Impact of population based indoor residual spraying with and without mass drug administration with dihydroartemisinin-piperaquine on malaria prevalence in a high transmission setting: a controlled trial in northeastern Uganda

Dorothy C. Echodu (dorothy@pilgrimafrica.org)
Pilgrim Africa
Adoke Yeka
Makerere University College of Health Sciences
Thomas Eganyu
Pilgrim Africa
Wycliff Odude
Pilgrim Africa
Fred Bukenya
Pilgrim Africa
Benjamin Amoah
Imperial College London
Humphrey Wanzira
Pilgrim Africa
Kathryn Colborn
University of Colorado Anschutz Medical Campus
Richard C. Elliott
Boise State University
Suzanne E. Powell
Pilgrim Africa
Maxwell Kilama
Pilgrim Africa
Ronald Mulebeke
Makerere University College of Health Sciences
Joaniter Nankabirwa
Infectious Diseases Research Collaboration
Emanuele Giorgi
Lancaster University

Mellisa Roskosky
Johns Hopkins University
Osborn Omoding
Pilgrim Africa
Samuel Gonahasa
Infectious Diseases Research Collaboration
Jimmy Opigo
Ministry of Health

Research Article

Keywords: MDA, malaria, IRS, high burden, Uganda, controlled trial, pirimiphos, dihydroartemisinin

Posted Date: April 5th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1510812/v1

RESEARCH

Impact of population based indoor residual spraying with and without mass drug administration with dihydroartemisinin-piperaquine on malaria prevalence in a high transmission setting: a controlled trial in northeastern Uganda

Dorothy C. Echodu[1*], Adoke Yeka[2], Thomas Eganyu[3], Wycliff Odude[3], Fred Bukenya[3], Benjamin Amoah[4], Humphrey Wanzira[3], Kathryn Colborn[5], Richard C. Elliott[1,6], Suzanne E. Powell[1], Maxwell Kilama[3], Ronald Mulebeke[2], Joaniter Nankabirwa[7], Emanuele Giorgi[4], Mellisa Roskosky[1,8], Osborn Omoding[3], Samuel Gonahasa[7] and Jimmy Opigo[9]

[*]Correspondence: dorothy@pilgrimafrica.org
[1]Pilgrim Africa, 8001 14th Avenue NE, Suite A, 98115 Seattle, WA, USA
Full list of author information is available at the end of the article

Abstract

Background:
Declines in malaria burden in Uganda have slowed. Modelling predicts that indoor residual spraying (IRS) and mass drug administration (MDA), when co-timed, have synergistic impact. This study investigated additional protective impact of population-based MDA on malaria prevalence, if any, when added to IRS, as compared with IRS alone and with standard of care (SOC).

Methods:
The 32-month prospective controlled community trial enrolled an open cohort of residents (46,765 individuals, 1st enumeration and 52,133, 4th enumeration) in Katakwi District in northeastern Uganda. Consented participants were assigned to three arms based on residential subcounty: MDA+IRS, IRS, and SOC (insecticide treated bednets and case management). IRS with pirimiphos methyl and MDA with dihydroartemisinin- piperaquine were delivered in 4 co-timed campaign-style rounds 8 months apart. The primary endpoint was population prevalence of malaria, estimated by 6 cross-sectional surveys, starting at baseline and preceding each subsequent round.

Results:
Comparing malaria prevalence in MDA+IRS and IRS only arms over all 6 surveys (intention-to-treat analysis), roughly every 6 months, post-interventions, a geostatistical model found a significant additional 15.5% (95% confidence interval (CI): [13.7%, 17.5%], Z=9.6, p= 5e-20) decrease in the adjusted odds ratio (aOR) due to MDA for all ages, a 13.3% reduction in under 5's (95% CI: [10.5%, 16.8%], Z=4.02, p= 5e-5), and a 10.1% reduction in children 5-15 (95% CI: [8.5%, 11.8%], Z=4.7, p= 2e-5). All ages residents of the MDA + IRS arm enjoyed an overall 80.1% reduction (95% CI: [80.0%,83.0%, p¡.0001] in odds of qPCR confirmed malaria compared with SOC residents. Secondary difference-in-difference analyses comparing surveys at different timepoints to baseline showed aOR (MDA + IRS vs IRS) of qPCR positivity between 0.28 and 0.66 (p<.001). Of three serious adverse events, one (nonfatal) was considered related to study medications. Limitations include the initial non-random assignment of MDA+IRS, which may have understated the impact of MDA, and lack of MDA-only arm, considered to violate equipoise.

Conclusions:
Despite being assessed at long timepoints 5-7 months post-round, MDA plus IRS provided significant additional protection from malaria infection over IRS alone. Future cohort studies of impact on incidence recommended.

Trial registration: This trial was retrospectively registered July 7th, 2018 with the Pan African Clinical Trials Registry (PACTR 201807166695568).

Keywords: MDA; malaria; IRS; high burden; Uganda; controlled trial; pirimiphos; dihydroartemisinin

Introduction

Background

Globally, progress against malaria morbidity has stalled, with the remaining burden concentrated in eleven countries, including Uganda[1]. Uganda is a stably endemic, high burden country with, as of 2020, the third highest number of malaria cases in the world[2, 3]. After some years of low movement against key malaria metrics[4], the

country made great strides in the decade between 2009 and 2019, including: a doubling of insecticide treated net (ITN) ownership and use, maintaining a commitment to indoor residual spraying (IRS) in high transmission areas[5, 6, 7, 8], emphasizing early diagnosis and prompt treatment of uncomplicated malaria with artemisinin combination therapies (ACTs), intermittent preventive treatment for pregnant women (IPTp)[9, 10], and improving national surveillance[11]. These efforts, along with growing urbanization and greater access to improved housing[12, 13, 14, 15], have resulted in dramatic national reduction in microscopy prevalence of children under 5 from 42% in 2009[16] to 9% in 2018[17]. In recent years, however, this progress is slowing. Further gains must come from accurately targeting control combinations towards remaining pockets of high transmission, where most national cases occur[18, 19].

While vector control remains the primary way to reduce malaria burden and transmission, chemoprevention may also have a role in high burden regions where progress has faltered [20, 21]. A growing enthusiasm to use chemoprevention in control settings is emerging. It is supported by evidence from, for example, China, who for nearly 40 years (1960-1999) used both radical treatment and mass drug administration (MDA) of antimalarials as primary malaria interventions. MDA was specifically targeted to reduce disease burden, with annual doses administered tracking the level of burden, and reducing with it[22]. During this time, national malaria transmission fell from hyperendemic to pre-elimination levels, and malaria cases shrank from an estimated 30 million per annum in the 1940s to a little over 30,000 in 2000[23]. In May of 2021, the WHO granted China official status as a malaria free country[24, 25]. More recently, there has been a push for new evidence on MDA in high burden settings. In 2020, the Director of the World Health Program Global Malaria Program called for new evidence for MDA in the context of the High Burden High Impact initiative[1], noting that it is one of the few tools whose "full potential has yet to be realized."

MDA is a full course of an antimalarial treatment given to the whole population in a given area at approximately the same time, irrespective of symptoms or infection status and with the exception of individuals for whom the medicine is contraindicated[26, 27]. In order for MDA to be effective, high coverage is essential[28, 29] and good engagement with stakeholders is required. For maximum impact, MDA should be performed with an artemisinin-combination therapy (ACT)[30], with Dihydroartemisinin-piperaquine (DP) often preferred for its efficacy, safety profile, and long post-treatment prophylactic protection[31, 32].

Absent of concurrent vector control, the duration of MDA impact in a high transmission setting is expected to be quite limited; rebound is predicted to occur rapidly after a transient period of chemoprophylactic prevention [33, 34]. A recent, clinical trial of intermittent preventive treatment in schoolchildren (IPTsc), conducted in a high transmission region of Uganda, underlined this effect: chemoprevention was extremely protective when ACTs were administered at monthly intervals, reducing incidence and prevalence in intervention subjects relative to placebo by 96% and 94% respectively, but was accordingly much less effective in suppressing clinical incidence if given quarterly[35]. Similarly, in a large cluster-randomized trial of MDA in Zambia, with asynchronous vector control present in the study region, the effects

of an MDA campaign after two rounds was estimated to last for 3-4 months[36]. In this case, MDA was shown to reduce cumulative incidence relative to control in a cohort[37, 38] in a high transmission setting; however, the differential impact of the MDA on prevalence was not significant in high burden areas at survey points 3-4 months after the campaign[38].

Prior work noted a robust impact of combining MDA with vector control, showing the strategy effective for burden reduction in high transmission regions, though not for achieving complete elimination[39]. Recent modeling has predicted a complimentary impact of MDA+IRS, especially when applied at the same time, with the IRS protecting and effectively extending the duration of the MDA's prophylactic effect for six months or more[33]. Because an MDA campaign initially removes so much infection in high transmission, the cooperative advantage of prolonging its impact is predicted to increase with transmission intensity, making the strategy of particular interest in high burden settings[34]. From a cost and compliance standpoint, the advantage of a single annual population-wide MDA over monthly or seasonal chemoprophylaxis in children is compelling, but to date an experimental study has not investigated the impact of delivering IRS and MDA simultaneously in a high-burden context. Here, we evaluated the impacts of a co-timed MDA campaign with DP with IRS with pirimiphos methyl in a setting of high transmission and burden. Based on modeled predictions of the benefit of co-timing interventions, especially at long times after MDA implementation, the primary objective of this study was to assess the impact on malaria prevalence of single rounds of population MDA+IRS at intervals five to seven months post-intervention, and to evaluate any additional protective impact of MDA when added to IRS over IRS alone and over standard of care (SOC). The comparison of MDA+IRS to IRS provides a picture of additional MDA impact, if any exists, at times well beyond the chemoprophylactic prevention period of the MDA campaign. This paper presents an overview of the interventions, procedures and primary prevalence outcomes.

Methods

Study design

This was a prospective controlled community trial, conducted between October 2016 and June 2019, for a duration of 32 months. This study had three assignment arms: MDA+IRS, IRS only, and SOC as the control arm, which included ITNs and case management at facilities with commodity support only. SOC interventions were present in all three arms. The MDA+IRS arm was not assigned randomly, but to the arm with the highest number of malaria cases in the previous year.

Study setting

The study took place in Toroma County in the Katakwi District of northeastern Uganda, a high transmission region within the country deemed by the Uganda Ministry of Health (MOH) National Malaria Control Division (NMCD) to be suitable for targeted IRS. With a combined population of 46,765 in 2016, the project area consisted of three adjacent rural farming sub-counties bordering Lake Bisina. These three sub-counties served as the three arms of the study, with assignment taking place before study enrollment. Malaria transmission in this marshy area is dominated by *Anopheles gambiae sensu lato* (s.l.) and *Anopheles funestus s.l.* vector

groups[40, 41, 42], and follows a bimodal rainfall pattern. The longer rainy season occurs between March-June, and a shorter season between October-November; malaria is hyperendemic year-round, with peak malaria transmission between May-July[43]. All three sub-counties received free ITNs through national universal coverage campaigns conducted in November 2013 and again in April 2017 by Uganda MOH. Public health clinics in the study area follow the national malaria case management guidelines. None of the three targeted sub-counties had received IRS in the 5 years prior to November 2016.

Study interventions and cluster assignment

This study had two main study interventions, IRS with pirimiphos methyl (Actellic 300 CS, Syngenta) and MDA with DP (Eurartesim, Sigma Tau). Population-wide IRS was conducted in two arms by the research team, and in one of the arms, a single round of MDA was also administered and co-timed with the IRS.

IRS was conducted using Actellic 300 CS, a WHO recommended non-pyrethroid insecticide formulation of an existing organophosphate insecticide, pirimiphos-methyl. Its features include being a broad spectrum mosquito control insecticide, non-staining after application, possessing acceptable odor, safe in use for human and the environment and passes the WHO pesticide evaluations scheme (WHOPES) risk assessment[44]. Actellic offers a number of benefits over existing alternatives; it is not a pyrethroid or a carbamate, and so is unaffected by pyrethroid or carbomate resistance, both of which can arise quickly; it has a longer residual effect than all other non-pyrethroid IRS formulations (over 6 months), and was during the study period the primary insecticide used by MOH in partnership with Vectorlink.

DP (Eurartesim, Sigma Tau) was used for MDA. Eurartesim is a pre-qualified malaria treatment medicinal product according to the United Nations pre-qualification program managed by the WHO.

The three contiguous sub-counties, shown in Fig. 1, were assigned to the three study arms in the following non-random manner: prior to the baseline study, the sub-county with the highest number of malaria cases reported to District Helath Information Sytem 2 (DHIS2) in the year prior to the study start was assigned to MDA+IRS, and the other two sub-counties were randomly assigned. Each arm received one of the following three malaria control packages:

- Arm A (Kapujan sub county): MDA with DP (Eurartesim) + IRS with pirimiphos methyl (Actellic) + SOC.
- Arm B (Toroma sub county): IRS with pirimiphos methyl (Actellic) + SOC.
- Arm C (Magoro sub county): SOC only, including ITNs distributed through universal coverage campaign, case management at facilities, and intermittent treatment of pregnant women IPTp.

Study participants: eligibility and consent

All residents in the three study sub-counties were assessed for inclusion in the study. An enumeration and consenting visit was conducted in all three arms prior to study start. In both intervention arms, an additional screening and consenting visit was conducted before each intervention round, to assess continued eligibility for receiving the intervention. Eligibility and exclusion criteria differed slightly by arm. In the

SOC arm, all residents were eligible, no screening was needed, written consent was sought for participation in the study, and all consenting participants were enrolled and assigned unique identification numbers. All residents in the IRS and MDA+IRS arms were eligible for IRS, screened for possible adverse reactions to the insecticides, and written consent was obtained from household heads on behalf of the family; all household members of consenting households were assigned unique identification numbers. All household residents in the MDA+IRS arm were additionally screened for MDA intervention eligibility. Exclusion criteria included: younger than 6 months, pregnant, current symptoms of severe malaria, reported allergies to DP, history of cardiac problems or fainting, family history of long QT syndrome, or currently taking medications known to prolong the QT interval (e.g. antiretrovirals). Eligible adults provided written consent for themselves and any minor children, and children between 8 and 18 also provided written assents. Consented participants in this arm were given unique identification cards that included name, geographical location and demographic information as well unique study ID, and requested to present them at the MDA site at time of treatment. After the first round, barcode scanners were used to confirm the identity, consent and screening status of each participant. Prior to each round, eligibility and consent for MDA+IRS was reassessed. At the MDA treatment sites, consents were confirmed and current medical eligibility reconfirmed. Mapping, enumeration, screening, consents, assents, and sample frames were updated prior to each of the four rounds in both intervention arms.

Study Procedures

Social and behavior change communication

To create awareness and uptake of the intervention, and to obtain high coverage rates for MDA and IRS, numerous innovative social and behavior change communication (SBCC) methods were used, before, during and after implementation. These included: inception meetings and engagement workshops with key macro-level stakeholders to obtain buy-in and support for the study; village meetings conducted at village venue sites to promote dialogue, create community awareness, and describe the study objectives and interventions; radio talk shows and radio messages to reinforce continued awareness and to disseminate important study information; publicly posted posters describing the interventions; village health team (VHT) coordinators were sensitized to strengthen interpersonal communication; and a gender-sensitive community advisory board comprised of community members was formed, to ensure continued engagement and community ownership for the interventions conducted over the 3-year period.

Household mapping, and individual enumeration and screening

With the help of the local leaders, all households within the study area were mapped to create a sampling frame for estimating coverage of interventions and subsequent evaluations. A household was defined as any single permanent or semi-permanent dwelling structure acting as the primary residence for a person or group of people that generally cook and eat together. Household locations were mapped using handheld eTrex global positioning system (GPS) receivers (Garmin Ltd., Olathe, KS) and readings were taken from the door of the household, if possible, or from a

point that was most representative of the household. In addition to the mapping, all household residents living in the mapped households were enumerated, screened if living in the intervention arms, and informed consent for study participation was sought as described above.

Indoor residual spraying

Spray operations were performed by the study team in compliance with WHO and national standards. IRS was conducted every 8 months in the IRS and MDA+IRS arms using both Hudson and Semco spray pumps fitted with pressure regulators. Both IRS arms received four co-timed rounds of IRS. Approximately 150 spray operators, 50 washpersons and 13 parish store operators were recruited from the target sub-counties, medically screened (pregnant and nursing persons were excluded), and trained on all spray operations including environmental monitoring and compliance, use, and maintenance of spray equipment and personal protective equipment (PPE). In advance of each spray round, the study team marked eligible households with chalk or pen. All communities were alerted to the spray campaign, spray dates, and special instructions in advance. Each spraying exercise in a given parish of 5-10 villages was conducted within a 10-day period, and the entire spray round was conducted within a month. Both VectorLink Uganda and visiting Innovative Vector Control Consortium (IVCC) East African regional teams provided specialized spray quality intensives and monitoring support. The numbers of houses/structures found and those sprayed by the spray operators were counted per parish and cumulative totals sent by short message service (SMS) on a daily basis.

Mosquito resistance to pirimiphos-methyl and other insecticides was monitored via susceptibility testing, including field rearing of captured larvae and exposure to insecticide. This was performed each year during planned spray activities. Quality control testing for IRS was done by cone bioassay testing of representative walls, with repeated cone bioassays providing information about the residual efficacy and the decay rate of the insecticide.

Mass drug administration

All eligible and consented residents in the MDA+IRS arm received a three-dose treatment course of DP within a two week period of IRS implementation. A mix of fixed campaign style and house-to-house sweeps approach was used to administer DP by MDA. Details of this approach are documented in an earlier publication[45]. In summary, the first dose of DP was administered by direct observation (DOT) from 18 fixed village centers to eligible participants. At these sites, each participant was provided instructions of the MDA process, screened, and weighed. Accurate DP dosing was provided according to weight-based guidelines in 8 weight bands. The second and third doses were given to the participants (in a distinctive easy to use packaging) with instructions on how the medication should be taken from home on the second and third day. For participants less than 15 years, instructions were provided to their care-takers on how to administer the medication. To ensure compliance, study VHTs conducted house-to-house follow-up sweeps to check if participants had taken their second and third doses, by asking for the empty blister packs/medication envelopes.

Standard of care

All sub counties received ITNs by mass campaign conducted nation-wide by Uganda's MOH in April 2017. In addition, malaria case management and provision of IPTp was performed in all three sub counties, according to national guidelines, in 8 facilities located in the study area. The study personnel slightly enhanced the commodity supply chain in the study area by ensuring buffer stocks of rapid diagnostic tests (RDTs), ACTs and intravenous (IV) artesunate to facilities as needed to limit their stock-out. Fig. 2 below provides a summary of the trial flow progress.

Evaluation Methods

To evaluate the impact of the study interventions on malaria prevalence, cross-sectional community surveys were conducted at baseline and every 5-7 months thereafter, with the exception of survey number three, which was conducted three months after the second spray round. The surveys collectively provide a composite picture of the prevalence response to the intervention rounds at the $\sim$6(+3) month points post-intervention.

Household surveys consisted of three components: (1) a survey questionnaire administered to heads of households, (2) a women's survey questionnaire, administered to women aged 15–49 years, adopted from the Roll Back Malaria Monitoring and Evaluation Reference Group[46], and (3) a clinical survey including laboratory testing of all household residents present at the time of the survey. Fig. 3 shows the timing of the interventions and surveys.

Survey sample size and selection

Six surveys were conducted as shown in the timeline of Fig. 3. The unit of survey selection was the household and sample size estimations were based on estimates from disease prevalence studies[47]. Using the following formula to calculate adequate sample size

$$n = Z^2 \frac{P(1-P)}{d^2}, \tag{1}$$

where $Z = 1.99$ is the critical value of the normal distribution, $P = 0.4$ is the presumed prevalence at baseline, and $d = 0.035$ is the effect size precision. The choice of precision, d, should depend on expected prevalence, and the ideal precision to choose for cross-sectional surveys is one-fourth or one-fifth of the prevalence[48]. Therefore, it was estimated that a sample size of 1200 persons per arm would detect an effect size of .175, or an absolute difference between arms of $\sim \pm 3.5\%$, with Z = 1.99 and P = 10%. In order to create a non-biased sampling frame, all households in the three sub-counties were enumerated before each survey. Thereafter a computerized number generator using a probability proportion to village size approach was used to randomly select approximately 200 households (for the first four surveys) and 300 households (for the fifth and sixth survey) from each of the sub-counties.

Laboratory procedures

The clinical survey component included a finger-prick blood sample for a thick blood smear and for an RDT, measurement of hemoglobin, and preparation of filter paper blood samples for later analysis by quantitative polymerase chain reaction (qPCR). All specimens were barcoded and linked to their corresponding surveys. Thick and thin blood smears were prepared in the field for microscopy. At the laboratory the blood smears were stained with 2% Giemsa for 30 minutes and evaluated for the presence of asexual and sexual parasites (gametocytes). A thick blood smear was considered negative if examination of 100 high-power fields revealed no asexual parasites. For quality control, all slides were read by a second microscopist, and a third reviewer settled any discrepant readings. qPCR was performed on the filter-paper samples. Hemoglobin estimation was carried out on site using a battery-operated portable HemoCue analyzer (HemoCue, Anglom, Sweden). Rapid diagnostic testing was also conducted by the field team using lateral flow assay from SD-Bioline. Filter paper blood samples taken off and stored at -20°C before being assessed for parasitemia by qPCR. During qPCR deoxyribonucleic acid (DNA) was extracted using Qiagen spin columns. Parasite DNA was detected using nested PCR targeting the 18S rRNA gene. Parasite density was estimated for all positive PCR samples. Duplex 10mL reactions amplifying both human (β-tubulin) and Plasmodium (Met transfer ribonucleic acid (tRNA) gene) targets were run for each sample in a 384-well format ABI qPCR machine, model 7500. Delta Ct values between the two targets were estimated for each sample and the mean delta Ct of duplicate wells normalized to the within-run quantitative standard, comprising the WHO International Standard for *P. falciparum* DNA (IS) and representing 500 parasites/mL. The ratio of parasite density in the sample relative to the IS was then multiplied by 500 parasites/mL to obtain the estimate of parasite density. Any samples negative by qPCR but positive by nested PCR were assigned an arbitrary parasite density value of half the minimum density detected.

Participants with a temperature of greater than 37.5°C were treated with paracetamol as appropriate and those with a positive malaria RDT and no evidence of severe malaria were treated with artemether-lumefantrine (AL) according to national guidelines. Children and adults with a positive malaria RDT plus any signs of severe disease were referred to the nearest health facility for further evaluation and treatment.

Analytical Methods

Prevalence outcomes. All comparisons of prevalence outcomes followed the intention to treat analysis. Population prevalence for each arm was estimated at each survey time point by qPCR positivity, and reported, with a 95% confidence interval, for three age groups of interest: all ages, children under 5, and children between 5 and 15. The baseline survey results for RDT, microscopy, and qPCR were examined separately and qPCR results subsequently compared with the follow-up surveys in the three age categories.

Geostatistical analysis. In order to compare the impact on prevalence for residence in the IRS+MDA arm versus residence in the IRS arm, qPCR prevalence

data from the six cross-sectional surveys in each of the three arms was modeled using a spatiotemporal Gaussian model with random effects, adjusted for age and seasonality. Model-based geostatistical methods[49] provide a principled likelihood-based approach to carry out spatio-temporal predictive inferences of geo-referenced health outcomes. More importantly, this approach combines all survey data mapped in space and time during the study period, and allows modeling of the residual spatio-temporal variation in disease prevalence unexplained by the measured covariates. This model is described in detail in Supporting Information, Appendix I. The spatio-temporal geostatistical model allows for a joint analysis of the data across all surveys and quantifies the effects of control interventions more reliably, by borrowing strength of information in space and time.

Difference-in-differences analysis. For comparison, secondary difference-in-differences (DiD) analyses were performed comparing all follow-up survey timepoints with baseline for qPCR. Using SAS 9.4, the model used binomial logistic regression models that compared trends in malaria prevalence in the MDA+IRS arm to trends in malaria prevalence in the IRS arm, adjusting for potential confounding variables, (age, ITN use, and gender). Statistical significance threshold was set at $\alpha = 0.05$ using two-tailed tests. Log odds were converted to odds ratios by calculating the exponentiated regression coefficient of the interaction terms in the model. Comparisons between each of the surveys and baseline, and MDA+IRS vs. IRS are presented, and additional results are provided in Supporting Information, Appendix II.

Results

Participant characteristics

A total of 46,765 individuals and 8,004 households across all three study arms were enumerated at baseline. Roughly 51% of the population were females, and 16% were children under 5 years of age. Table 1 shows study population demography enumerated through household visits prior to the baseline survey.

Baseline prevalence

The initial survey was performed in November 2016, before the first IRS and MDA rounds in December 2016. All arms were found to be highly infected at baseline, with all ages qPCR prevalence of 62-66%, and between 73-75% in children ages 5-15 (Table 1). Described further in Supporting Information, Appendix III, microscopy prevalence was between 21-26%, with the MDA+IRS arm most highly infected and the SOC arm least infected. In contrast, RDT prevalence was between 36-47%, and showed the opposite trend, with the MDA+IRS arm least infected and the SOC arm most infected. The qPCR trends tracked the microscopy trends more closely than they tracked the RDT trends, but were considerably more sensitive than either, and showed less overall variation between arms than did either the microscopy or the RDT. Baseline malaria prevalence by age group and study arm is summarized in Supporting Information, Appendix III.

Intervention Coverage

IRS coverage

IRS coverage in both arms in all 4 rounds was over 97% of structures sprayed over structures found. This method of measuring coverage can be inaccurate when used for targeted spray operations by spray operators who are unfamiliar with the area they are spraying; however in this study, spray operators sprayed their own villages and neighboring villages, and all houses in the designated area were mapped, enumerated and targeted for spraying, which created positive social pressure not to miss compounds. Due to strong SBCC programs prior to spraying, almost all residents were home with belongings already prepared outside their home when spray operators arrived. As noted previously, IRS was extremely welcome in this community[50] and very few homes were found locked. Table 2 contains household information on structures sprayed by intervention arm.

MDA coverage

High MDA compliance was the main goal for the SBCC programs, and the investment in these activities was robust, with high community participation resulting. The denominator for MDA coverage included all persons normally resident in the study site, whether eligible or not. For rounds 1,3 and 4, MDA directly observed first dose coverage was approximately 80% or more, with ¡ 1% fall off for second and third dose compliance ascertained by blister pack and verbal confirmation (See Table 3.) Round 2 MDA coverage was slightly higher at 83% for directly observed first dose, and 82.2% after second and third dose compliance.

Cross-sectional surveys and qPCR testing

Primary analysis was based on qPCR results, because the qPCR and microscopy results proved more consistent across arms than RDT findings, and because qPCR was more sensitive throughout than either microscopy or RDT, while qPCR results were more tightly clustered at baseline than those from microscopy. During the six cross-sectional community surveys, 15925 qPCR tests for *P. falciparum* were conducted, of which 6730 (42.3%) were positive. Cross-sectional qPCR prevalence results by survey, number, date and intervention arm are presented for different age categories for all 6 surveys in Fig. 4.

Differential impact on malaria qPCR positivity of IRS over standard of care, and of MDA+IRS over IRS, measured over all surveys: geospatial analysis

The differential impact of IRS over standard care, and of MDA+IRS over IRS alone, over all 6 surveys, was analyzed using a geostatistical model with results summarized in Fig. 5. Residence in the IRS arm was associated with a 70% reduction in odds of being found infected relative to the standard care arm for children of age 5-15, and a 65% reduction for all ages as well as for children under 5. A resident of any age in the arm with both IRS and MDA had an average 80% decrease in odds of being found infected as compared with a person under the same conditions living in the standard care arm. This result, with one exception the result of surveys conducted more than half a year after the MDA campaign, was consistent across age groups, with children under 5 and 5-15 resident in the MDA+IRS arm having a 79%

decrease. Comparing the MDA+IRS and IRS only arms, we estimate a significant additional 15.5% (95% CI: [13.4%, 17.9%], p=5e-20) decrease in the adjusted odds ratio (aOR). For children under 5 and children 5-15 residence in the MDA+IRS arm was also associated with significant additional protection over IRS only, measured on average 5-7 months post-campaign. For children 5-15: aOR reduced 13.3% (95% CI: [10.5-16.7%], p=5e-5) and for children under 5: aOR reduced 10.1% (95% CI: [8.5-11.8%], p=2e-5). The geostatistical model estimated the temporal and spatial correlation for the qPCR results based on the date and geolocation of each sample. The estimated range of the spatial correlation was found to be ∼1.0km, beyond which the spatial correlation took on values smaller than 0.05. Fig. 6 shows the predicted geography of malaria prevalence, including non-surveyed locations, for children under 5 at the six survey time points of Fig. 3.

Differential impact of MDA+IRS over IRS on malaria qPCR positivity measured after each survey: DiD Analyses

Fig. 7 summarizes results from a secondary DiD analysis comparing the change in the MDA+IRS arm to the change in the IRS arm at different survey points from baseline. The aOR of qPCR malaria confirmation was 45% lower in residents who received one round of MDA+IRS compared to the IRS arm (DiD aOR=0.55, 95% CI: [0.40, 0.76], p<.001), and remained consistent when measured six months following round 2 (aOR=0.58, 95% CI: [0.43, 0.80], p<.001). When measured three months following round 2, the adjusted odds of qPCR malaria infection in residents who received MDA+IRS were 66% lower than residents who received IRS, (aOR=0.34, 95% CI: [0.23, 0.50], p<.001). Six months following rounds 3 and 4, the adjusted odds of qPCR malaria confirmation were not as low: (aOR=0.74, 95% CI: [0.57, 0.98], p<.05) and (aOR 0.72, 95% CI: [0.54, 0.98], p<.05) respectively. Details of this analysis and these comparisons may be found in Supporting Information, Appendix II.

Adverse events

Both adverse events and serious adverse events (SAEs) were monitored by the study team and SAEs reported in writing to Sigma Tau as well as to University of Makerere's internal review board (IRB) and the study's project advisory committee (PAC), a subset of whose members functioned as a data safety and monitoring board (DSMB). Three SAE's were reported. The only one with a high likelihood of being related to the study medication was a case of toxic epidermal necrolysis in a two year old girl who fully recovered.

Discussion

At present, MDA is considered to be a malaria control intervention appropriate for lower transmission environments, especially for elimination settings, although there is recent interest in investigating the untapped potential of chemoprevention as a control tool [20, 21]. We have demonstrated here that co-timed MDA and IRS campaigns may provide a new role for MDA as an augmentation for a vector control campaign in high burden environments. The quick, initial impact of the MDA collectively reduces the parasite reservoir of hosts, and the concurrent IRS extends protection against re-infection to times well beyond initial chemoprophylaxis

[33, 34]. This study examines the impact of these co-timed interventions, MDA+IRS versus IRS, and MDA+IRS and IRS versus standard of care, on population malaria prevalence at long time points (5-7 months) past a single MDA round.

Visual inspection of measured qPCR results over all 6 surveys, depicted in Fig. 4, shows that every demographic category was highly infected at baseline in November 2016, especially children 5-15, who have been shown to account for more than half of the infectious reservoir in a similar transmission environment in Uganda[51]. However, after interventions, the arms clearly separated. The SOC arm, which like all the others received new ITNs in April 2017, was consistently higher than the others, with seasonal and/or annual fluctuations. Some possible intervention impact in the SOC arm, presumably from nets, is seen at Survey 3. Both IRS arms measured much lower prevalence than SOC at all surveys post-baseline, while the MDA+IRS arm consistently contained fewer infected individuals than the IRS arm. The differential gains from MDA+IRS over IRS at the single survey that measured prevalence three months after the round, Survey 3, are particularly striking when compared with the seasonally equivalent baseline: in children under 5 qPCR positivity dropped more than an order of magnitude, from 58% at baseline to 5% one year later. By comparison, positivity for children under 5 in the IRS-only arm dropped from 53% to 15% (Fig. 4), a factor of roughly 3.5. Additional tables of malaria prevalence by study arm, age and diagnostic tool can be found in Supporting Information, Appendix III.

Geostatistical modeling analysis using all six cross-sectional surveys and an intention to treat approach showed that, over the 32 months of the study after baseline, residents of the IRS arm were ∼65% less likely to be found infected with malaria than those living in the standard of care arm with universal ITN coverage only, a large preventative difference. These results highlight the strong additional protection in this high transmission setting provided by an IRS campaign over ITNs alone. Significant additional protection was observed when a co-timed MDA campaign was included, as residents in the MDA+IRS arm were ∼80% less likely to be found infected than those resident in the standard of care arm, and had a 15.5% (95% CI: [13.4%, 17.9%], p=5e-20) decrease in the adjusted odds ratio as compared with those resident in the IRS only arm, measured roughly six months after the campaigns. For child populations, residence in the MDA+IRS arm was also associated with significant additional protection over the IRS-only arm. For children 5-15: aOR reduced 13.3% (95% CI: [10.5-16.7%], p=5e-5) and for children under 5: aOR reduced 10.1% (95% CI: [8.5-11.8%], p=2e-5) (Fig. 5).

Secondary DiD analysis, also intention to treat, compared single prevalence survey timepoints to baseline, and confirmed the significant protective impact of MDA+IRS over IRS alone (Fig. 7). These comparisons showed significantly reduced aOR for the MDA+IRS arm compared with the IRS, with regression coefficients ranging from 0.28 to 0.66 for surveys 2-6. MDA+IRA appears even more protective when compared with IRS by DiD analysis than by geospatial modeling, but as the DiD analyses involve a necessarily more limited selection of the data, the geospatial analysis is presented as primary. Some of the variation between survey points could be seasonal: the DiD analysis was adjusted for age, gender and net use, but not for seasonality. The smallest protective advantage for MDA+IRS over IRS was noted in

survey six (an expected seasonal low point), compared to survey one (an expected seasonal high point). Survey three, on the other hand, is an expected seasonal high point, conducted at the same time of year as the baseline survey, but because it was conducted only 3 months rather than 6 months after the MDA round, provided an alternate window into the dynamic preventive effect of the MDA. Additional DiD comparisons between MDA+IRS and SOC and between IRS and SOC can be found in Supporting Information, Appendix II.

It's striking that survey data, measured 5-7 months after a single treatment round of MDA in this high transmission environment, still show significant protective advantage from MDA+IRS over IRS. However, cross-sectional measurements of prevalence would almost certainly be lower and even more differentiated at points in time closer to the MDA round. High-coverage MDA immediately lowers population prevalence which then slowly rebounds, as chemoprophylaxis expires and reinfection occurs. Under the assumption of ideal DP protection and compliance with medication regimen, in the first month after the intervention, ∼79% of the population presumably enjoyed protection through the ∼28 day chemoprophylactic period of DP[52]. Survey three, performed three months after the round, showed the lowest prevalence captured in the MDA+IRS arm, and also a much more pronounced differential impact for the co-timed MDA, with 66% reduced aOR of infection for residents in the MDA+IRS arm compared with residents in the IRS arm, as opposed to reductions of 28-45% for other survey times points (see Fig. 7). This protection waned steadily in the months following the MDA round, as treated individuals became reinfected. Survey four, taken several months later, indicate the resurgent return of parasitaemia in the study area as expected. Because prevalence in most of the surveys was measured at 5-7 months after the MDA, the deepest impacts of MDA almost certainly occurred outside the survey observation window. Health facility catchment areas are not constrained, so it is difficult to reliably quantify this effect through facility based case surveillance trends. Monthly cross-sectional surveys following an MDA+IRS and an IRS intervention, or a cohort study of incidence following the interventions, could help capture the full protective impact of MDA+IRS.

Conclusion

This trial showed that a significant protective impact of MDA was sustained for long times (5-7 months) after a treatment round, a surprising result in high transmission. The 2013 Cochrane review of MDA explicitly evaluated studies for sustained impact beyond 6 months, finding only a few low transmission trials that met this criterion[53, 54]. Similar findings from a large comparative modelling study suggested that MDA was less likely to have durable impact in high transmission[55]. This finding is also in distinction to other trials of MDA impact in similar settings[38], and to cohort studies of individual treatment in absence of vector control[35]. The results suggest that MDA impact in this high transmission setting was protracted by co-timed vector control as predicted by modelling.

Limitations of this study include the fact that population-based interventions were assigned without blinding. In addition, the MDA+IRS arm was non-randomly assigned to the subcounty with the highest number of clinical cases in the year preceding the study start, which may have reduced the relative impact of MDA + IRS

compared with IRS alone. Due to prohibitive cost constraints in creating large-scale IRS clusters, and the concern of contamination through mosquito flight at smaller scales (for instance, at village level), a single large community intervention cluster (an entire subcounty, with 18- 30 villages) was used for each arm. As equipoise precluded the establishment of a control arm without any malaria prevention in place, and also the use of MDA without IRS, it is not possible to separately distinguish the effect of ITNs vs no control or to evaluate the impact of MDA in the absence of IRS. Only the first dose of MDA was observed, with the second and third dose inferred from collection of empty blister packs. If compliance was imperfect, MDA coverage would be lower than assumed, which would reduce the additional impact of MDA. Intervention impact on prevalence, with one exception, was measured at timepoints 5-7 months from each of the four rounds of intervention; these measures are unable to provide a comprehensive window into the population response to the intervention at shorter intervening time periods.

As previously reported, campaign-style all-ages MDA was both easy to implement[45], and highly acceptable in this high transmission environment[50], and achieved high coverage of ∼79% for all four rounds. IRS for vector control requires extensive community engagement and mobilization just as MDA does, and the two activities can benefit from joint investment in SBCC activities and joint community momentum. MDA's possible contribution to antimalarial resistance[56] is a valid concern, but in Uganda can be mitigated by the use of DP for MDA while artemether-lumefantrine (AL) is used for frontline therapy; the observed counter-selection between DP and AL[57, 58, 59] may offer some protection against the development of resistance.

Sustainability and cost effectiveness may be additional concerns for the use of MDA. Absent a change to the underlying forces of infection in a high transmission area, resurgence will reliably occur when control interventions cease[60]. Moreover, the more reduction a control tool achieves, the swifter will be the rebound when it is withdrawn[33]. But even where control cannot be maintained and resurgence occurs, the gains may be greater than the losses. Recently, a multi-year examination of surveillance data at reference health centers in Uganda showed that while stopping IRS was associated with a 5-fold increase in infections in the ensuing 10 months, starting IRS was associated with a more than 5-fold decrease in 8 months, a reduction that increased still further after 4 years of continuous control[61]. Effective interventions are also associated with a rapid shift in the remaining burden of malaria from younger people to older people, an advantage not captured in burden data alone[62].

To continue to make global gains against malaria, its necessary to optimize and target tools for burden reduction specifically to high transmission areas. Vector control is still the mainstay of prevention, but chemoprevention strategies are an important additional tool for high burden settings. Increased control impact from careful co-timing is predicted for all forms of vector control and has been modeled for MDA+ITNs as well as MDA+IRS[33]. Because vector control is usually delivered less frequently than chemoprevention, a co-timed use of MDA represents a low-frequency use of chemoprevention, and though maintenance and continuity are always needed in control settings, the reapplication demands, and therefore the associated costs, are modest. In highly infected communities, an annual round of

MDA does not represent additional drug pressure on a community, but instead a demographic reorganization (as most treated clinical infections are in children) and synchronization of treatment. Considered not as an elimination tool, but as a control tool in this high burden setting, co-timed IRS+MDA is an effective, practical and acceptable intervention for sustained burden reduction. Co-timed MDA is likely to be cost effective, to offer low pressure on the development of drug resistance, and could be combined with ITN distribution as easily as with IRS.

Abbreviations

ACT: artemisinin combination therapy
AL: artemether-lumefantrine
aOR: adjusted odds ratio
CI: confidence interval
DHIS2: District Health Information System Version 2
DiD: difference-in-differences
DOT: directly observed therapy
DP: dihydroartemisinin- piperaquine
DNA: deoxyribonucleic acid
DSMB: data safety and monitoring board
GPS: global positioning system
IPTp: intermittent preventive treatment for pregnant women
IPTsc: intermittent preventive treatment in schoolchildren
IRB: internal review board
IRS: indoor residual spraying
ITN: insecticide treated net
IV: intravenous
IVCC: Innovative Vector Control Consortium
MDA: mass drug administration
MOH: Ministry of Health
PAC: project advisory committee
PMI: President's Malaria Initiative
PPE: personal protective equipment
qPCR: quantitative polymerase chain reaction
RDT: rapid diagnostic test
SAE: serious adverse events
SBCC: social and behavior change communication
SMS: short message service
SOC: standard of care
tRNA: transfer ribonucleic acid
U5: under 5
VHT: village health team
WHO: World Health Organization
WHOPES: World Health Organization Pesticide Evaluation Scheme

Declarations

Ethics approval and consent to participate

The study was approved by the Makerere University School of Biomedical Sciences Higher Degrees Research and Ethics Committee (SBS-HDREC) and the Uganda National Council for Science and Technology (UNCST) ethics bodies. All study team members were annually trained in Good Clinical Practices (GCP) compliance to assure following guidelines for participant privacy and informed consent. All participants interviewed gave their informed consent or assent (for those above 8 years of age) to participate in this survey and for the information derived to be published. The datasets used in this analysis are de-identified.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article are available in the figshare repository, [https://figshare.com/account/articles/19470125].

Competing interests

The authors declare that they have no competing interests.

Funding

The study was supported by a grant from the Bill & Melinda Gates Foundation to Pilgrim Africa (OPP1148566). This study also received financial support from US-based Rotary clubs, The Rotary Foundation and Malaria Partners International through a Rotary Global Grant (GG1423515) for which Pilgrim Africa was the implementing organization. Pirimiphos-methyl (Actellic) was purchased at a reduced price from Sigma-Tau made possible by Pilgrim Africa's inclusion in IVCC's subsidy agreement with next generation IRS providers. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author's contributions

DE, AY, RE and JO contributed to the overall conceptualization of the study; DE and AY were responsible for study oversight; DE, AY, TE, WO, HW, RE, RM, SG, and JO were integral in the study design and execution; TE, WO, FB, HW, MK, RM, JN, OO and SG supported the field activities, data acquisition, and management; DE, AY, BA, HW, KC, TE, WO, RE, SP, EG and MR contributed to the analytical approaches for the study, various analyses, validation, interpretation and visualization of the data. DE wrote the original manuscript draft; BA and SP made contributions to Methods and Supporting Information; and BA, HW, RE, SP, JN and EG reviewed and edited drafts of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

This project would not have been successful without the support, dedication and passion of our administrative, data management and financial staff members: Angella Amuron, Claire Ogullei, Samson Ebalu, Jude Emenyu, JaneKakai, Doris Akello, Dorcus Achan, James Ocan, Patrick Aliau, Robert Emugu, RichardKirunda, Ketty Acan, John Bakibinga, James Adiga, Sally Opus, Emmanuel Data, Hellen Alamo, Nicholas Wendo, Dr. Mary Kyohere, Stephen Odeke, and Elizabeth Aigi. We would also like to acknowledge our CAB members: MartinOkello, Jackline Ibiara, and Fr. Paul Ekwenyu, whose gracious service to this project was invaluable. Finally, we acknowledge and thank all of the District Health Officers, Local Council members, Health Facility Professionals, In-Charge officers, HMIS focal points and Data Volunteers for their tireless dedication to not only this project, but also towards their continued perseverance in reducing malaria burden in Katakwi District. We thank you.

Author details

[1]Pilgrim Africa, 8001 14th Avenue NE, Suite A, 98115 Seattle, WA, USA. [2]Makerere University College of Health Sciences, School of Public Health P.O. Box 7072, Kampala Uganda. [3]Pilgrim Africa, Plot 8 Engwau Road, PO Box 577, Soroti Uganda. [4]Lancaster University Furness College, B73 Lancaster, United Kingdom LA1 4YG UK. [5]University of Colorado Anschutz Medical Campus 12631 East 17th Avenue Aurora, CO 80045 USA. [6]Micron School of Materials Science and Engineering, Boise State University, Engineering Building, Suite 338, Boise, ID, 83725 USA. [7]Infectious Diseases Research Collaboration Kampala, Uganda UG. [8]Johns Hopkins Bloomberg School of Public Health Baltimore, MD USA. [9]National Malaria Control Division Ministry of Health Uganda Kampala, Uganda UG.

References

1. World Health Organization: High Burden to High Impact: a Targeted Malaria Response. World Health Organization (2018)
2. World Health Organization: World Malaria Report 2019. World Health Organization (2020)
3. World Health Organization: World Malaria Report 2020: 20 years of global progress and challenges. World Health Organization (2020)
4. Yeka, A., Gasasira, A., Mpimbaza, A., Achan, J., Nankabirwa, J., Nsobya, S., Staedke, S.G., Donnelly, M.J., Wabwire-Mangen, F., Talisuna, A., *et al.*: Malaria in Uganda: Challenges to control on the long road to elimination: I. Epidemiology and current control efforts. Acta Tropica **121**(3), 184–195 (2012)
5. Steinhardt, L.C., Yeka, A., Nasr, S., Wiegand, R.E., Rubahika, D., Sserwanga, A., Wanzira, H., Lavoy, G., Kamya, M., Dorsey, G., *et al.*: The effect of indoor residual spraying on malaria and anemia in a high-transmission area of northern Uganda. The American Journal of Tropical Medicine and Hygiene **88**(5), 855 (2013)
6. Kigozi, R., Baxi, S.M., Gasasira, A., Sserwanga, A., Kakeeto, S., Nasr, S., Rubahika, D., Dissanayake, G., Kamya, M.R., Filler, S., *et al.*: Indoor residual spraying of insecticide and malaria morbidity in a high transmission intensity area of Uganda. PloS one **7**(8), 42857 (2012)

7. Nankabirwa, J., Arinaitwe, E., Rek, J., Kilama, M., Kizza, T., Staedke, S.G., Bousema, T., Drakeley, C., Kamya, M., Dorsey, G., *et al.*: Malaria transmission, infection, and disease following sustained indoor residual spraying of insecticide in Tororo, Uganda. The American Journal of Tropical Medicine and Hygiene **103**(4), 1525 (2020)
8. Kamya, M.R., Kakuru, A., Muhindo, M., Arinaitwe, E., Nankabirwa, J.I., Rek, J., Bigira, V., Kapisi, J., Wanzira, H., Achan, J., *et al.*: The impact of control interventions on malaria burden in young children in a historically high-transmission district of Uganda: a pooled analysis of cohort studies from 2007 to 2018. The American Journal of Tropical Medicine and Hygiene **103**(2), 785 (2020)
9. Okethwangu, D., Opigo, J., Atugonza, S., Kizza, C.T., Nabatanzi, M., Biribawa, C., Kyabayinze, D., Ario, A.R.: Factors associated with uptake of optimal doses of intermittent preventive treatment for malaria among pregnant women in Uganda: analysis of data from the Uganda Demographic and Health Survey, 2016. Malaria Journal **18**(1), 1–8 (2019)
10. Musoke, D., Ndejjo, R., Wafula, S.T., Kasasa, S., Nakiyingi-Miiro, J., Musoke, M.B.: Malaria health seeking practices for children, and intermittent preventive treatment in pregnancy in Wakiso District, Uganda. African Health Sciences **21**(4), 1722–32 (2021)
11. Nuwa, A., Oola, J., Obonyo, S.O., Feldman, M., Karungi, S.C., Kertho, E., Odong, D.S., Kimera, I., Magumba, G., Beinomugisha, G., et al.: District-led malaria surveillance and response as an effective way to manage malaria upsurges following the withdrawal of indoor residual spraying: A case study from Nwoya District, northern Uganda (2021)
12. Tusting, L.S., Bisanzio, D., Alabaster, G., Cameron, E., Cibulskis, R., Davies, M., Flaxman, S., Gibson, H.S., Knudsen, J., Mbogo, C., *et al.*: Mapping changes in housing in sub-Saharan Africa from 2000 to 2015. Nature **568**(7752), 391–394 (2019)
13. Tusting, L.S., Ippolito, M.M., Willey, B.A., Kleinschmidt, I., Dorsey, G., Gosling, R.D., Lindsay, S.W.: The evidence for improving housing to reduce malaria: a systematic review and meta-analysis. Malaria Journal **14**(1), 1–12 (2015)
14. Rek, J.C., Alegana, V., Arinaitwe, E., Cameron, E., Kamya, M.R., Katureebe, A., Lindsay, S.W., Kilama, M., Staedke, S.G., Todd, J., *et al.*: Rapid improvements to rural Ugandan housing and their association with malaria from intense to reduced transmission: a cohort study. The Lancet Planetary Health **2**(2), 83–94 (2018)
15. Liu, J.X., Bousema, T., Zelman, B., Gesase, S., Hashim, R., Maxwell, C., Chandramohan, D., Gosling, R.: Is housing quality associated with malaria incidence among young children and mosquito vector numbers? evidence from Korogwe, Tanzania. PloS one **9**(2), 87358 (2014)
16. The Uganda Bureau of Statistics (UBOS), National Malaria Control Programme (NMCP), Inner City Fund Macro (ICF): Uganda Malaria Indicator Survey, 2009, Kampala, Uganda, and Calverton, Maryland, USA (2010)
17. The Uganda Bureau of Statistics (UBOS), National Malaria Control Programme (NMCP), Inner City Fund Macro (ICF): Uganda Malaria Indicator Survey, 2018–19, Kampala, Uganda, and Rockville, Maryland, USA (2020)
18. Nkumama, I.N., O'Meara, W.P., Osier, F.H.: Changes in malaria epidemiology in Africa and new challenges for elimination. Trends in Parasitology **33**(2), 128–140 (2017)
19. Feachem, R.G., Chen, I., Akbari, O., Bertozzi-Villa, A., Bhatt, S., Binka, F., Boni, M.F., Buckee, C., Dieleman, J., Dondorp, A., *et al.*: Malaria eradication within a generation: ambitious, achievable, and necessary. The Lancet **394**(10203), 1056–1112 (2019)
20. Rosenthal, P.J., John, C.C., Rabinovich, N.R.: Malaria: how are we doing and how can we do better? The American Journal of Tropical Medicine and Hygiene **100**(2), 239 (2019)
21. Alonso, P.L.: The role of mass drug administration of antimalarials. The American Journal of Tropical Medicine and Hygiene **103**(2 Suppl), 1 (2020)
22. Xu, J.-W., Lee, R., Li, X.-H., Liu, H.: Transition of radical, preventive and presumptive treatment regimens for malaria in China: a systematic review. Malaria Journal **20**(1), 1–14 (2021)
23. Zu-Jie, Z.: The malaria situation in the People's Republic of China. Bulletin of the World Health Organization **59**(6), 931 (1981)
24. World Health Organization: From 30 million cases to zero: China is certified malaria-free by WHO. https://www.who.int/news/item/30-06-2021-from-30-million-cases-to-zero-china-is-certified-malaria-free-by-who. Accessed: 8/2021
25. Chen, J.-H., Fen, J., Zhou, X.-N.: From 30 million to zero malaria cases in China: lessons learned for China–Africa collaboration in malaria elimination. Infectious Diseases of Poverty **10**(1), 1–4 (2021)
26. World Health Organization: The role of mass drug administration, mass screening and treatment, and focal screening and treatment for malaria: recommendations. World Health Organization (2015)
27. World Health Organization: Mass drug administration for falciparum malaria: a practical field manual. World Health Organization (2017)
28. Gerardin, J., Eckhoff, P., Wenger, E.A.: Mass campaigns with antimalarial drugs: a modelling comparison of artemether-lumefantrine and DHA-piperaquine with and without primaquine as tools for malaria control and elimination. BMC Infectious Diseases **15**(1), 1–14 (2015)
29. Eisele, T.P.: Mass drug administration can be a valuable addition to the malaria elimination toolbox. Malaria Journal **18**(1), 1–5 (2019)
30. Sawa, P., Shekalaghe, S.A., Drakeley, C.J., Sutherland, C.J., Mweresa, C.K., Baidjoe, A.Y., Manjurano, A., Kavishe, R.A., Beshir, K.B., Yussuf, R.U., *et al.*: Malaria transmission after artemether-lumefantrine and dihydroartemisinin-piperaquine: a randomized trial. The Journal of Infectious Diseases **207**(11), 1637–1645 (2013)
31. Zani, B., Gathu, M., Donegan, S., Olliaro, P.L., Sinclair, D.: Dihydroartemisinin-piperaquine for treating uncomplicated Plasmodium falciparum malaria. Cochrane Database of Systematic Reviews **1** (2014)
32. Hung, T.-Y., Davis, T.M., Ilett, K.F., Karunajeewa, H., Hewitt, S., Denis, M.B., Lim, C., Socheat, D.: Population pharmacokinetics of piperaquine in adults and children with uncomplicated falciparum or vivax malaria. British Journal of Clinical Pharmacology **57**(3), 253–262 (2004)

33. Elliott, R., Smith, D., Echodu, D.: Medical and entomological malarial interventions, a comparison and synergy of two control measures using a Ross/Macdonald model variant and openmalaria simulation. Mathematical Biosciences **300**, 187–200 (2018)
34. Elliott, R.C., Smith, D.L., Echodu, D.C.: Synergy and timing: a concurrent mass medical campaign predicted to augment indoor residual spraying for malaria. Malaria Journal **18**(1), 1–22 (2019)
35. Nankabirwa, J.I., Wandera, B., Amuge, P., Kiwanuka, N., Dorsey, G., Rosenthal, P.J., Brooker, S.J., Staedke, S.G., Kamya, M.R.: Impact of intermittent preventive treatment with dihydroartemisinin-piperaquine on malaria in Ugandan schoolchildren: a randomized, placebo-controlled trial. Clinical Infectious Diseases **58**(10), 1404–1412 (2014)
36. Eisele, T.P., Silumbe, K., Finn, T., Chalwe, V., Kamuliwo, M., Hamainza, B., Moonga, H., Bennett, A., Yukich, J., Keating, J., *et al.*: Assessing the effectiveness of household-level focal mass drug administration and community-wide mass drug administration for reducing malaria parasite infection prevalence and incidence in Southern Province, Zambia: study protocol for a community randomized controlled trial. Trials **16**(1), 1–13 (2015)
37. Steketee, R.W., Miller, J.M., Kawesha, E.C.: Implications of the MDA Trial in Southern Province, Zambia, for malaria control and elimination. The American Journal of Tropical Medicine and Hygiene **103**(2 Suppl), 98 (2020)
38. Eisele, T.P., Bennett, A., Silumbe, K., Finn, T.P., Porter, T.R., Chalwe, V., Hamainza, B., Moonga, H., Kooma, E., Kawesha, E.C., *et al.*: Impact of Four Rounds of Mass Drug Administration with Dihydroartemisinin–Piperaquine Implemented in Southern Province, Zambia. The American Journal of Tropical Medicine and Hygiene **103**(2 Suppl), 7 (2020)
39. Molineaux, L., Gramiccia, G., Organization, W.H., *et al.*: The Garki Project: Research on the Epidemiology and Control of Malaria in the Sudan Savanna of West Africa. World Health Organization, Geneva (1980)
40. Ministry of Health, U.: The Uganda Malaria Reduction Strategic Plan 2014–2020. Malaria Control Programme, Ministry of Health Kampala, Uganda (2015)
41. Oguttu, D.W., Matovu, J.K., Okumu, D.C., Ario, A.R., Okullo, A.E., Opigo, J., Nankabirwa, V.: Rapid reduction of malaria following introduction of vector control interventions in Tororo District, Uganda: a descriptive study. Malaria Journal **16**(1), 1–8 (2017)
42. Okia, M., Ndyomugyenyi, R., Kirunda, J., Byaruhanga, A., Adibaku, S., Lwamafa, D.K., Kironde, F.: Bioefficacy of long-lasting insecticidal nets against pyrethroid-resistant populations of anopheles gambiae ss from different malaria transmission zones in Uganda. Parasites & Vectors **6**(1), 1–10 (2013)
43. Kilama, M., Smith, D.L., Hutchinson, R., Kigozi, R., Yeka, A., Lavoy, G., Kamya, M.R., Staedke, S.G., Donnelly, M.J., Drakeley, C., *et al.*: Estimating the annual entomological inoculation rate for Plasmodium falciparum transmitted by Anopheles gambiae s.l. using three sampling methods in three sites in Uganda. Malaria Journal **13**(1), 1–13 (2014)
44. Haji, K.A., Thawer, N.G., Khatib, B.O., Mcha, J.H., Rashid, A., Ali, A.S., Jones, C., Bagi, J., Magesa, S.M., Ramsan, M.M., *et al.*: Efficacy, persistence and vector susceptibility to pirimiphos-methyl (Actellic® 300CS) insecticide for indoor residual spraying in Zanzibar. Parasites & Vectors **8**(1), 1–7 (2015)
45. Mulebeke, R., Wanzira, H., Bukenya, F., Eganyu, T., Collborn, K., Elliott, R., Van Geertruyden, J.-P., Echodu, D., Yeka, A.: Implementing population-based mass drug administration for malaria: experience from a high transmission setting in North Eastern Uganda. Malaria Journal **18**(1), 1–10 (2019)
46. World Health Organization and others: Malaria indicator survey: basic documentation for survey design and implementation (2005)
47. Daniel, W.W., Cross, C.L.: Biostatistics: a Foundation for Analysis in the Health Sciences. Wiley, New Jersey (2018)
48. Pourhoseingholi, M.A., Vahedi, M., Rahimzadeh, M.: Sample size calculation in medical studies. Gastroenterology and Hepatology from bed to bench **6**(1), 14 (2013)
49. Diggle, P., Giorgi, E.: Model-based Geostatistics for Global Public Health: Methods and Applications. Chapman and Hall/CRC Press, London (2019)
50. Wanzira, H., Naiga, S., Mulebeke, R., Bukenya, F., Nabukenya, M., Omoding, O., Echodu, D., Yeka, A.: Community facilitators and barriers to a successful implementation of mass drug administration and indoor residual spraying for malaria prevention in Uganda: a qualitative study. Malaria Journal **17**(1), 1–8 (2018)
51. Andolina, C., Rek, J.C., Briggs, J., Okoth, J., Musiime, A., Ramjith, J., Teyssier, N., Conrad, M., Nankabirwa, J.I., Lanke, K., et al.: Sources of persistent malaria transmission in a setting with effective malaria control in eastern Uganda: a longitudinal, observational cohort study. The Lancet Infectious Diseases (2021)
52. Agarwal, A., McMorrow, M., Onyango, P., Otieno, K., Odero, C., Williamson, J., Kariuki, S., Kachur, S.P., Slutsker, L., Desai, M.: A randomized trial of artemether-lumefantrine and dihydroartemisinin-piperaquine in the treatment of uncomplicated malaria among children in western Kenya. Malaria Journal **12**(1), 1–8 (2013)
53. Poirot, E., Skarbinski, J., Sinclair, D., Kachur, S.P., Slutsker, L., Hwang, J.: Mass drug administration for malaria. Cochrane Database of Systematic Reviews (12) (2013)
54. Newby, G., Hwang, J., Koita, K., Chen, I., Greenwood, B., Von Seidlein, L., Shanks, G.D., Slutsker, L., Kachur, S.P., Wegbreit, J., *et al.*: Review of mass drug administration for malaria and its operational challenges. The American Journal of Tropical Medicine and Hygiene **93**(1), 125 (2015)
55. Brady, O.J., Slater, H.C., Pemberton-Ross, P., Wenger, E., Maude, R.J., Ghani, A.C., Penny, M.A., Gerardin, J., White, L.J., Chitnis, N., *et al.*: Role of mass drug administration in elimination of plasmodium falciparum malaria: a consensus modelling study. The Lancet Global Health **5**(7), 680–687 (2017)
56. von Seidlein, L., Greenwood, B.M.: Mass administrations of antimalarial drugs. Trends in Parasitology **19**(10), 452–460 (2003)
57. Conrad, M.D., LeClair, N., Arinaitwe, E., Wanzira, H., Kakuru, A., Bigira, V., Muhindo, M., Kamya, M.R., Tappero, J.W., Greenhouse, B., *et al.*: Comparative impacts over 5 years of artemisinin-based combination therapies on Plasmodium falciparum polymorphisms that modulate drug sensitivity in Ugandan children. The Journal of Infectious Diseases **210**(3), 344–353 (2014)

58. Okell, L.C., Reiter, L.M., Ebbe, L.S., Baraka, V., Bisanzio, D., Watson, O.J., Bennett, A., Verity, R., Gething, P., Roper, C., *et al.*: Emerging implications of policies on malaria treatment: genetic changes in the Pfmdr-1 gene affecting susceptibility to artemether–lumefantrine and artesunate–amodiaquine in Africa. BMJ Global Health **3**(5), 000999 (2018)
59. Rasmussen, S.A., Ceja, F.G., Conrad, M.D., Tumwebaze, P.K., Byaruhanga, O., Katairo, T., Nsobya, S.L., Rosenthal, P.J., Cooper, R.A.: Changing antimalarial drug sensitivities in Uganda. Antimicrobial Agents and Chemotherapy **61**(12), 01516–17 (2017)
60. Cohen, J.M., Smith, D.L., Cotter, C., Ward, A., Yamey, G., Sabot, O.J., Moonen, B.: Malaria resurgence: a systematic review and assessment of its causes. Malaria journal **11**(1), 1–17 (2012)
61. Namuganga, J.F., Epstein, A., Nankabirwa, J.I., Mpimbaza, A., Kiggundu, M., Sserwanga, A., Kapisi, J., Arinaitwe, E., Gonahasa, S., Opigo, J., *et al.*: The impact of stopping and starting indoor residual spraying on malaria burden in Uganda. Nature Communications **12**(1), 1–9 (2021)
62. Kigozi, S.P., Kigozi, R.N., Epstein, A., Mpimbaza, A., Sserwanga, A., Yeka, A., Nankabirwa, J.I., Halliday, K., Pullan, R.L., Rutazaana, D., *et al.*: Rapid shifts in the age-specific burden of malaria following successful control interventions in four regions of Uganda. Malaria Journal **19**(1), 1–12 (2020)

Figures

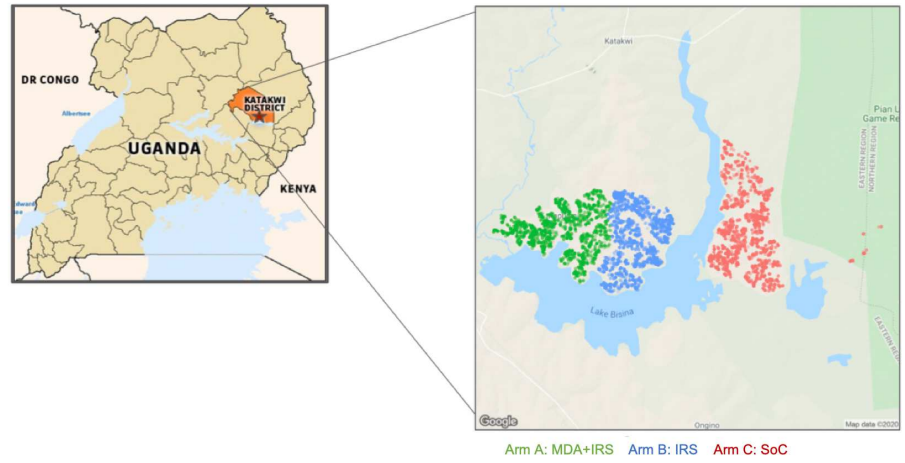

Figure 1 The study site with mapped households and arm assignments. Katakwi district on a map of Uganda, with an inset map showing the study area bordering Lake Bisina. The points on the inset map show geolocated households in 85 villages, color coded by adjacent intervention arms: green for Arm A with MDA+IRS, blue for Arm B with IRS, red for Arm C, standard of care. All sites have ITNs, case management, and IPTp which constitutes standard of care.

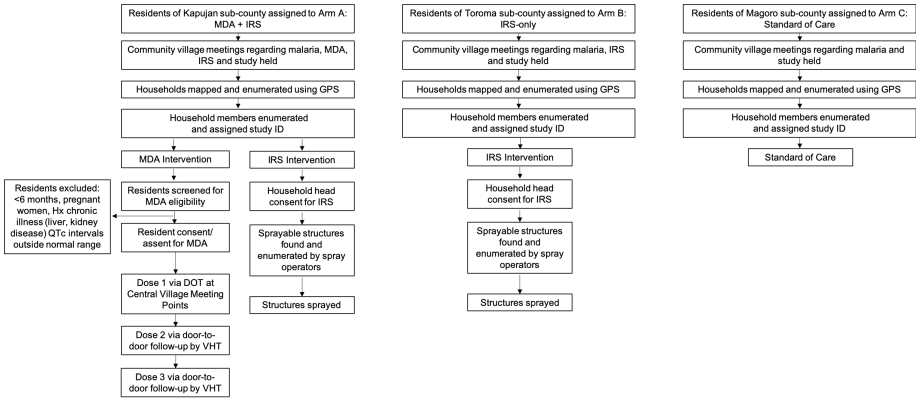

Figure 2 Flow chart of study intervention implementation.

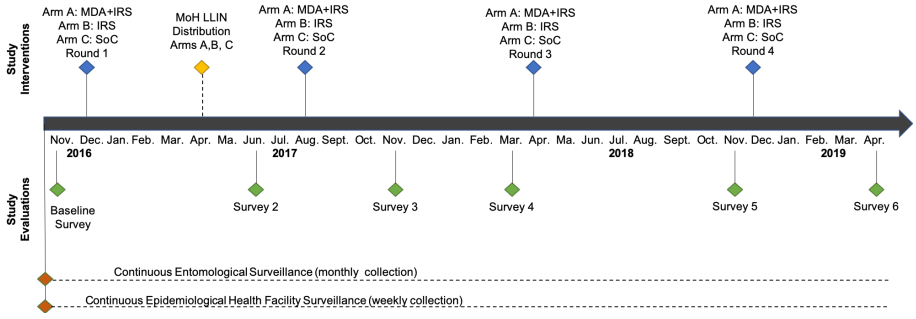

Figure 3 Chronology of the study interventions and monitoring activities. The bottom six green diamonds represent the six cross-sectional surveys in November 2016, June 2017, November 2017, March 2018, November 2018 and April 2019. The four top blue diamonds represent the co-timed intervention rounds (Arms A B) in late November/ early December 2016, August 2017, April 2018, and late November/early December 2018. The top yellow diamond shows the universal ITN coverage campaign conducted in April 2017 by MOH. The bottom two orange diamonds show ongoing entomological and health facility epidemiological surveillance.

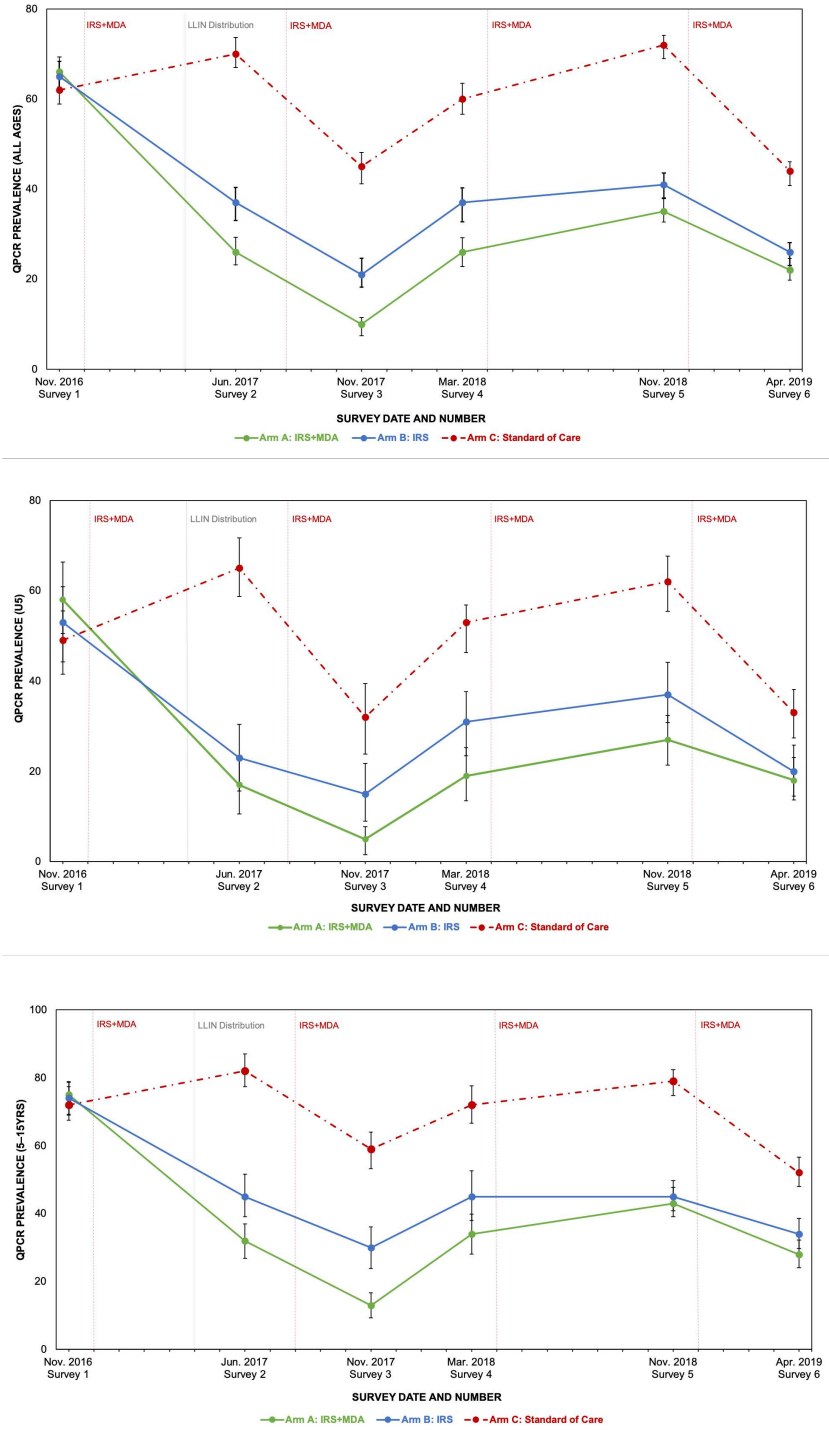

Figure 4 Cross-sectional malaria prevalence by arm, at six time points (all ages, under 5, and children 5-15). The vertical dashed red lines show the co-timed IRS + MDA and IRS only intervention rounds in the IRS arms, while the vertical grey dashed line shows the universal ITN coverage campaign in all three arms. The points show the cross-sectional survey sample percent qPCR positivity at the times of the surveys, while the bars represent the associated 95% confidence intervals for population prevalence.

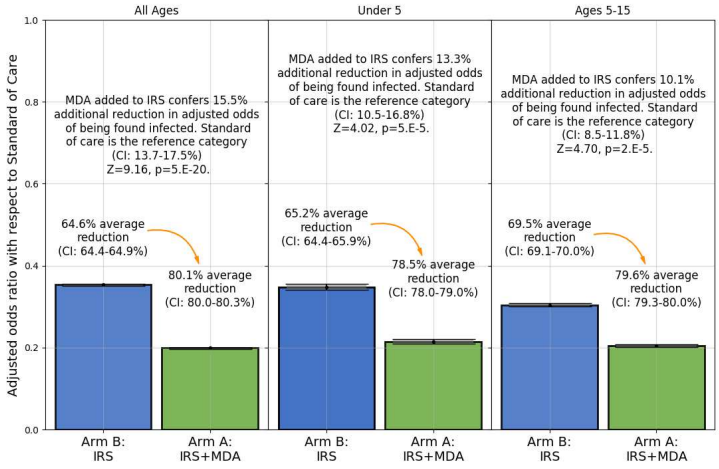

Figure 5 Adjusted odds of being found infected if resident in IRS + MDA or IRS arm relative to resident in standard care (children under 5, children 5-15, and all ages in panels left to right).

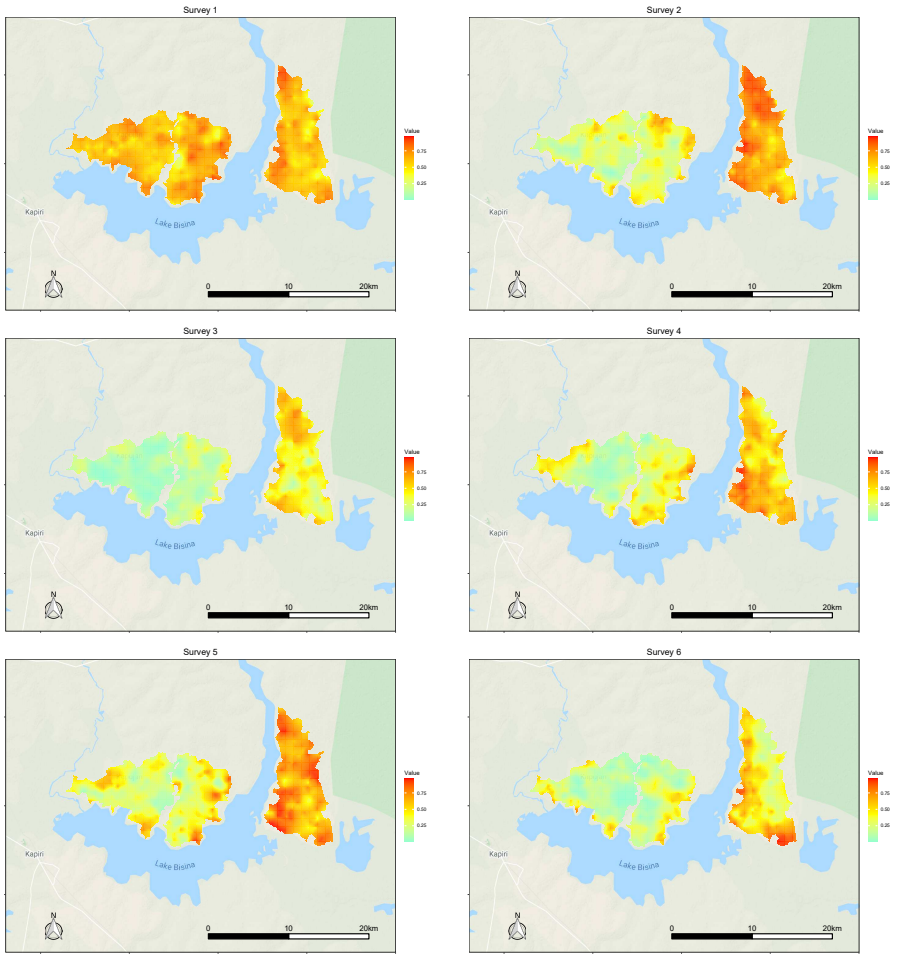

Figure 6 Heat maps of predicted spatial heterogeneity in malaria prevalence in children under 5 in surveys 1-6.

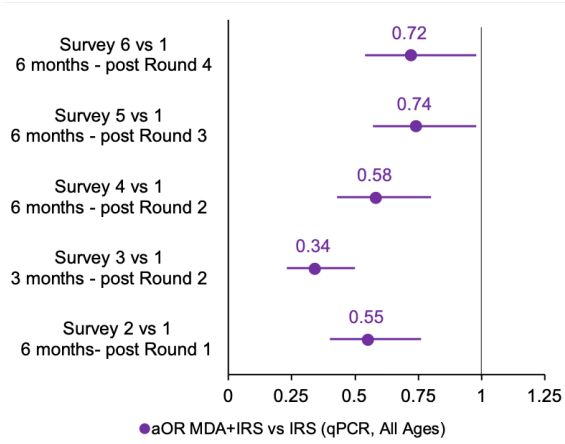

Figure 7 DiD adjusted odds ratio of qPCR confirmed malaria (all ages), MDA+IRS vs IRS, by survey timing compared to baseline.

Tables

Table 1 Baseline populations and qPCR malaria prevalence by study arm and age category

Population & Baseline qPCR Prevalence by Age	Study Arms		
	Arm A: MDA+IRS	**Arm B: IRS**	**Arm C: SoC**
Total enumerated population	15,738	10,503	20,524
Total children under 5 years (U5), %	2,551 (16.2)	1,606 (15.3)	3,501 (17.1)
Total children 5-15 years, %	5,666 (36.0)	3,585 (34.1)	7,169 (34.9)
All Ages			
Sampled population	807	809	912
qPCR +/n[1]	514/779	510/785	520/839
Malaria Prevalence, % (95% CI)	66.0 (62.6-69.3)	65.0 (61.6-68.3)	62.0 (58.9-65.3)
U5			
Sampled population	155	141	213
qPCR +/n	87/149	72/137	95/196
Malaria Prevalence, % (95% CI)	58.4 (50.5-66.3)	52.6 (44.2-60.9)	48.5 (41.5-55.5)
5-15 Years			
Sampled population	319	323	348
qPCR +/n	231/312	234/317	229/316
Malaria Prevalence, % (95% CI)	75.0 (69.2-78.9)	73.8 (69.0-78.7)	72.5 (67.5-77.4)

[1] qPCR results missing, n=125.

Table 2 SMS/Sprayer operator-based IRS coverage: houses sprayed/houses found

Intervention Round & Characteristic	Study Arms		Total
	Arm A: MDA+IRS	**Arm B: IRS**	
Round 1: Dec, 2016			
Houses sprayed	6483	5179	**11,662**
Houses found	6509	5339	**11,852**
Coverage (%)	99.6	97.0	**98.4**
Population protected			**30,741**
Round 2: Aug, 2017			
Houses sprayed	6173	5429	**11,602**
Houses found	6235	5597	**11,827**
Coverage (%)	99.0	97.0	**98.1**
Population protected			**31,663**
Round 3: Apr, 2018			
Houses sprayed	6658	5541	**12,199**
Houses found	6718	5712	**12,435**
Coverage (%)	99.1	97.0	**98.1**
Population protected			**32,979**
Round 4: Dec, 2018			
Houses sprayed	6355	5280	**11,635**
Houses found	6426	5399	**11,824**
Coverage (%)	98.9	97.8	**98.4**
Population protected			**32,438**

Table 3 MDA coverage by method and round (Arm A), December 2016–December 2018.

Coverage by Dose & Method	Round (Month, Year)			
	Round 1, Dec 2016 n(%)	**Round 2, Aug 2017 n(%)**	**Round 3, Apr 2018 n(%)**	**Round 4, Dec 2018 n(%)**
Dose 1				
Fixed distribution	12,536 (80.0)	12,586 (83.0)	12,366 (80.0)	12,449 (80.2)
Dose 2				
Door-to-door monitoring	NA	12,412 (81.8)	12,344 (79.8)	12,399 (79.9)
Dose 3				
Door-to-door monitoring	NA	12,408 (81.8)	12,343 (79.8)	12,399 (79.9)
Total (N)	**15,668**	**15,170**	**15,460**	**15,525**

Supporting Information

Appendix I. Spatiotemporal geostatistical model

Let $p_j(x_i, t_i)$ denote the probability of a positive qPCR result from the j-th individual sampled at i-th location x_i and month t_i, where $t_i \in \{1, \ldots, 31\}$, with $t_i = 1$ representing November 2016. Conditionally on a spatio-temporal Gaussian process $S(x_i, t_i)$ and unstructured random effects $Z(x_i, t_i)$, we modeled the probability of positive qPCR test $p_j(x_i, t_i)$ as logit-linear regression given by,

$$\begin{aligned}\log\left\{\frac{p_j(x_i,t_i)}{1-p_j(x_i,t_i)}\right\} &= \beta_0 + s(a_{ij}) + \beta_4 t_i + \beta_5 I(t_i \in HTS) + \\ &\beta_6 I(t_i \in Baseline) + \beta_7 I(t_i \in Kap_{base}) + \beta_8 I(t_i \in Tor_{base}) + \\ &\alpha_1 I(x_i \in Tor) + \alpha_2 I(x_i \in Kap) + S(x_i, t_i) + Z(x_i, t_i), \end{aligned} \quad (2)$$

where $s(a_{ij})$ is a linear spline expressed by,

$$\begin{aligned} s(a_{ij}) &= \beta_1 \min(a_{ij}, a_0) + \beta_2 I(a_{ij} > a_1)\min(a_{ij} - a_1, a_1 - a_0) + \\ &\beta_3 \max(a_{ij} - a_1, 0). \end{aligned} \quad (3)$$

In this expression, a_{ij} denotes the age of person j at location x_i, and $a_0 = 10$ and $a_1 = 29$ are ages where a change in the slope of the linear spline is imposed. The values of 10 and 29 years were chosen based on a deviance profile of all possible combinations for a_0 and a_1 using a standard generalized linear model. In the above equation, β_1, β_2 and β_3 are the slopes of age in different age groups, that is the effects of age on the log-odds of prevalence in the age groups $0-10$, $10-29$, and $30+$ respectively.

We used linear functions of time (corresponding to β_4) to account for long-term trends. Seasonality was included by classifying the year into a high transmission season (June-August), with prefactor β_5 and low transmission season otherwise.

We accounted for differences in prevalence between different trial arms at baseline by including indicator variables of whether or not a data point was sampled at baseline in ($Baseline$), Kapujan during baseline (Kap_{base}) and Toroma during baseline (Tor_{base}) corresponding to $\beta_6\, \beta_7, \beta_8$, respectively.

To account for the different intervention strategies, Tor represents Toroma, Arm B, which received IRS only while Kap represents Arm A, Kapujan, which received both IRS and MDA. The main regression parameters of interest are therefore α_1, α_2, respectively, which when lesser, represents a greater impact of the corresponding intervention. Arm C, Magoro, the SOC arm, is the reference category.

Table 4 Estimates of the geostatistical parameters.

Variable	Parameter	Point estimate	95% CI
Other covariates effects			
Intercept (Control, low trans.)	$\exp(\beta_0)$	0.4234	(0.3405, 0.5264)
Age trend in $0-10$ y/o	$\exp(\beta_1)$	1.2006	(1.1806, 1.2210)
Age trend in $10-29$ y/o	$\exp(\beta_2)$	0.9368	(0.9288, 0.9448)
Age trend in ≥ 29 y/o	$\exp(\beta_3)$	0.9913	(0.9862, 0.9965)
Time trend	$\exp(\beta_4)$	1.0107	(1.0029, 1.0187)
Seasonal effect (High trans. season)	$\exp(\beta_5)$	1.7408	(1.4697, 2.0619)
Baseline main effect	$\exp(\beta_6)$	1.6108	(1.2547, 2.0680)
Baseline effect in the arm with IRS Only	$\exp(\beta_7)$	2.5774	(1.9520, 3.4033)
Baseline effect in the arm with MDA + IRS	$\exp(\beta_8)$	5.4293	(4.0901, 7.2069)
Interventions effects			
IRS Only	$\exp(\alpha_1)$	0.3533	(0.3150, 0.3963)
MDA + IRS	$\exp(\alpha_2)$	0.1987	(0.1768, 0.2233)
Residual spatiotemporal effects			
Signal variance	σ^2	5.4445	(4.8036, 6.1710)
Range parameter	ϕ	1.0260	(0.8526, 1.2347)
Nugget effect	τ^2	0.4559	(0.3611, 0.5757)
Temporal effect	ψ	2.3645	(1.5550, 3.5954)

We modelled the spatially and temporally correlated random variations $S(x_i, t_i)$ as a stationary and isotropic Gaussian process with the separable correlation function,

$$\rho(u, v; (\sigma^2, \phi, \psi)) = \rho_1(u; (\sigma^2, \phi))\rho_2(v; \psi), \quad (4)$$

where the spatial component of the correlation function is modelled as $\rho_1(u; (\sigma^2, \phi)) = \exp(-u/\phi)$, where ϕ regulates the pace at which the spatial correlation decays for increasing distance u between any two locations, and the temporal correlation function as $\rho_2(v; \psi) = 1/(1 + v/\psi)$ with v being the difference between any two time points. We modelled the spatially unstructured random effects $Z(x_i, t_i)$ as independent and identically distributed Gaussian random variables with variance τ^2.

The final data consisted of 15925 qPCR tests for *P. falciparum*, of which 6730 (42.3%) were positive. Table 4 shows parameter estimates of the geostatistical model of equations 2-3. As expected, the odds ratio increases sharply in

the early years of life until age 10, and it decreases moderately thereafter until around the age of 30, after which there is very slow decrease in later years (Fig. 8). The estimate range of the spatial correlation is about 1.0km, beyond which the spatial correlation takes values smaller than 0.05. The estimated range of the temporal correlation is about one month. As indicated by the larger estimate of σ^2 than τ^2, the spatial variation dominates substantially the unexplained variation on a scale smaller than the minimum observed distance.

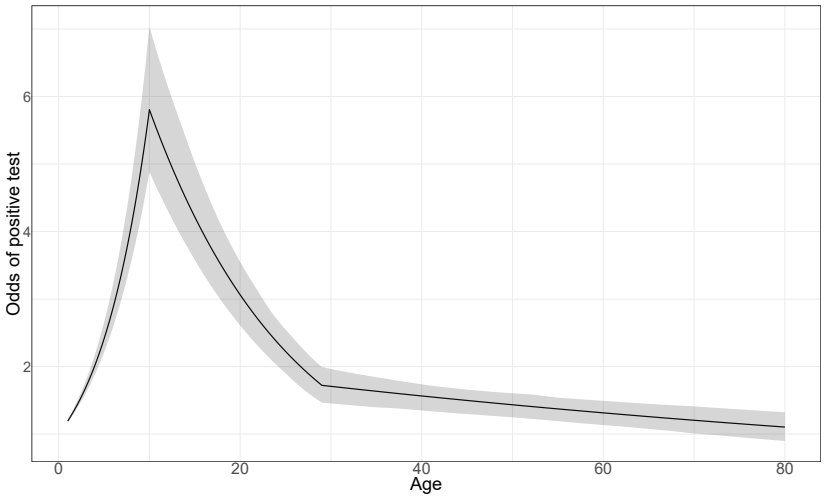

Figure 8 The effect of age on odds ratio. The solid line indicates the odds ratio at different ages, and the shaded grey area is the associated 95% confidence interval.

Appendix II. Additional DiD Analyses

The DiD design is a quasi-experimental method that relies on the assumption that in the absence of any intervention, the study arms receiving the enhanced malaria interventions have identical trends in outcomes as the SOC (control) arm.

Using SAS 9.4, the model used a binomial logistic regression with the proportion of positive malaria cases by diagnostic tool (qPCR, microscopy and RDT) and age as the dependable variables. Indicator variables for survey timing (baseline/post-intervention surveys) and study arms were used, with co-variates determined through backwards stepwise procedure, and an interaction term between survey timing and study arms. Statistical significance threshold was set at alpha = .05 using two tailed tests. Log odds were converted to odds ratios by calculating the exponentiated regression coefficient of the interaction terms in the model. DiD analyses were not done for positive malaria cases in the 'all ages' group by RDT, since malaria prevalence at baseline was significantly higher in the SoC (Arm C) compared to Arms A and B by this metric.

After adjusting for age, ITN use and gender, Fig. 9 (upper left) shows the odds of qPCR confirmed malaria in residents receiving MDA+IRS were significantly lower compared to residents receiving SOC, at all survey time points. The aOR of qPCR malaria confirmation was 90% lower in residents who received 1 round of MDA+IRS compared to the SoC arm (DiD aOR = .10 [95% CI: .08 –.14], p$< .001$); adjusted odds remained consistent 6 months following rounds 2 and 3 (DiD aOR = .18 [95% CI: .07 – .15], p$< .001$) and (DiD aOR = .17 [95% CI: .13 – .31], p$< .001$), respectively. The odds of malaria 6 months following 4 full rounds of MDA+IRS was 70% lower than the SoC arm (DiD aOR = .30 [95% CI: .23 – .40], p$< .001$).

Residents in the IRS arm (Fig. 9,upper right) also showed significantly lower odds of qPCR confirmed malaria in relation to SoC residents. All surveys measured impact 5 – 7 months following intervention rounds, with the exception of survey 3, which showed significant impact in residents receiving MDA+IRS 3 months after receiving 2 rounds of the intervention compared to residents receiving SoC (DiD aOR = .11 [95% CI: .07 – .15], p$< .001$) and residents receiving IRS (DiD aOR = .30 [95% CI: .21 – .41], p$< .001$). The lower panels of Fig. 9 show the same trends in microscopy confirmed malaria for all ages.

These comparisons highlight the large protective impact of not only adding chemoprevention to IRS, but also the protective impact IRS+ITNs have over ITNs alone in this high transmission setting.

Appendix III. Malaria prevalence tables

See included excel spreadsheet.

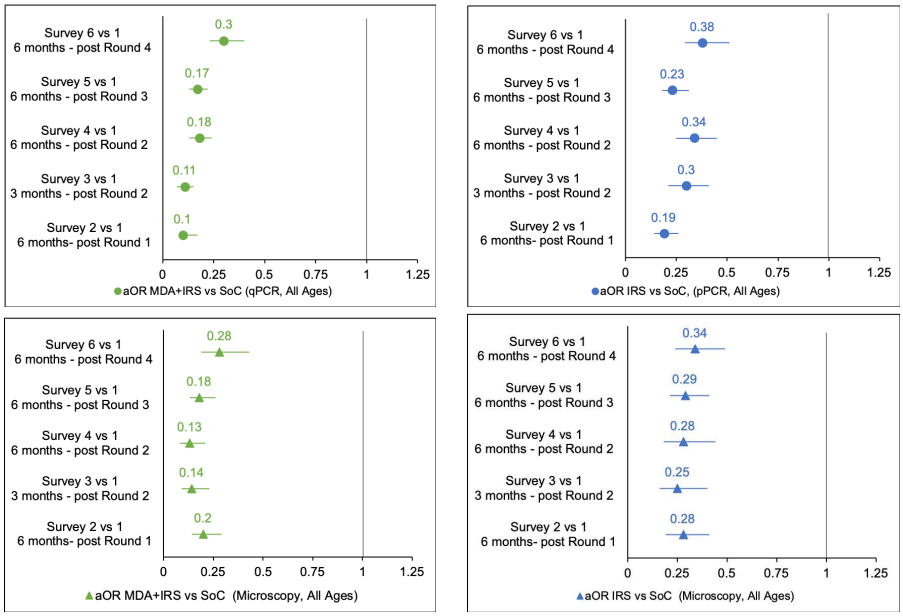

Figure 9 Top left: the DiD adjusted odds ratio for qPCR confirmed malaria in residents of all ages receiving MDA+IRS versus those with standard of care (SoC). Top right: the same DiD adjusted odds ratio for qPCR confirmed malaria in residents of all ages receiving IRS, without MDA, versus those with standard of care. The lower panels display the same as the panels above except for malaria in residents confirmed by microscopy. Horizontal bars indicate 95% confidence intervals.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- MDAandIRSmain.tex
- SIMalariaPrev.Tables033122.xlsx
- SupplementaryInformation.pdf
- malariaRefs.bib
- supplement.tex