Indoor residual spraying in combination with insecticide-treated nets compared to insecticide-treated nets alone for protection against malaria: Study Documentation

1 Investigators

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2 Context of data collection

2.1 Summary

The proposed project addresses a critical research question (objective 2 of USAID/URC Request for Application) concerning the operational use of Long Lasting Insecticidal Nets (LLINs) and Indoor Residual Spraying (IRS), namely: Can LLINs sustain transmission reduction gains made by IRS following withdrawal of IRS?

Muleba is an area that was holoendemic for *Plasmodium falciparum* malaria before PMI IRS intervention in 2007. PMI has been conducting IRS in Muleba for the past three years with a single pyrethroid spray round annually. This IRS intervention has already reduced malaria prevalence significantly. Therefore, the setting in Muleba is ideal for research question objective 2. We aim to evaluate the scaling-up LLIN coverage across the whole of the study area and withdrawing IRS in one study arm whilst maintaining a single IRS round in the other arm. The study will run for two years.

The trial design will involve randomised selection of stratified clusters for 2 study arms. The primary outcome measure will be prevalence of parasitaemia and anaemia in children aged 0.5-10 years, measured in cross sectional surveys.Secondary outcomes will include malaria transmission as measured by entomological inoculation rates (EIR) of the mosquito vector species and serological prevalence of malaria, as well as user acceptability of LLINs compared with IRS. It is hoped that a measure of incidence can be introduced, based on clinical malaria diagnosed using RDTs in the health facilities of the district.

The study location and the proposed trial design will provide PMI and National Malaria Control Programme with valuable answers to the key objectives. Findings from this study are expected to inform decision making so that resource utilization can be optimised.

2.2 Background

In Tanzania the 2010 program of the National Malaria Control Programme (NMCP), in collaboration with several international donors (including President Malaria Iinitiative), will scale up LLIN distribution under the Universal Coverage Campaign (UCC) and spray IRS insecticides in selected

regions with the highest malaria prevalence (USAID, 2009). The universal coverage campaign is scheduled to take place in Muleba district at the end of March 2011. Historically control programs have focussed either on IRS or ITN/LLINs. This trend is changing with ambitions towards elimination and we are to see implementation of both IRS and LLIN in several African countries under PMI. One potential control strategy involves using IRS in areas of high transmission to first reduce transmission to a low level before using LLINs to maintain the low parasite rates while withdrawing IRS. It is essential to conduct cluster randomised trials to determine whether LLINs at high coverage can provide a non inferior replacement of IRS after several cycles of the latter.

The results of the proposed trial will help inform PMI, the Tanzanian NMCP and other African Departments of Health of the potential benefits and detrimental effects of maintaining or introducing IRS alongside scaling up of LLIN distribution. The results will be beneficial to the study communities and similar populations in Tanzania and elsewhere. The study will also provide evidence regarding the cost and effectiveness of 1 round of IRS per year in comparison to scaling up LLINs.

2.3 Objectives

The aim of this research is to determine whether it is necessary to maintain IRS once malaria transmission has been reduced or whether following the scaling-up of LLINs the IRS can be withdrawn and low transmission rates can be maintained equally well with LLINs alone. It will specifically address objective 2 of the RFA:

“Objective 2. In areas where one or more rounds of IRS have been carried out and malaria transmission has been reduced, can LLINs be used to sustain the transmission reduction gains made by IRS following the withdrawal of IRS?”

2.4 Basic Study Design:

The study objective will be addressed as a two-arm cluster-randomised intervention trial.

Study arms:

Study arm A. Yr. 1: One round per annum of high coverage IRS and high coverage LLIN,

Yr. 2: One round per annum of high coverage IRS and high coverage LLIN.

Study arm B. Yr. 1: One round per annum of high coverage IRS and high coverage LLIN,

Yr. 2 – No IRS and high coverage LLIN.

The null hypothesis would be that the intervention arm in which IRS was withdrawn (Study arm B) is inferior to the reference arm in which IRS is retained (Study arm B). The alternative hypothesis is that the LLIN only arm (Study arm B) tis non-inferior to the LLIN plus IRS study arm (A), as demonstrated by a difference in prevalence of infection in the two study arms to be no more than a pre-specified margin. If IRS is eventually withdrawn programmatically from areas currently given IRS and LLIN universal coverage, this study would provide assurance that it would be safe to do so without endangering a return to higher transmission levels.

2.5 Outcomes:

Primary outcomes:

1. Prevalence of malaria infection in children 0.5-10 years
2. Mean haemoglobin (g/dL) in children under 5 years.

Secondary outcomes:

1. Incidence of confirmed malaria episodes in children and adults through passive case detection at district health facilities
2. Sero-conversion rates
3. Entomological Inoculation Rate (EIR) for each mosquito vector species.
4. Relative population density for each mosquito vector species
5. Usage and perception of existing LLIN in baseline year
6. Evaluation of the Universal Coverage Campaign of LLIN
7. Perception and acceptance of IRS in baseline year
8. Usage and perception of LLIN in an environment of reduced IRS.
9. Detection and monitoring of resistance markers including *kdr*

2.6 Specific objectives of the mosquito collection

- To determine abundance and relative proportion of *Anopheles gambiae* and *An. funestus* sibling species between study arms
- To record differences in Entomological Inoculation Rate (EIR give the intensity of malaria transmission) between study arms

3 Data collection methods

3.1 Protocols

From April 2011, a series of 19 monthly entomological cross sectional surveys (seven in the baseline and twelve in the intervention year) were undertaken in the 20 clusters that were randomly selected in each arm of the study for the measurement of entomological outcomes. Each month, in eight randomly selected houses from each cluster, mosquito density was monitored using CDC light traps during one night. After obtaining informed consent from the family, a light trap was installed at the foot of a bed occupied by a family member sleeping under a treated or untreated bed net. Information was collected on house structure (type of wall and roof, presence of open eaves, ceiling and window screens), presence of livestock inside or outside the house, whether the house was sprayed, and bed net ownership and usage. Houses were randomly sub-sampled from the list of houses that had been sampled for the pre-ceding cross-sectional household survey. Mosquito collections were identified to species using a simplified morphological key adapted from Gillies and Coetzee, and subsequently tested by ELISA for detection of *Plasmodium falciparum* circumsporozoite protein (Pf-CSP). A sub-sample of *An.gambiae* s.l. was tested using Real time PCR Taq Man assay to distinguish between the two sibling species *An.gambiae* s.s. and *An.arabiensis*.

The quality and coverage of IRS was investigated using the carbamate Insecticide Quantification Kit in the intervention year (IQK™ [Innovative Vector Control Consortium, www.ivcc.com]). Wall scrapings of prescribed area were taken from the living rooms and bedrooms of 368 households in

April 2012 and 490 household in June 2012, respectively four months after the first spraying and one month after the second spraying. The concentration of bendiocarb residue on the wall was assessed by a colorimetric assay which reacts to the presence of insecticide.

Household data were collected using PendragonTM Forms (Pendragon Corporation Software, Libertyville, USA) on Personal Digital Assistants (PDA) and analysed using STATA^{TM} (STATAcorp, Texas, USA, version 11.2). Mosquito data were collected on paper form, and double-entered into an access database.

4 Information on data files

There are 4 data files:

- Two data files (one for the baseline collection and the second for the post intervention collection) at the household level the unique identifier is an aggregate including the round collection number (1 digit), the cluster number (2 digits) and the household number (3 digits).
    - HH_Muleba_database_entomo_baseline_2013_for_repository: 2313 records and 70 variables
    - HH_Muleba_database_entomo_post_2013_for_repository: 4192 records and 71 variables

- Two data files at mosquito level where the unique identifier is the mosquitoes. The database can be link with the household database using the round, cluster and the household number that also appear in the mosquito's database.
    - Mosquito_Muleba_database_entomo_baseline_2013_for_repository: 5862 records and 14 variables
    - Mosquito_Muleba_database_entomo_post_2013_for_repository: 4054 records and 14 variables

5 Data quality

Paper forms have numbered and coded items to ensure straightforward and accurate data entry and processing. Quality control on paper forms and PDA was done by checking for missing data and completeness and internal consistency of responses. Electronic questionnaire had built in checks for missing data, implausible responses and internal consistency.

All quantitative data collected on paper forms were double-entered into an Access database independently by two data clerks. Validation to resolve any discrepancies in the data was performed by data manager.

6 More information on the study

The following publications are related to the study.

- West PA, Protopopoff N, Wright A, Kivaju Z, Tigererwa R, Mosha FW, Kisinza W, Rowland M, Kleinschmidt I: Indoor residual spraying in combination with insecticide-treated nets compared

to insecticide-treated nets alone for protection against malaria: a cluster randomised trial in Tanzania. *PLoS Med* 2014, 11:e1001630.

- West PA, Protopopoff N, Rowland M, Cumming E, Rand A, Drakeley C, Wright A, Kivaju Z, Kirby MJ, Mosha FW, Kisinza W, Kleinschmidt I: Malaria risk factors in North West Tanzania: the effect of spraying, nets and wealth. *PLoS One* 2013, 8:e65787.
- West PA, Protopopoff N, Wright A, Kivaju Z, Tigererwa R, Mosha FW, Kisinza W, Rowland M, Kleinschmidt I: Enhanced protection against malaria by indoor residual spraying in addition to insecticide treated nets: is it dependent on transmission intensity or net usage? *PLoS One* 2015, 10:e0115661.
- Protopopoff N, Matowo J, Malima R, Kavishe R, Kaaya R, Wright A, West PA, Kleinschmidt I, Kisinza W, Mosha FW, Rowland M: High level of resistance in the mosquito Anopheles gambiae to pyrethroid insecticides and reduced susceptibility to bendiocarb in north-western Tanzania. *Malar J* 2013, 12:149.
- West PA, Protopopoff N, Rowland MW, Kirby MJ, Oxborough RM, Mosha FW, Malima R, Kleinschmidt I: Evaluation of a national universal coverage campaign of long-lasting insecticidal nets in a rural district in north-west Tanzania. *Malar J* 2012, 11:273.
- Thawer NG, Ngondi JM, Mugalura FE, Emmanuel I, Mwalimu CD, Morou E, et al. Use of insecticide quantification kits to investigate the quality of spraying and decay rate of bendiocarb on different wall surfaces in Kagera region, Tanzania. Parasit Vectors 2015;8:242.
- Matowo J, Kitau J, Kaaya R, Kavishe R, Wright A, Kisinza W, et al. Trends in the selection of insecticide resistance in Anopheles gambiae s.l. mosquitoes in northwest Tanzania during a community randomized trial of longlasting insecticidal nets and indoor residual spraying. Med Vet Entomol 2015 Mar;29(1):51-9.