov (NCT03705624) and is completed.

Findings A total of 906 individuals from 181 households were enrolled during two phases, and participated in the study. 412 individuals were enrolled between Aug 9 and 17, 2018, and participated in phase 1 and 494 individuals were enrolled between Jan 10 and 31, 2019, in phase 2. In the end-of-study cross-sectional survey (conducted between Jan 13 and 21, 2020), *P falciparum* prevalence by qPCR was significantly lower in group 3 (29·26%; 79 of 270), but not in group 2 (45·66%; 121 of 265), when compared with group 1 (48·72%; 133 of 273; risk ratio 0·65 [95% CI 0·52–0·81]; p=0·0001). Total parasite and gametocyte prevalence and density were also significantly lower in group 3 in all surveys. The largest differences were seen at the end of the dry season, with gametocyte prevalence 78·4% and predicted transmission potential 98·2% lower in group 3 than in group 1.

Interpretation Active monthly RDT testing and treatment can reduce parasite carriage and the infectious reservoir of *P falciparum* to less than 2% when used during the dry season. This insight might inform approaches for malaria control and elimination.

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Introduction

Asymptomatic malaria is common in endemic areas and contributes substantially to ongoing *Plasmodium* spp transmission.[1] Approaches that specifically target this clinically silent malaria reservoir would likely accelerate progress towards elimination.[2] The effect of interventions on *Plasmodium* spp transmission should be examined to fully understand and optimise their use.

Plasmodium spp transmission from humans to mosquitoes requires the presence of gametocytes, which is the transmissible stage of malaria parasites. Gametocytes develop from asexual parasite precursors and, in *Plasmodium falciparum* infections, they sequester during maturation and appear in peripheral circulation 10–12 days later.[3] Blood-feeding female *Anopheles* mosquitoes can become infected when ingesting mature gametocytes, with the likelihood and intensity of mosquito infection increasing with gametocyte density.[4] Therefore, shortening the time between initial infection and treatment could reduce the presence and density of gametocytes in individuals with *P falciparum* and reduce the risk of onward transmission.

Chronic *Plasmodium* spp infections that do not prompt treatment seeking can remain undetected for many months or years, with continuous gametocyte production.[5]

Research in context

Evidence before this study

We searched PubMed for publications, without language restrictions, from database inception until June 21, 2023, using the search terms ("plasmodium falciparum") AND ("gametocyte" OR "infectious reservoir") AND ("mass screen and treat" OR "mass screening" OR "MSAT" OR "mass test and treat" OR "mass testing" OR "MTAT" OR "MTT" OR "enhanced case management" OR "CCM" OR "fever screening") and identified 12 studies. Eight of these studies were observational studies on gametocyte carriage or gametocyte infectivity among individuals who were asymptomatic and symptomatic, where the potential implications of gametocyte carriage in relation to diagnostic sensitivity were discussed but not empirically tested. Two modelling studies were identified that predicted a large effect of community treatment campaigns, including monthly mass testing and treatment (MTAT), on gametocyte carriage and onward transmission potential with the magnitude of this effect depending on diagnostic sensitivity and the level of transmission intensity. One observational study was identified that reported lower gametocyte prevalence and lower commitment to gametocyte formation in incident infections that were detected by weekly molecular screening compared with chronic infections where exact infection duration was unknown but infections were present at screening and still detectable 4 weeks later, when intensive follow-up started. We found two intervention studies that measured gametocyte carriage after single or multiple rounds of testing and treatment with conventional rapid diagnostic tests (RDTs). In one of these studies, 253 school-age children (5–15 years) from Malawi were screened for parasite carriage by conventional RDT, given artemether–lumefantrine if RDT positive, and followed up for 6 weeks. Among individuals treated with artemether–lumefantrine, gametocyte prevalence by molecular methods was reduced over the follow-up period. Gametocyte infectivity was not assessed and gametocyte density was used to extrapolate infectivity (binary; infectious or not infectious) based on a threshold density of 10 gametocytes per µL. The second study was a cluster-randomised trial conducted in Burkina Faso involving 18 clusters that were randomly assigned to standard of care or four rounds of mass testing and treatment in the dry season. Conventional RDTs were used, followed by treatment of individuals who tested positive with artemether–lumefantrine. The transmissibility of gametocytes was not assessed but their prevalence and density were determined by microscopy and molecular methods. This study showed a transient effect of the intervention on clinical incidence and asexual parasite carriage and no effect on gametocyte prevalence beyond month 3 of the study, which was 28 days after the second round of mass testing and treatment. Among miscroscopically detected gametocyte carriers, gametocyte density was not different between intervention and control groups at any timepoint during the 12 months of follow-up.

Added value of this study

Our study is, to our knowledge, the first to directly measure parasite carriage, gametocyte carriage, and gametocyte transmissibility after weekly fever screening alone or in combination with MTAT. By implementing these interventions in all age groups for 18 months, across two transmission seasons and the intervening dry season, it was possible to quantify the number of detected infections per age group and identify infection transmissibility. The findings indicate that fever screening alone detects infections in a minority of the population and has a negligible effect on parasite carriage, gametocyte carriage, and transmissibility. MTAT resulted in a reduced parasite prevalence and had an even more pronounced effect on gametocyte carriage and transmissibility with the largest effect being observed in the dry season.

Implications of all the available evidence

Active weekly fever screening combined with monthly testing and treatment, when sustained over a prolonged period, reduces both parasite and gametocyte carriage. By reducing infection duration, the likelihood that gametocytes are produced at levels that allow onward transmission to mosquitoes is greatly reduced, considerably shrinking the reservoir for mosquito infection. Our study supports sustained MTAT as a strategy to reduce the parasite reservoir in areas of high endemicity. The effect of the interventions in areas with lower endemicity, the effect of targeting specific demographics, and the cost and cost-effectiveness require further study.

Understanding the detectability of these asymptomatic infections in relation to their transmission potential is paramount for determining if and how they can be targeted by malaria interventions. Importantly, some asymptomatic infections might initially present with mild symptoms, offering an opportunity for identification and treatment before gametocytes reach densities that are infectious to mosquitoes. In a 2015–17 longitudinal cohort study comparing the contribution of chronic and incident *P falciparum* infections to transmission,[6] chronic infections were more likely to carry gametocytes, had higher gametocyte densities, and were more infectious to mosquitoes. Almost all incident infections were accompanied by mild but detectable symptoms, resulting in treatment before gametocytes were mature or of sufficient density to infect mosquitoes.[6] These results suggested that active screening for mild symptoms could enable the detection of infections before they become transmissible to mosquitoes.

Malaria community case management (CCM) strategies implemented since the 1980s in Africa aim to increase access to early diagnosis and treatment of symptomatic malaria. These approaches rely on passive detection of cases (traditional CCM) by trained community members and have increased malaria intervention coverage and reduced

malaria prevalence and malaria-attributed mortality.[7] Since around 2010, research has also examined the addition of weekly or bi-weekly active fever screening by community health workers to CCM, often termed proactive CCM (pro-CCM). In low-to-moderate malaria transmission areas where it has been evaluated, pro-CCM increased the detection of febrile malaria cases[8–11] and reduced malaria prevalence.[11] A similar effect might also be possible in high-transmission areas, although the effect of active fever screening will depend on the proportion of infections accompanied by symptoms, including mild symptoms. If most incident infections never elicit symptoms, active testing with malaria diagnostics would be needed to improve early detection of asymptomatic infections. Active monthly mass testing and treatment (MTAT) approaches aim to detect and treat infections by testing populations with rapid diagnostic tests (RDTs), regardless of symptoms.[12] The proportion of infections detected by MTAT will depend on the sensitivity of the diagnostic used,[13] with some infections only detectable by the most sensitive molecular methods and detectability varying by transmission setting.[14] In areas of high transmission, the effect of MTAT might be transient,[15] thus the importance of MTAT timing, the number of rounds, and targeting specific demographics needs to be understood.[12,16–18]

In this study, we examined the relationship between the detectability and transmission potential of asymptomatic infections to understand how active screening or testing approaches can affect both malaria infection prevalence and transmissibility. We hypothesised that these approaches would reduce the human infectious reservoir of *P falciparum* by detecting infections early and reducing the density and prevalence of gametocytes in the population.

Methods

Study design

In this cluster-randomised trial, we assessed the effect of two active screening strategies on parasite carriage, gametocyte carriage, and infectiousness to mosquitoes. We compared three groups: group 1 included participants given standard of care with passively monitored *Plasmodium* spp infections at two designated local health facilities (LHFs); group 2 included participants given standard of care (as in group 1) plus weekly fever screening, testing using an RDT if febrile, and treatment if RDT positive; and group 3 included participants given standard of care and weekly fever screening, testing, and treatment (as in group 2) plus a monthly RDT regardless of symptoms. The study took place in Sapone district in Burkina Faso, an area with seasonal rainfall and malaria transmission, during 17 months and 13 days covering two high-transmission seasons and the low-transmission dry season. We recruited less than 50% of the population in the area into the study to minimise the community-wide effect and enable the effect of the interventions to be continually assessed at the individual level.

Written informed consent was obtained from all participants before random assignment and enrolment. For participants younger than 16 years, assent was obtained in addition to written informed consent given by a parent or legal guardian. The protocol was approved by London School of Hygiene and Tropical Medicine ethics committee (14724), The Centre National de Recherche et de Formation sur le Paludisme institutional review board (2018/000002/MS/SG/CNRFP/CIB), and Burkina Faso national ethics committee for health research (2018-01-010) and was published previously.[19] The trial is registered at ClinicalTrials.gov (NCT03705624).

This trial protocol is provided in the appendix (pp 12–41). See Online for appendix

Participants

Participants were permanent residents in the Sapone Marche and Pissy LHF catchment areas and were enrolled from a total of 181 households. A household refers to a single dwelling consisting of multiple inhabited structures determined by an initial census and georeferencing survey. Eligible households had a minimum of three permanent residents, one in each age group (<5 years, 5–15 years, and >15 years), all of whom were willing to use a designated LHF. Eligible participants had no pre-existing health conditions that would affect study participation, no intolerance to artemether–lumefantrine, and no current or recent participation in a malaria vaccine trial (assessed through verbal interview). Full inclusion and exclusion criteria are listed in the appendix (p 23). Sex data were collected during the initial census using dichotomous identification approach as culturally acceptable in the area. To maximise coverage and optimise intervention logistics, we enrolled participants in two phases. Approximately half of the participants were enrolled before the first transmission season (August, 2018; phase 1) and the remainder after the first transmission season (January, 2019; phase 2).

Randomisation

Although we did not expect a community effect, we used a cluster-randomised design, with a cluster being a household since it was unfeasible to deliver different interventions to members of the same household. To account for spatial differences in malaria exposure, distance from LHFs, and treatment-seeking behaviour, neighbouring households were grouped based on proximity before random assignment (resulting in 53 groups of three households, four groups of four households, and two groups of two households). Random assignment (1:1:1) to one of the three study groups was done by simple randomisation stratified by proximity group and performed by an independent statistician.

Procedures

For standard of care with passive case detection (PCD; groups 1, 2, and 3), all participants received unique identification cards for use when attending the two designated LHFs (Pissy and Sapone Marche). Clinical malaria episodes were passively monitored, with axillary temperature

and medical history recorded and malaria diagnosed by conventional RDT, as used in standard practice (First Response Malaria Ag pLDH/HRP2, Premier Medical Corporation, Sarigam, India) specific for either *P falciparum* histidine-rich protein 2 or lactate dehydrogenase (or both) of *P falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*.

For weekly fever screening, testing, and treatment (groups 2 and 3), all participants in groups 2 and 3 were visited weekly at their homes by a community health worker to screen for fever. Participants with a current fever (≥37·5°C) or a history of fever in the last 24 h were referred to the designated LHF and an RDT was done.

For monthly MTAT (group 3), one weekly fever screening visit per month was replaced by MTAT, in which participants presented at a central meeting point for testing by conventional RDT. Participants who had a positive RDT were referred to the designated LHF for treatment.

RDT-confirmed malaria was treated according to national guidelines. For uncomplicated malaria, the first dose of artemether–lumefantrine was given at the LHF, with follow-up doses observed by a community health worker. Infections detected within 3 weeks of previous antimalarial treatment were confirmed by microscopy whenever feasible before new treatment was administered. RDT-confirmed and treated infections were defined as new infections when detected at least 14 days since the last recorded infection, or at least 10 days since the last recorded infection and accompanied by new malaria symptoms (fever ≥37·5°C or history of fever in the last 24 h). RDT-confirmed malaria was defined as symptomatic if accompanied by a fever of 37·5°C or more.

At the start and end of each transmission season, a cross-sectional survey was conducted for all study participants (four surveys in total). During home visits, fingerprick whole blood samples were taken for molecular assessment of parasite and gametocyte prevalence and density and axillary temperature was measured. Participants with a current fever (≥37·5°C) or history of fever in the last 24 h were referred to a LHF for malaria diagnosis by RDT and treatment.

Total *P falciparum* parasitaemia was detected by quantitative PCR (qPCR) targeting the var acidic terminal sequence (varATS) and male and female gametocyte densities by quantitative RT-PCR (qPCR).[20,21] For a subset of infections detected by PCD, fever screening, or MTAT, (based on clinical and logistical feasibility) direct membrane feeding assays (DMFAs) were done before treatment. DMFAs were also done on asymptomatic infections identified by weekly qPCR testing of a subset of households on a rolling basis, such that participants from each household were sampled once roughly every 10 weeks. The number of DMFAs performed was based on logistic feasibility and laboratory capacity (~30 DMFAs per week), and aimed to include samples spanning the range of parasite densities measured each week. All DMFAs were done with whole blood collected in lithium heparin vacutainers fed directly to laboratory-reared *Anopheles gambiae* (appendix p 11).[22] Where logistically possible, natural exposure to mosquitoes was monitored in study households (169 of 181) once every 2 weeks using a US Centers for Disease Control and Prevention miniature light trap in one sleeping space for one night. Mosquito species and sex were morphologically determined by microscopy and infection status was determined by sporozoite ELISA. Baseline coverage of seasonal malaria chemoprevention (SMC; participants younger than 5 years with reported participation in the August, 2018, SMC round) and insecticide-treated nets (ITN; participants reporting sleeping under an ITN the night before the visit) were assessed during cross-sectional survey 1. The National Malaria Control Programme in Burkina Faso distributed ITNs in June, 2019, before the second transmission season.

Outcomes

All primary and secondary endpoints in groups 2 and 3 were compared to group 1 at an individual level. The primary endpoint was *P falciparum* parasite prevalence measured by qPCR in the end-of-study cross-sectional survey (cross-sectional survey 4).

Secondary endpoints were parasite and gametocyte prevalence and density measured by qPCR in all cross-sectional surveys following intervention implementation (surveys 2, 3, and 4), the number of incident infections, and infectivity of *P falciparum* infections to mosquitoes. Other secondary endpoints were the association between total parasite density and gametocyte density, the relationship between the proportion of infected mosquitoes and gametocyte density, *P falciparum* transmission potential based on measured gametocyte densities, and the association between gametocyte density and mosquito infection rates.

Statistical analysis

The study was powered to detect a reduction in parasite prevalence in the intervention groups (groups 2 and 3) compared with the control group (group 1) during the cross-sectional surveys. With a conservative parasite prevalence of 40% in the control group,[22] 60 clusters per group, an average of five participants per cluster and assuming a conservative coefficient of variation of 0·4 for between-cluster variation in prevalence, would be a sufficient sample size in each group to detect a 50% reduction in parasite prevalence during cross-sectional surveys with greater than 99% power and a 33% reduction with greater than 80% power. Observed coefficient of variation is provided in the appendix (p 11). The sample size in each group would also give greater than 90% power to detect a reduction in prevalence of gametocyte-positive infections (secondary objective) if we assume that at least 80% of infections detected in cross-sectional surveys are also gametocyte-positive.[22]

Data analyses were done in Stata (version 17·0). We analysed the effect of interventions in groups 2 and 3 when compared with group 1 during post-implementation cross-sectional surveys 2, 3, and 4. Parasite or gametocyte prevalence was compared between groups by logistic regression and parasite or gametocyte densities (natural log parasites

per mL of blood) were compared between groups by tobit regression to account for densities below the limit of detection (LOD), with a boundary set at the lower limit of *P falciparum* detection for the qPCR test used (0·01 parasites per mL). Histograms generated of all densities above the LOD confirmed normality assumptions for the tobit model were not violated. Models accounted for clustering by specifying household identification numbers as a random intercept and including fixed effects for the stratum variable (group of households) and cluster-averaged baseline values of the dependent variable. When analysing data based on age, the participants' age at time of enrolment was used, except for analysis of the effect of the interventions during cross-sectional surveys. The proportion of mosquitoes that became infected in DMFAs was used as a quantitative estimate of transmission potential. DMFA results were used to determine the association between gametocyte density and the proportion of infected mosquitoes using generalised linear models with a binomial distribution and a log-link. This association was used to predict transmission potential for individuals with gametocyte density measurements who were not enrolled in DMFAs (appendix p 11).[20]

Role of the funding source

The Bill & Melinda Gates Foundation reviewed the protocol during drafting and provided general input on study design, but had no role in data collection, analysis, interpretation, or reporting. Other funders had no role in study design, data collection, analysis, interpretation, or reporting.

Results

In total, 906 individuals (figure 1) from 181 households (figure 2A) were enrolled in two phases, and participated in the study. A mean of five participants were recruited per household (range three to 11). Between Aug 9 and 17, 2018, 412 individuals were enrolled from 82 households (phase 1), with an additional 494 individuals enrolled from 99 households between Jan 10 and 31, 2019 (phase 2). The number of participants, age distribution, and baseline parasite and gametocyte prevalence and density were similar between groups (table 1). Baseline parasite prevalence was 64·4% (255 of 396) during enrolment at phase 1 and 54·4% (257 of 472) during phase 2. Reported use of SMC and ITNs was similar between groups at baseline (SMC range 70–88%; ITN range 93–97%; table 1). Female *A gambiae* sensu lato mosquitoes were caught in 158 (93%) of 169 of households and densities followed expected seasonal patterns (figure 2B). Mosquito density was highly heterogeneous (range 0–98 per mosquito trapping night), but neither mosquito density nor the proportion of sporozoite-infected mosquitoes differed between groups (figure 2C).

Weekly fever-screening plus MTAT (group 3), but not weekly fever-screening alone (group 2), had statistically significant lower prevalence of infections and density of parasites when compared with the control group. In the end-of-study cross-sectional survey 4, parasite prevalence

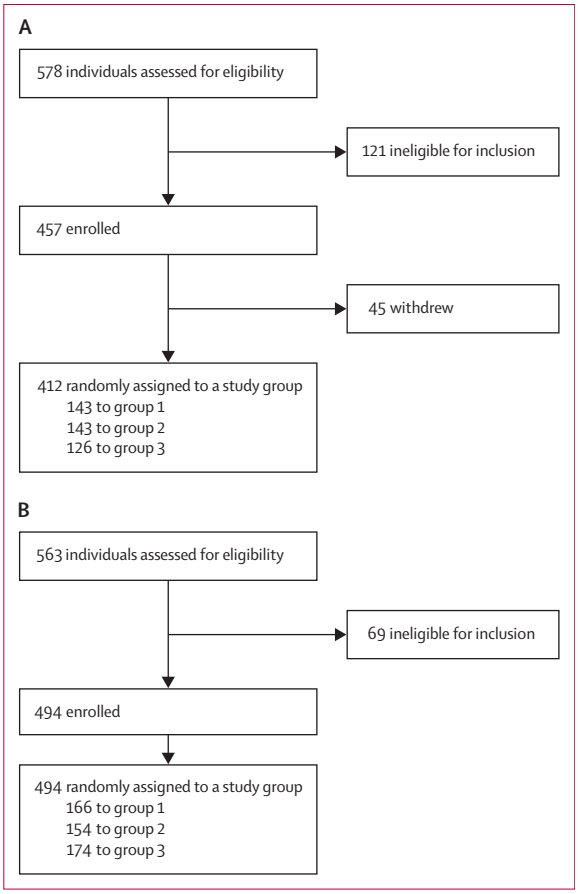

Figure 1: **Trial profile**
In total, 906 individuals from 181 households. (A) Study recruitment during phase 1. (B) Study recruitment during phase 2.

(group 1 48·72% [133 of 273] *vs* group 3 29·26% [79 of 270]; risk ratio [RR] 0·65 [95% CI 0·52–0·81], p=0·0001) and parasite density (group 1 geometric mean 76·74 [95% CI 34·51–170·67] parasites per mL *vs* group 3 5·24 [2·60–10·56] parasites per mL, effect size 0·04 [0·01–0·20], p=0·0001) were significantly lower in group 3 compared with group 1, but not in group 2 (figure 3; table 2). These differences were consistent in all other end-of-season cross-sectional surveys (surveys 2 and 3). Gametocyte prevalence (group 1 36·06% [97 of 269] *vs* group 3 17·84% [48 of 269], RR 0·54 [95% CI 0·40–0·72], p=0·0001) and density (group 1 geometric mean 4·94 [95% CI 2·77–8·80] parasites per mL *vs* group 3 0·78 (0·49–1·26) parasites per mL, effect size 0·07 [0·02–0·25], p<0·0001) were significantly lower in group 3 compared with group 1 in the end-of-study cross-sectional survey 4, and in all other end-of-season cross-sectional surveys (figure 3; table 2). The largest differences were observed at the end of the dry season, with parasite prevalence being 79·1% lower in group 3 (7·64%) compared with group 1 (36·59%) and gametocyte prevalence being 78·4% lower in group 3 (5·84%) compared with group 1 (27·02%). These differences were greatest in individuals aged 5–15 years (appendix p 3).

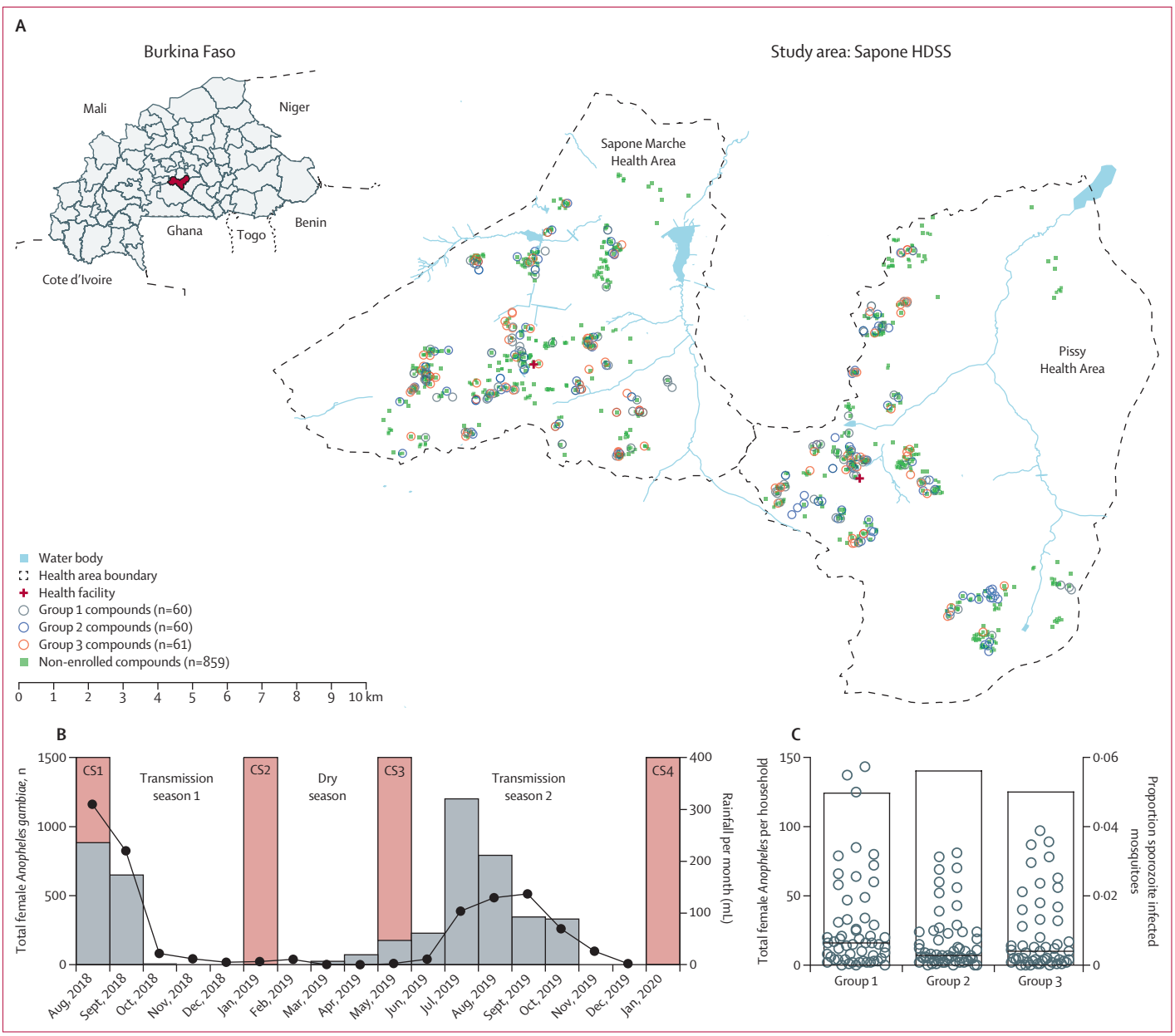

Figure 2: **Study area**

(A) Map of the study area. (B) Seasonal variation in entomological exposure and rainfall during the study. Bars show number of female *Anopheles* mosquitoes collected each month from enrolled households. The line shows volume of rainfall each month. Red bars indicate timing of the four cross-sectional surveys. (C) Entomological exposure in each group during the whole study period. Dots show total number of female *Anopheles* mosquitoes collected from each household, with the line indicating the mean, and the bars show the proportion of female *Anopheles* mosquitoes that were infected with sporozoites in each group. CS=cross-sectional survey. HDSS=heath and demographic surveillance system.

Intervention coverage was high, with 94·0% (28 054 of 29 838) of weekly fever-screening visits and 86·6% (3560 of 4109) of MTAT visits being completed. Of the participants referred to LHFs, 85·7% (126 of 147) and 90·0% (609 of 677) presented for follow-up visits, respectively. MTAT was overall more effective at detecting infections than weekly fever screening, with 14·0% (500 of 3560) of MTAT visits resulting in a treated infection compared with only 0·4% (107 of 28 054) of weekly fever screening visits. MTAT also detected infections in a much larger proportion of individuals receiving each intervention (76·3%; 229 of 300) than did weekly fever screening (15·2%; 91 of 597). The majority of MTAT-detected infections were in children aged 5–15 years (53·4%; 267 of 500), with 94·6% (106 of 112) of this age group having an infection detected by MTAT. A larger proportion of the children younger than 5 years (22·1% [33 of 149]) had an infection detected by fever screening than did participants older than 5 years

(5–15 years 16·0% [35 of 219]; >15 10·0% [23 of 229]; appendix p 4 and p 7).

Of all LHF visits during the study, 55·0% (922 of 1675) were RDT-confirmed malaria. The proportion of participants presenting with at least one symptomatic RDT-confirmed infection (group 1 52·4% [162 of 309]; group 2 55·2% [164 of 297]; group 3 52·0% [156 of 300]) and the number of passively detected infections (group 1 74·2 per 1000 person-months; group 2 76·7 per 1000 person-months; group 3 62·9 per 1000 person-months) were similar between groups (appendix p 7), suggesting the interventions did not interfere with treatment seeking behaviour. However, when considering the total number of infections detected and treated both passively (PCD) and with the active interventions (fever screening and MTAT), a much larger proportion of participants had an infection treated in group 3 (91·3% [274 of 300]) compared with group 1 (52·4% [162 of 309]), with 2·6 times more treated infections (group 3 189·6 per 1000 person-months *vs* group 1 74·2 per 1000 person-months). This improved infection detection rate was particularly notable in children aged 5–15 years, with 100% (112 of 112) in group 3 having an infection treated compared with 54·8% (63 of 115) in group 1 (appendix p 8).

Asymptomatic infections detected during cross-sectional surveys in control group 1 participants who did not receive the active screening interventions (infections that are thus more likely to remain untreated for longer periods of time) were more likely to carry gametocytes (65·2% [311 of 477]) than infections detected by PCD (28·3% [26 of 92]), weekly fever-screening (32·6% [28 of 86]), and MTAT (48·0% [74 of 154]; figure 4A). Where gametocytes were detected, there was a trend towards fewer gametocytes per parasite in the fever screening and MTAT detected infections compared with asymptomatic infections in group 1 (median for fever screening 0·8% (IQR 0·0–8·0) of all parasites are gametocytes; PCD 0·7% (0·0–24·7); MTAT 1·0% (0·2–12·0); group 1 asymptomatic 2·3% (0·4–19·5); appendix p 5).

5·1% (47 of 914) of DMFAs were infectious to mosquitoes, with mosquito infection rates per DMFA ranging from 1·3% to 84·9% and the mean number of oocysts ranging from one to 47 oocysts per infected mosquito. Participants who were positive for parasites in group 3 were the least infectious to mosquitoes (group 1 6·5% [18 of 278]; group 2 5·5% [16 of 290]; group 3 3·8% [13 of 346]). Among individuals who were positive for parasites, children aged 5–15 years were more infectious than other age groups (<5 years 2·8% [three of 109]; 5–15 years 7·4% [29 of 394]; >15 years 3·6% [15 of 411]; figure 4B–C). We observed the expected positive association between parasite and gametocyte density and infectivity to mosquitoes, with infectivity to mosquitoes increasing with gametocyte densities greater than 10 000 gametocytes per mL (figure 4D and appendix p 8). To extrapolate transmission potential of all individuals, we used the relationship between gametocyte density and infectivity to impute the infectiousness of each participant from gametocyte density data collected during the cross-sectional surveys. When considering both the prevalence of infections and imputed transmissibility, the predicted proportion of mosquitoes infected was significantly lower in group 3 compared with group 1 in all three end-of-season cross-sectional surveys (appendix p 6 and p 9). This was most notable at the end of the dry season, where gametocyte prevalence was 78·4% lower in group 3 (5·8%) compared with group 1 (27·0%) and the predicted reduction in transmission to mosquitoes was 98·2% (appendix p 9).

	Group 1	Group 2	Group 3
Enrolled participants			
Total	309/906 (34·1%)	297/906 (32·8%)	300/906 (33·1%)
Phase 1	143/412 (34·7%)	143/412 (34·7%)	126/412 (30·6%)
Phase 2	166/494 (33·6%)	154/494 (31·2%)	174/494 (35·2%)
Clusters (households)			
Total clusters	60	60	61
Cluster size, mean (SD)	5·1 (1·0)	4·9 (1·1)	4·9 (1·0)
Sex			
Male	140/309 (45·3%)	157/297 (52·9%)	140/300 (46·7%)
Female	169/309 (54·7%)	140/297 (47·1%)	160/300 (53·3%)
Age			
Age, years	11 (6–34)	12 (5–33)	11 (4–33)
<5 years	68/309 (22·0%)	72/297 (24·2%)	77/300 (25·7%)
5–15 years	115/309 (37·2%)	107/297 (36·0%)	112/300 (37·3%)
>16 years	126/309 (40·8%)	118/297 (39·7%)	111/300 (37·0%)
Malaria total parasite prevalence at baseline			
Phase 1	88/135 (65·2%)	90/138 (65·2%)	77/123 (62·6%)
Phase 2	90/157 (57·3%)	82/152 (54·0%)	85/163 (52·2%)
Malaria total parasite density at baseline, geometric mean (95% CI)			
Phase 1	585·9 (200·0–1716·8)	810·0 (287·00–2290·0)	455·96 (141·3–1471·1)
Phase 2	296·7 (99·2–887·8)	121·0 (42·0–348·0)	101·71 (36·0–287·7)
Malaria gametocyte prevalence at baseline			
Phase 1	26/135 (19·3%)	22/138 (15·9%)	14/123 (11·4%)
Phase 2	73/157 (46·5%)	69/152 (45·4%)	71/163 (43·6%)
Malaria gametocyte density at baseline, geometric mean (95% CI)			
Phase 1	1·0 (0·5–1·7)	0·9 (0·5–1·6)	0·5 (0·3–0·9)
Phase 2	15·4 (6·5–36·7)	13·3 (5·7–31·0)	11·0 (4·9–24·9)
Malaria control coverage			
SMC*	30/34 (88·2%)	26/37 (70·3%)	35/43 (81·4%)
ITN†	129/136 (94·9%)	130/140 (92·9%)	122/126 (96·8%)
Mosquito exposure per household			
Female *Anopheles*‡	16 (4·0–40·5)	7 (3·0–23·0)	10 (3·0–36·5)
Sporozoite rate§	0·047 (75/1595)	0·053 (48/908)	0·047 (56/1180)

Data are in n/N (%), median (IQR), and proportion (n/N), unless specified. ITN=insecticide treated nets; SMC=seasonal malaria chemoprevention. *Coverage of SMC during the August, 2018, round, reported during cross-section survey 1. †Coverage of ITN use reported during cross-section survey 1 (August, 2018). ‡Median number of female *Anopheles gambiae* sensu lato mosquitoes collected from each household over the whole study. §Proportion of all mosquitoes assessed per group that were sporozoite positive (n/N).

Table 1: **Baseline characteristics**

Discussion

This study evaluated the ability of two active screening and testing strategies to detect and treat *P falciparum* infections that are not identified by current standard of care and

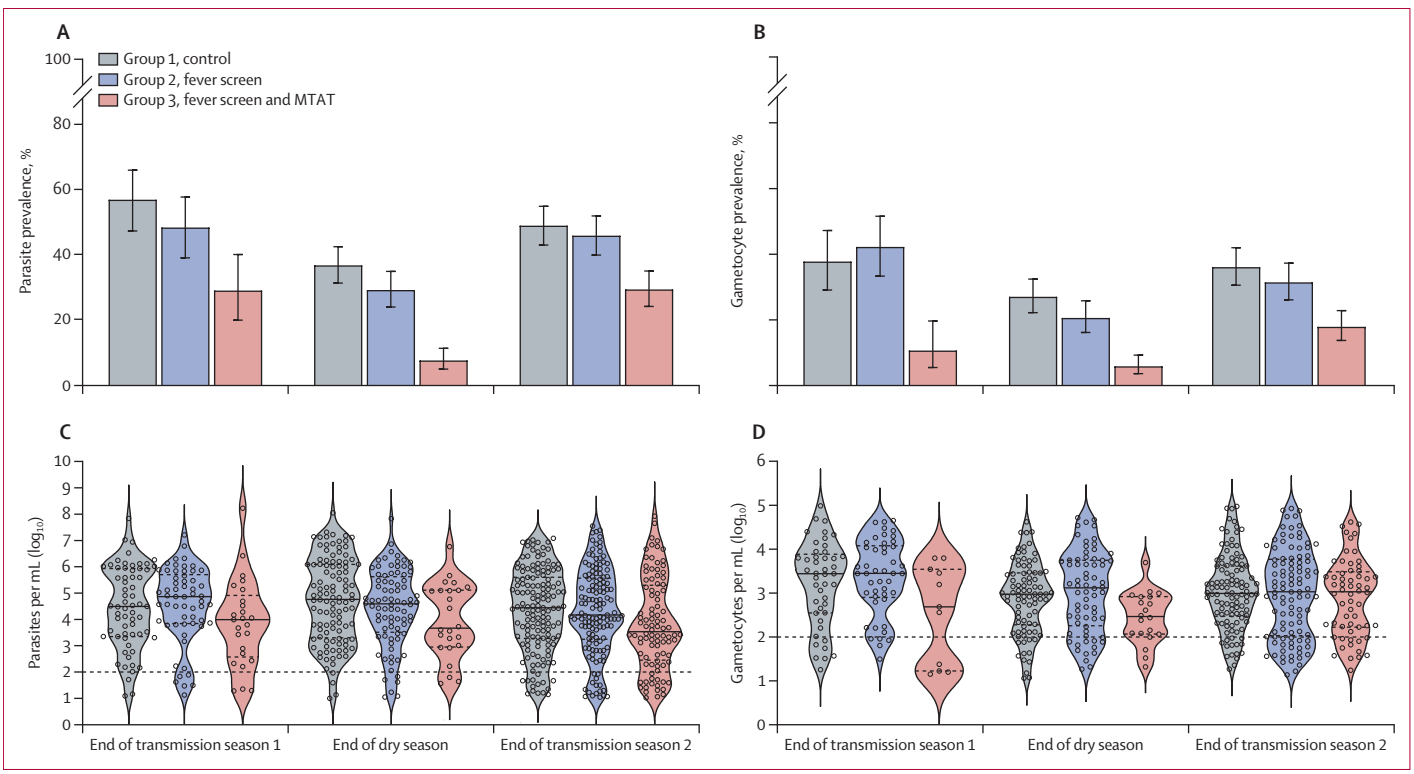

Figure 3: **Reductions in malaria due to interventions**

Malaria prevalence and density in each group, in the three end-of-season cross-sectional surveys, as determined by PCR. (A) Prevalence (95% CI) of total malaria parasites. (B) Prevalence (95% CI) of gametocytes. (C) Density of total malaria parasites. (D) Density of gametocytes. Dots show individual values, with the thick line indicating the mean. Total parasitaemia was determined by quantitative PCR targeting the var acidic terminal sequence (varATS)[20] and total gametocytes is the sum of male and female gametocyte densities determined by quantitative RT-PCR targeting PfMGET and CCp4 transcripts.[21] MTAT=mass testing and treatment.

assessed their effect on infection prevalence and transmissibility. We showed that regular monthly MTAT detected asymptomatic infections in the majority of individuals (76·3%) and fever screening plus MTAT greatly improved the infection detection rate (2·6-fold) compared with standard of care alone, resulting in more infections being treated when gametocytes were at low or undetectable densities. This increased infection detection rate led to a

	Group 1 (control)	Group 2 (weekly fever screen)	Group 3 (weekly fever screen plus MTAT)	Group 2 *vs* group 1	Group 3 *vs* group 1
Malaria prevalence					
End transmission season 1	56·60% (60/106)	48·15% (54/111)	28.95% (22/76)	RR 0·85 (0·65–1·10); 0·21	RR 0·56 (0·37–0·84); 0·0055
End dry season	36·59% (105/287)	29·10% (78/268)	7·64% (21/275)	RR 0·81 (0·64–1·02); 0·073	RR 0·24 (0·15–0·37); <0·0001
End transmission season 2	48·72% (133/273)	45·66% (121/265)	29·26% (79/270)	RR 0·95 (0·80–1·14); 0·60	RR 0·65 (0·52–0·81); 0·0001
Gametocyte prevalence					
End transmission season 1	37·74% (40/106)	41·12% (46/110)	10·67% (8/75)	RR 1·13 (0·82–1·56); 0·45	RR 0·32 (0·15–0·65); 0·0017
End dry season	27·02% (77/285)	20·60% (55/267)	5·84% (16/274)	RR 0·81 (0·60–1·08); 0·15	RR 0·24 (0·14–0·40); <0·0001
End transmission season 2	36·06% (97/269)	31·42% (82/261)	17·84% (48/269)	RR 0·91 (0·73–1·15); 0·44	RR 0·54 (0·40–0·72); <0·0001
Parasite density, parasites per mL					
End transmission season 1	177·51 (48·00–656·80)	96·93 (26·22–358·32)	4·01 (1·08–14·83)	ES 0·29 (0·03–2·65); 0·27	ES 0·01 (0·00–0·23); 0·0029
End dry season	15·00 (6·81–33·07)	5·06 (2·43–10·55)	0·27 (0·18–0·40)	ES 0·14 (0·02–1·12); 0·06	ES 0·00 (0·00–0·00); <0·0001
End transmission season 2	76·74 (34·51–170·67)	55·30 (24·64–124·09)	5·24 (2·60–10·56)	ES 0·86 (0·21–3·53); 0·83	ES 0·04 (0·01–0·20); 0·0001
Gametocyte density, gametocytes per mL					
End transmission season 1	8·14 (20·00–22·10)	11·19 (4·01–32·25)	0·40 (0·18–0·87)	ES 1·44 (0·24–8·45); 0·69	ES 0·01 (0·00–0·09); 0·0001
End dry season	1·75 (0·05–2·93)	1·06 (0·64–1·76)	0·18 (0·14–0·23)	ES 0·41 (0·11–1·49); 0·17	ES 0·00 (0·00–0·01); <0·0001
End transmission season 2	4·94 (2·77–8·80)	4·51 (2·48–8·22)	0·78 (0·49–1·26)	ES 1·22 (0·40–3·71); 0·73	ES 0·07 (0·02–0·25); <0·0001

Data are in % (n/N), RR or ES (95% CI); p, or geometric mean (95% CI). ES=effect size . RR=risk ratio.

Table 2: **Efficacy of interventions in reducing parasite and gametocyte prevalence and density**

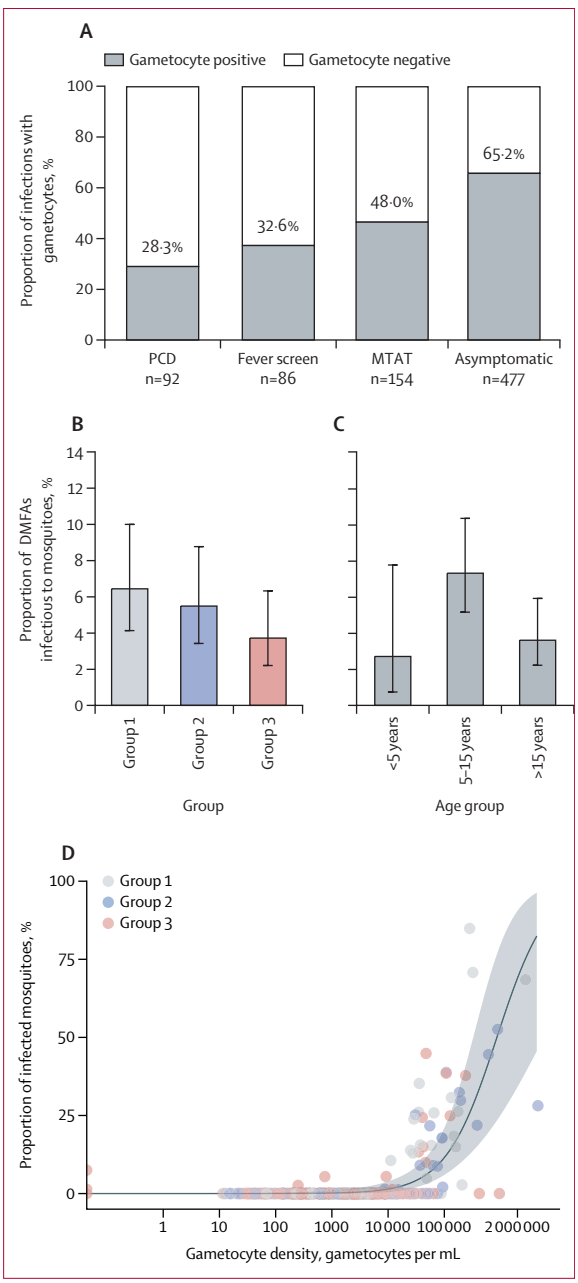

Figure 4: **Gametocyte carriage and transmissibility of infections to mosquitoes**

(A) Proportion of infections, detected by each method, that carry gametocytes, as measured by quantitative RT-PCR. (B) Proportion of infections that were infectious to mosquitoes during direct membrane feeding assays (DMFAs) in each group. (C) Proportion of infections that were infectious to mosquitoes during direct membrane feeding assays (DMFAs) in each age category. Bars show the proportion and lines represent 95% CI. (D) The relationship between gametocyte density (measured by PCR) and the proportion of mosquitoes infected in each DMFA. DMFA=direct membrane feeding assay. MTAT=mass testing and treatment. PCD=passive case detection.

significantly reduced prevalence of *P falciparum* infections in group 3 in all end-of-season cross-sectional surveys and an estimated 98·2% reduction in transmission potential at the end of the dry season, compared with standard of care (group 1).

Although we cannot rule out a contributing effect of fever screening on the effect of MTAT in group 3, in our study, weekly fever screening alone was much less effective at detecting infections than MTAT. Infections detected by fever screening were most common in children but, even in children, the occurrence of fever was low and similar in children younger than 5 years and children aged 5–15 years, possibly influenced by the existing interventions and local transmission intensity. Previous studies observed greater improvements in infection detection with active fever-screening approaches.[8–11] However, these studies were either conducted in lower transmission settings,[9–11] where infections might be more likely to result in symptoms, or also included on-call community health-care workers[8] who might have been more able to detect very transient fevers. In our study, RDTs were only done with a current measured fever or history of fever within the previous 24 h. Extending the time for recall of symptoms up to 48 h[9,10] or 7 days might have identified more infections with mild transient fevers, resulting in a larger effect.

MTAT detected considerably more infections than weekly fever screening, which were most common in school-age children (5–15 years). Almost all school-age children in group 3 were treated at least once due to MTAT (94·6% [106 of 112]), consistent with the highest prevalence of asymptomatic infections being in this age group.[23] Importantly, infections detected and treated by both interventions used in group 2 and 3 were considerably less likely to carry gametocytes at molecularly detectable densities than were asymptomatic infections in individuals not receiving the study interventions in group 1 and were less transmissible to mosquitoes. This finding supports our hypothesis that enhanced surveillance can detect asymptomatic infections earlier in their life history than the current standard of care, reducing prevalence and also density of gametocytes. Infections detected by weekly fever screening and PCD (ie, symptomatic malaria) were less likely to be gametocyte positive than were MTAT-detected infections, which was likely to be due to early symptom onset in an infection, thus shortening time between initial infection and treatment even further.[6]

Although infections detected by weekly fever screening were less likely to carry gametocytes than MTAT detected infections, due to the low infection detection rate, fever screening had little effect on overall parasite and gametocyte carriage when used alone in group 2. In contrast, in group 3 (fever screening plus MTAT), parasite and gametocyte prevalence and density were significantly lower than in the control group in all post-implementation cross-sectional surveys. The largest relative reductions in parasite (79·1%) and gametocyte (78·4%) prevalence in group 3 were observed at the end of the dry season, a period when reinfections are generally less common, suggesting that these interventions can detect the majority of asymptomatic infections in this setting. Almost all of the infections (17 of 21)

detected in group 3 during the end of dry season cross-sectional survey (and thus likely missed by interventions during the dry season) were below the conventional RDTs LOD (~200 000 parasites per mL; figure 3). Studies suggest ultra-sensitive RDTs (LOD ~10 000 parasites per mL), could improve the detectability of asymptomatic infections, although some very low-density infections might still remain undetected.[13,24]

When we estimated the transmission potential of each individual at the end of the dry season, transmission to mosquitoes (98·2%) was reduced even more than the gametocyte prevalence (78·4%), further supporting the hypothesis that the interventions not only reduce *P falciparum* infection prevalence, but by detecting infections early, they can also reduce gametocyte densities and thereby the likelihood of transmission to mosquitoes.

A limitation of this study is that we cannot make conclusions on the effect of the predicted 98·2% reduction in transmission on overall malaria burden. This is because the study was not designed to assess the community-wide effect of these interventions and instead designed to ensure that overall transmission in the area was unaffected so the intervention effect on infection detectability and transmissibility could be continuously evaluated. If the interventions reduced both the prevalence and transmissibility of infections in a whole community, the number of infected mosquito bites in the community would also likely reduce, resulting in a continuous reduction in incident infections. Therefore, modelling studies are underway using these data to estimate the effect on malaria burden if interventions were deployed community-wide and to understand how factors, such as local epidemiology, and the coverage, duration, timing, and age targeting of interventions affect effectiveness. Other limitations include the use of a single setting with intense malaria transmission, which limited the translatability of the results to other settings, the absence of an MTAT only group preventing us from fully understanding whether fever screening contributed to the effect in group 3, and the use of short-acting drugs for treatment. It is conceivable that drugs with longer action or specific gametocyte activity might increase the intervention effectiveness.

The design of the study, to purposefully ensure overall transmission was unaffected, is also a key difference between this and most previous MTAT studies. The existing evidence on the effectiveness of MTAT is limited and mixed. Studies that showed no[25–28] or modest[15,23,29–31] effect had short intervention durations with few MTAT rounds,[23,26] had infrequent MTAT rounds,[27,28,30] assessed prevalence or incidence based on symptomatic or microscopy or RDT positive infections,[25,27–29,31] or assessed their effect a long time after interventions ceased.[15,25,31] Previous studies that instead assessed asymptomatic parasite or gametocyte reservoirs by PCR in high-transmission areas reported considerable reductions when assessed soon after MTAT delivery (within 6 weeks), with MTAT delivered in the dry season[15] or via schools.[23] In our study, impact was likely high due to sustained, monthly delivery of MTAT during 18 months of follow-up, with impact assessed within 4 weeks of intervention delivery. This is consistent with modelling studies that have shown high efficacy of MTAT being dependent on regular and sustained delivery, and often influenced by transmission intensity.[16–18] Previous studies have also suggested that traditional MTAT is feasible to deliver[29,30,32] and could be a cost-effective approach for malaria reduction depending on local epidemiological context and existing interventions.[12,18,29,33] Scalability of the monthly MTAT approach used in our study was not assessed, but weekly fever screening has been found to be operationally feasible in many areas either as pro-CCM or as part of integrated CCM. Therefore, it is conceivable that regular RDT testing could be added to CCM approaches that already involve weekly home visits with minimal additional costs.

In conclusion, our study adds novel information on the ability of fever screening or RDT testing to detect asymptomatic infections and the effect this has on the transmission potential of infections. Regular monthly MTAT identified significantly more infections than fever screening alone. This enhanced detection reduces the duration of parasite carriage and significantly reduces the likelihood that an infection will be transmitted to mosquitoes. Importantly, in our study area, parasite and gametocyte burden were highest in school-age children and, consequently, MTAT had the most pronounced effect in this age group. An operationally attractive option could be to adapt our findings to target school-age children through MTAT or chemoprevention, although whether demographic targeting would reduce the (community) effect of the intervention would need to be evaluated. This detailed description of the intervention effect on parasite transmissibility should be considered when adapting existing or assessing new interventions and should improve data and assumptions underlying modelling approaches that assess effectiveness to more clearly understand the effect that screening approaches have on transmission of *P falciparum* and resulting onward malaria burden.

Contributors

ABT, TB, CD, and KAC conceived and designed the study. WMG, AO, SSA, IS, AN, PS, JG, SBS, JB, and WS contributed to study design. AO, KAC, WMG, IS, MSO, SS, NO, ASC, AN, KL, SSA, SSS, NH, INO, and AD collected the data or processed samples. KAC, TB, JR, JB, PS, JG, TMH, and SS analysed the data. KAC, AO, CD, TB, and ABT wrote the manuscript. KAC, JB, and SS verified the data. All authors saw the draft of the manuscript, contributed to data interpretation, and provided input on writing. All authors reviewed and approved the manuscript final draft. All authors had full access to study data and had the final responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

All deidentified data used in this Article are available online (https://doi.org/10.5061/dryad.fxpnvx117).

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Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps.

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