ISGlobal - Barcelona Institute for Global Health

Broad One Health Endectocide-based Malaria Intervention in Africa

BOHEMIA

STATISTICAL ANALYSIS PLAN

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WORK PACKAGE: Safety and Efficacy

WORK PACKAGE PROTOCOL NAME: A Phase III cluster-randomized, open-label, clinical trial to study the safety and efficacy of ivermectin mass drug administration to reduce malaria transmission in two African settings**.**

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Work Package: Safety and Efficacy

Approval Page

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Abbreviations

AE	Adverse Event
AL	Artemeter-Lumefantrine
AUC	Area Under the Curve
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Form
GEE	Generalized Estimated Equations
HR	Hazard Ratio
IQR	Interquartile Range
IR	Incidence Rate
IRR	Incidence Rate Ratio
IRS	Indoor Residual Spraying
ITT	Intention To Treat
LFU	Lost to Follow Up
LLIN	Long Lasting Insecticidal Nets
LMP	Last Menstrual Period
MAR	Missing At Random
MCAR	Missing Completely At Random
MDA	Mass Drug Administration
NTD	Neglected Tropical Disease
OR	Odds Ratio
PCR	Polymerase Chain Reaction
PK	Pharmacokinetics
pLDH	Parasite Lactate Dehydrogenase
PoS	Probability of Success
PP	Per Protocol
PPC	Preferred Product Characteristics
RDT	Rapid Diagnostic Test
RR	Risk Ratio
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SES	Socio Economic Status
SUSAR	Suspected Unexpected Serious Adverse Reaction
WHO	World Health Organization

1 Introduction

1.1 Preface

Mass drug administration with ivermectin is being considered as a potential new tool to reduce malaria transmission and contribute towards the WHO malaria goals for 2030.

1.2 Purpose of the analyses

To evaluate the safety and efficacy of ivermectin MDA as a complementary malaria vector control tool in two cluster-randomized trials in Tanzania and Mozambique.

2 Study Objectives and Endpoints

2.1 Main Study Objectives

To determine the safety (in humans) and efficacy of ivermectin MDA (to humans or human and livestock simultaneously) for the prevention of malaria.

Note these are co-primary objectives determined in different populations. Efficacy is primarily determined in children (under 5 years of age in Mozambique and 5-15 in Tanzania) and safety is determined by anyone who receives the drug. Given inclusion criteria there might be a small overlap in the two populations.

2.2 Secondary Study Objectives

- To assess the efficacy of the intervention using complementary methods (efficacy).
- To assess the safety of the intervention with complementary methods (safety).
- To assess the PK of the proposed ivermectin dose/regime in its relationship with efficacy and safety outcomes (efficacy and safety).
- To assess the impact of ivermectin MDA at the proposed regimen on the prevalence of selected ectoparasitic NTDs (efficacy on NTDs and acceptability).
- To assess the relationship between malaria incidence in children under 5 and community prevalence at the peak of the malaria season (this serves for prevalence outcomes and paves the way for future studies of future evaluation using this outcome which could require fewer resources).
- To assess the relationship between active and passive surveillance for malaria at health facility (this serves as validation passive surveillance and paves the way for future studies using this outcome which is much less resource-consuming while ensuring no key safety events are missed).
- To assess the accuracy for malaria diagnosis of two different malaria rapid diagnostic tests (RDTs) used in comparison to PCR (this is directly linked to efficacy as determined by RDTs).

2.3 Exploratory Study Objectives

- To assess the relationship between self-reported pregnancy status, the LMP and the results of pregnancy tests in women of reproductive age participating in the study.
- To assess all-cause and malaria-related mortality in intervention and control arms.
- Estimate prevalence of relevant CYP and P-gp variations in the target population and subjects suffering from CNS AEs.

2.4 Endpoints

2.4.1 Primary

2.4.1.1 Efficacy

- Infection incidence in the most vulnerable age group (children under 5 years of age in Mozambique and 5-15 years in Tanzania) for 6 months from the moment of the first MDA round in their community.

Infection incidence has been chosen as primary endpoint based on the WHOs PPC for endectocides, that states that in areas of moderate to high transmission, the minimally acceptable efficacy criterion would be "at least 20% reduction in the incidence of clinical malaria (as primary outcome) and incidence of infection (as secondary outcome) in children under 5 (5-15 in Tanzania), lasting for at least 1 month following a single regimen". The monthly frequency of visits has been chosen given that infected children will receive treatment with Coartem (artemether-lumefantrine), which has an established post-treatment prophylaxis period of two weeks [1], [2], monthly visits will allow for at least 14 days-at-risk between visits.

Modeling for the BOHEMIA trials has predicted a reduction of up to 40% in yearly malaria incidence, and thus a 20% target is conservative (see protocol, section 3.5). In addition, the main finding of the RIMDAMAL (the first field randomized trial of ivermectin MDA against malaria) was a 20% reduction in the cumulative uncomplicated malaria incidence in children under 5 living in the treated villages, so there is a precedent for such a reduction.

Infection incidence will be determined in a cohort of children in the target age that is followed prospectively for six months post receipt of first dose in the community by a dedicated field team. Each child will be tested at home using RDTs (Parasite Lactate Dehydrogenase (pLDH) and HRP2 based). Two different tests will be used given the known persistence of HRP2 antigen after treatment with up to 50% residual positivity after six weeks while LDH-based tests become negative in just 48 hours [2].

Treatment for children with positive tests will be provided according to **Table 1**. Quality control of RDT results will include PCR assessment of 10% of the samples.

Case definition

Given the use of two different RDTs, there are four possible results combinations at each visit. The potential implications for treatment and inclusion as an incident case are detailed in **Table 1**. In summary, any positive RDT will result in treatment but not all will be considered an incident case.

HRP2	pLDH	Treatment	Interpretation	Inclusion as incident case
Negative	Negative	No	Negative	No
Positive	Positive	Yes	Incident case	Yes
Positive	Negative	Yes	Potential false positive[1]	Yes if enrolment visit, then onwards only if HRP2 negative in previous visit
Negative	Positive	Yes	Potential false negative[2]	Yes[3]

Table 1. Sampling schedules by group with times given post direct observed intake of drug.

[1]If this child received full treatment in the last month, the most likely outcome is that this is the result of residual false-positive HRP2 given two weeks of prophylaxis by Coartem and incubation period of at least 10 days. [2]This result is unlikely given higher sensitivity of HRP2 but could occur in the rare event of an infection with a parasite with HRP2 gene deletion. [3]if this event occurs more than once during follow-up it will warrant PCR analysis for potential HRP2 deletion screening.

Selection of tests as primary trial outcome

Although PCR assay is more sensitive to detect infections, it can have remarkable variations across laboratories, adds considerable costs and needs for standardization/validation with little added benefit in the context of detecting malaria in a cohort of children with relatively high parasitemia given no or limited acquired immunity. Additionally, it cannot be used for treatment decisions in the field.

PCR will however be used to determine parasite prevalence in the cross-sectional surveys done to the whole population one month after the last MDA round given that a high proportion of sub-microscopic and sub-RDT infections can be expected among adults in moderate-high transmission areas.

2.4.1.2 Safety

- Rate of AEs and serious adverse events (SAEs) and difference between ivermectin and albendazole.

2.4.2 Secondary

2.4.2.1 Complementary efficacy analysis

- Time to first positive RDT in children in the cohort
  - *This is derived from the RDTs performed in the cohort of children*
- Molecular force of infection in a subset of children in the cohort
  - *This is derived from the PCR performed for quality control of the RDTs in the cohort of children*
- Malaria case incidence in all ages presenting at health facility
  - *This is the result of the passive surveillance installed at health facilities and supports the active surveillance results.*
- Malaria prevalence in all ages one month after the last dose
  - *This is derived from the cross-sectional studies*
- Multiplicity of infection in all ages one month after the last dose
  - *This is derived from the cross-sectional studies*

2.4.2.2 Complementary safety analysis

- Observed tolerability of the dose
- Rate of SUSARs
- AEs and SAEs by organ system

2.4.2.3 Pharmacokinetics

- Whole blood concentrations of ivermectin in dried blood spots.

For BOHEMIA it is assumed that whole blood ivermectin concentrations are approximately 70% of the plasma concentration based on previous work from Duthaler et al [3]. This will facilitate interpretation of results and extrapolation of supporting studies based on either plasma or whole blood concentrations. The dry blood spot method to be used in BOHEMIA has been validated according to EMA standards [3].

2.4.2.4 Impact of ivermectin against selected ectoparasites and NTDs in the dosage regimen chosen

- Serial prevalence of scabies using a simplified version of the algorithm described by Mahe et al. [4] which consists of two questions and evaluation of exposed skin on hands, knees, elbows, armpits, wrists, and feet.
- Serial prevalence of head lice by visual inspection over three minutes in scalp sites of predilection for head lice: the back of the ears, temples and neck [5].
- Serial prevalence of Tunga penetrans via visual inspection of the skin in both feet and applying the Fortaleza scale [6].
- Serial prevalence and severity of bed bug infestation by direct questions about bedbugs in the house, and visual inspection of exposed skin and sleeping rooms for evidence of bed bug bites or bed bug infestation.

2.4.2.5 Prevalence - incidence correlation

- Infection incidence in children (under 5 years in Mozambique and 5-15 years in Tanzania) in the pediatric active cohort at community and health facility levels
- Malaria prevalence at all ages

2.4.2.6 Relationship between active and passive surveillance

- Infection incidence in children at community level (active surveillance)
- Infection incidence in children at health facility level (passive surveillance)

2.4.2.7 Performance of RDTs vs PCR

- Results correlation between HRP2 and pLDH-based RDTs
- Results correlation between RDTs and PCR
- Proportion of RDT negative but PCR positive infections

2.4.3 Exploratory

2.4.3.1 Accuracy of self-reported pregnancy status and LMP

- Proportion of pregnant women among those self-reporting as non-pregnant
- Proportion of pregnant women among those reporting LMP more than 2 weeks before the test.

2.4.3.2 All-cause mortality

- Rate of all-cause and malaria-related mortality as determined by health facility records and BOHEMIA safety reporting during the trial
- Verbal autopsies of deaths of participants on both cohorts

2.4.3.3 Pharmacogenomics

- Case-control association study of ivermectin-associated neurological adverse effects with genetic variation in *CYP3A5* and *ABCB1* and assess the association of the same genetic variants with ivermectin PK.

3 Study Methods

3.1 General Study Design and Plan

The two BOHEMIA clinical trials are open label, cluster randomized, controlled, parallel arm trials that will be conducted during the peak malaria season in Mozambique and Tanzania respectively.

The interventions will be implemented for one year (**Figure 1**). The study events planned for the first year are summarized in **Figure 2**.

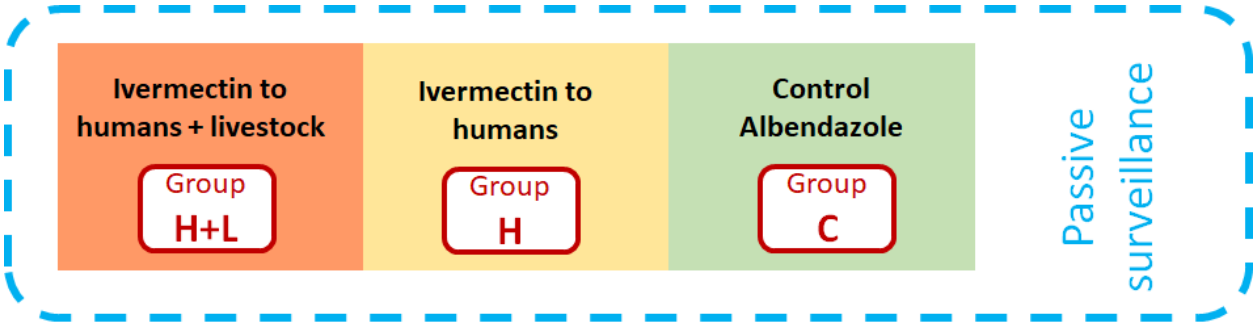

Figure 1. Study groups and intervention sequence

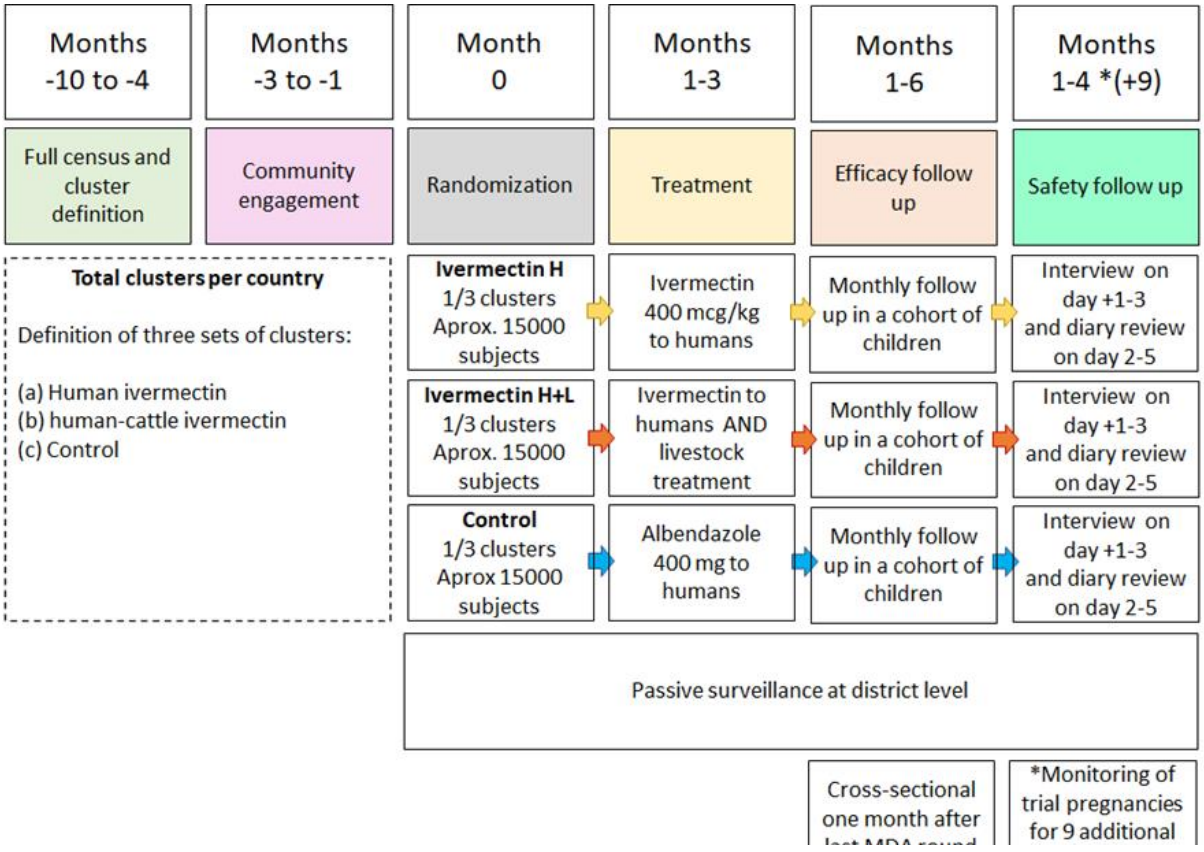

Figure 2 Simple schematic with sequence of activities

3.2 Inclusion-Exclusion Criteria and General Study Population

3.2.1 Inclusion criteria

3.2.1.1 For human treatment/safety cohort

- Residents of the study area
- Male or female weighing more than 15kg
- Adult able to provide written consent
- Minors aged 12 to 17 able to provide assent
- Parent/guardian's able to provide consent for minors
- Agreement to adhere to study visits and procedures

3.2.1.2 For pediatric active cohort:

- Children in the age of highest burden at the time of enrollment (under 5 years of age in Mozambique or 5-15 in Tanzania)
- Residents of the study area
- Parent/guardian's able to provide consent for minors
- Minors aged 12 to 15 in Tanzania able to provide assent

3.2.1.3 For cross sectionals

- Residents of the area for at least 3 months prior to enrolment
- Parent/guardian's consent for minors
- Ability to provide assent for minors aged 12 to 17
- Written consent from adults

3.2.1.4 For livestock treatment:

- Owner/guardian able to provide consent
- Animal expected to spend at least one week every study month inside the cluster border

3.2.2 Exclusion criteria

3.2.2.1 For human treatment/safety cohort:

- Known hypersensitivity to ivermectin or albendazole
- Risk of Loa as assessed by travel history to Angola, Cameroon, Chad, Central African Republic, Congo, DR Congo, Equatorial Guinea, Ethiopia, Gabon, Nigeria or Sudan
- Pregnant women
- Lactating women in the first week postpartum
- Children < 15 kg
- Currently participating in another clinical trial
- Unwilling to provide informed consent or assent
- Unwilling to adhere to study visits and/or procedures
- Severely ill either self-reported or in the eyes of the investigator, e.g. defined as need for clinical care, or active or progressive disease interfering with activities of daily living. If in doubt, these criteria can be confirmed after a call with either the site PI/MD/safety officer against a pre-defined list.
- Currently under treatment with inhibitors of CYP3A or P-gp or other drugs that can interfere with the study (examples given in **Table 2**)

Class	Drug	Rationale
Antiarrhytmic/ Antihypertensive	Quinidine	May increase ivermectin exposure by inhibiting its metabolism and excretion or competing with CYPs or the P-gp.
	Amiodarone	
	Diltiazem	
	Spironolactone	
	Verapamil	
Antibiotic- Macrolides	Clarithromycin	
	Erythromycin	
Antifungal agents	Itraconazole	
	Ketoconazole	
Inmunosupressants	Cyclosporine	
	Tacrolimus	
Anti HIV therapy	Indinavir	
	Ritonavir	
Anticoagulant	Warfarin	
H-2 blockers	Cimetidine	May increase albendazole metabolite levels by inhibiting its metabolism and excretion
Steroids	Dexamethasone	

Table 2. Examples of concurrent treatment used as exclusion criteria for the treatment/safety cohort

3.2.2.2 For active pediatric cohort:

- Non-residents

3.2.2.3 For cross sectionals

- Non-residents

3.2.2.4 For livestock treatment

- Received ivermectin less than four weeks ago
- Intention to milk or slaughter the animal for human consumption during the withdrawal period
- Calves under 8 weeks and piglets under 6 weeks of age

3.3 Randomization and Blinding

3.3.1 Randomization

Cluster randomization implies that all individuals in the same cluster will receive the same intervention. Once all clusters in the district are defined, the target sample will be randomized using a computer-generated algorithm.

3.3.2 Allocation

Clusters will be randomized 1:1:1 into three study arms. The treatment status of each cluster will be assigned during cluster delineation and then transmitted to the population during a randomization ceremony.

3.3.3 Blinding

The study will be open label but outcome assessor-blinded. Participants in the ivermectin and control arms will receive products that differ in aspect and numbers. Participants will be informed that they

are taking one of two antihelminthics. The sponsor and the study statistician will remain blinded to the assignment of each cluster group. All unblinded DSMB reports will be prepared by an independent statistician.

3.4 Study Variables

A graphic timeline for the study is presented in **Figure 3**. Study procedures in both treatment/safety and active pediatric cohort are presented in **Table 3** and **Table 4**, respectively.

Study variables description is provided in Annex A.

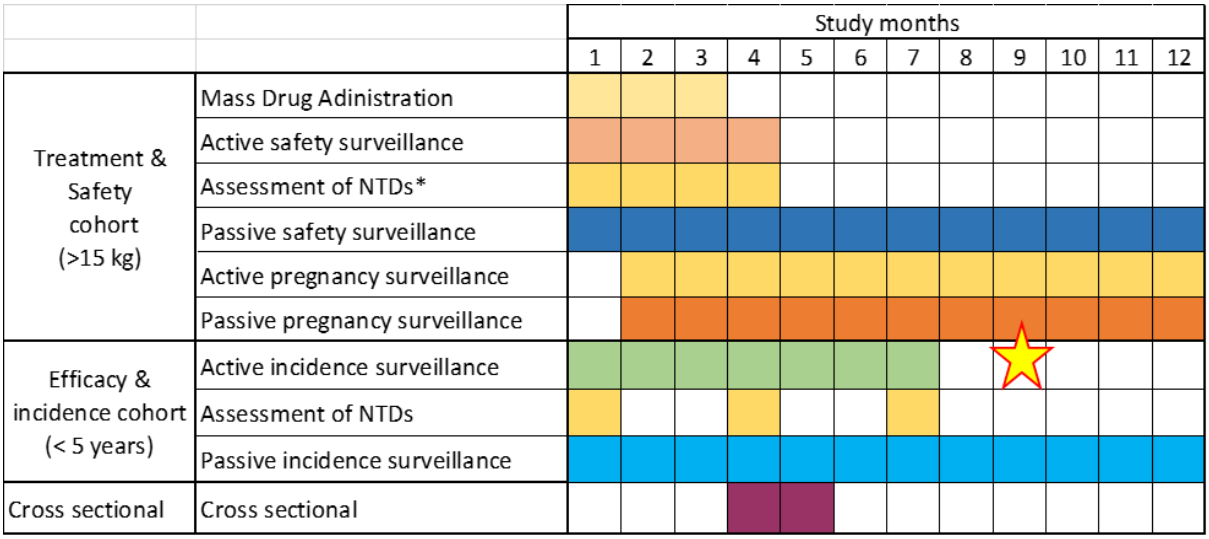

Figure 3 A graphic study timeline. The star marks the availability of first efficacy data.

Procedures in treatment/safety cohort	**Census & clustering** Months -10 to -4	**Treatment enrollment visit** 1-30 days before dosing	**Study visit 1(S)** Day 1	**Study visit 2(PK)** Day 2	**Study Visit 3(S)** Day 3 +/-1 day	**Study Visit 4(S)** Day 6 +/- 1 day	**Study Visit 5(S)** Day 31 +/-3 days	**Study Visit 7(S)** Day 36 +/-1 day	**Study Visit 8(S)** Day 61 +/-3 days	**Study visit 10(S)** Day 66 +/-1 day	**Final safety visit 11(S)** Day 91 +/-1 day	**End of passive safety surveillance** Day 365+/-3 days	**Final pregnancy safety visit(S)** [c] Day 371 +/-3 day
Informed consent census *(separate protocol)*	X												
Demographic data collection	X												
Cluster randomization	X												
Informed consent for treatment		X					X[d]		X[d]				
Complete visit template		X	X	X	X	X	X	X	X	X	X		X
Anthropometry		X					X		X				
Assessment of selected NTDs [a]		X[a]					X[a]		X[a]		X[a]		X[a]
Review of infant vaccination card (if applicable)		X					X		X		X		
Collection of pharmacology samples [a]			X	X	X								
Urine Pregnancy test [c]			X				X		X		X		
Administer study intervention			X				X		X				
Review of side effect personal diary							X		X		X		
Passive surveillance of side effects				X----------							----------X		
Adverse event review and evaluation				X----------							----------X		
Active pregnancy surveillance							X		X		X	X	X
Passive pregnancy surveillance (health facility)							X----------						----------X

[a]randomly selected sub-sample
[b]in participating female participants aged 13-49 that request one as indicated in the protocol
[c]only pregnancies occurring post-treatment
[d]only subjects not previously enrolled

Table 3 Study procedures for the treatment/safety cohort

Procedures in efficacy (active pediatric cohort)	**Census & clustering** Months -10 to -4	**Enrollment/Baseline(E)** Visit 1, Day 1	**Study Visit 2(E)** Day 31 +/-3 days	**Study Visit 3(E)** Day 61 +/- 3 days	**Study Visit 4(E)** Day 91 +/-3 days	**Study Visit 5(E)** Day 121 +/-3 days	**Study visit 6(E)** Day 151 +/-3 days	**Study visit 7(E)** Day 181 +/-3 days
Informed consent for census	X							
Demographic data collection	X							
Randomization	X							
Informed consent		X						
Anthropometry		X			X			X
Review infant vaccination card			X					X
Complete visit template		X	X	X	X	X	X	X
Malaria RDT		X	X	X	X	X	X	X
Malaria treatment [a]		X	X	X	X	X	X	X
Assessment of selected NTDs		X			X			X
Plasmodium PCR for quality control and molFOI[b]		X	X	X	X	X	X	X
Passive incidence surveillance at health facilities (all ages)		X----------						----------X
[a]only if RDT is positive (see case definition) [b]only in a randomly selected 10% sub-sample								

Table 4 Study procedures for the efficacy/incidence cohort

4 Sample Size

The sample size for each country is based on the main outcome (malaria incidence in a cohort of children followed prospectively in the cluster's core area for six months), an outcome chosen based on WHO's PPC for endectocides. This sample size has been corrected for cluster effect following Hayes and Bennett formula for unmatched rates [7].

The magnitude (20% reduction) was selected based on WHO's recommended PPC for endectocides [8]. Additionally, the results of the RIMDAMAL trial suggest that a 20% reduction in malaria incidence can be achieved using a dosing regimen with a similar cumulative dose [9], these results although not statistically significant [10] do point towards an expected effect size. Mathematical modeling based on the Imperial College malaria model incorporating ivermectin [11] was conducted for this project and predicts a 40% reduction in malaria incidence in both countries. The model is described in detail in the protocol (section 3.5).

The final sample size is dependent on the population distribution as identified in the demography protocol.

The number of children per cluster can vary in order to streamline the cluster generation once the demographic data is available. The power, significance level and target effect size will remain unchanged. The final number of clusters depends on the cluster size (the number of children in the

active pediatric cohort recruited in the core of all clusters). Smaller cluster sizes require a higher number of clusters to render the same power. **Figure 4**).

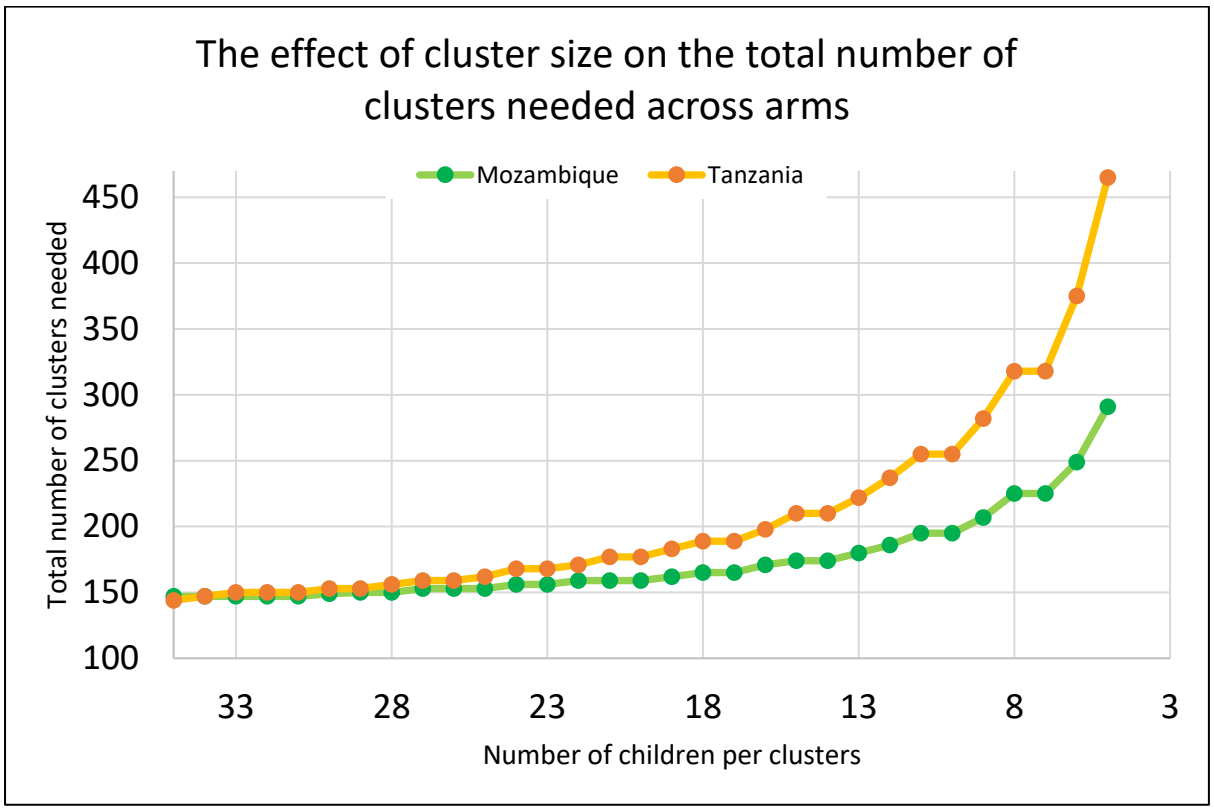

Figure 4 Cluster size and total clusters needed.

The number of clusters required increases exponentially as the number of children per cluster (cluster size) decreases. This is particularly marked below 13 children per cluster. The number of children represented is the number of eligible children required at the beginning, not accounting for 15% non-consenting and up to 20% LFU.

The target number of children to be included in every cluster is defined by the expected enrollment rate and loss to follow up rate. We have estimated these as 15% and 20% respectively. So, for a cluster size to be 24 i.e., 24 children in the cohort finishing the study, the cluster must include 35 eligible children in the beginning (35 eligible of which an estimated 5 [15%] do not consent, 30 consent, of which 6 [20%] are lost to follow up).

4.1 Mozambique

Peak incidence age: < 5 years

Power: 80%

Significance level: 5%

Expected incidence in control group (λ_0): 4.20

Expected incidence in intervention (λ_1): 3.36

Incidence reduction: 20%

Optimal cluster size: 20 children (assuming 3 non consenting and 3 LFU)

Follow up time: 6 months starting post community dosing

Coefficient of variation (k_m): 0.35

People treated per cluster: approximately 300

Optimal total clusters required: 159 (53 per arm)

The final sample size may have to be adjusted as by the table below. However, the power and affect size will remain constant as does the ceiling of treatable adults (not to exceed 48,000 eligible adults).

Total clusters needed	Total children eligible per cluster	Non-consenting 15%	Included	LFU 20%	Final size	Total children in clusters	Total children enrolled	Total children completing trial
147	35	5	30	6	24	5145	4373	3499
149	30	5	26	5	20	4470	3800	3040
153	25	4	21	4	17	3825	3251	2601
159	20	3	17	3	14	3180	2703	2162
174	15	2	13	3	10	2610	2219	1775
195	10	2	9	2	7	1950	1658	1326
291	5	1	4	1	3	1455	1237	989

4.1.1 Preliminary data

The baseline incidence and the coefficient of variation used for the sample size calculation for Mozambique are considered robust as they have been obtained from a recently finished cluster-randomized trial in Mopeia, the very same district where BOHEMIA will be conducted. The previous trial assessed the cost-effectiveness of combining LLIN and IRS [12].

4.1.2 Calculations

Based on the demographic data to be confirmed in the preceding census, the clusters are planned to include approximately 420 people, of which 280 will be above 4-5 years of age and potentially eligible for **treatment** and 140 will be children under 5 potentially eligible for **follow-up**. There will be 53 clusters per arm in Mozambique.

Clusters in Mozambique will be randomized in three arms as per **Figure 1**, resulting in inclusion of approximately 45,000 participants to receive treatment or control and approximately 2,000-4,000 children to be followed for six months.

With this sample size the study has 80% power at 5% significance to detect a 20% reduction in malaria incidence infection, from 4.20 cases/child-year at risk to 3.36 for the human-only intervention, using a coefficient of variation (k_m) of 0.35 for Mopeia/Mozambique. This value for k_m has been back-calculated from a cluster randomized trial recently-conducted in the same study site [13].

For the human and livestock intervention, this sample size has 80% power to detect a further 20.5% reduction in malaria incidence infection between the human and human + livestock intervention arms, from 3.36 cases/child-year at risk (the lower incidence expected in the human only arm) to 2.67.

The total number of clusters needed per arm has been increased by one for all scenarios to account for potential LFU of a whole cluster (withdrawal of community consent, displacement, etc.)

4.2 Tanzania

Peak incidence age: 5-15 years

Power: 80%

Significance level: 5%

Expected incidence in control group (λ_0): 1.50

Expected incidence in intervention (λ_1): 1.16

Incidence reduction: 22.5%

Cluster size: 25 children assuming 4 non-consenting and 4 LFU)

Follow up time: 6 months starting post community dosing each year

Coefficient of variation (k_m): 0.35

People treated per cluster: approximately 300

Total number of clusters required: 162 (54 per arm)

The final sample size may have to be adjusted as by the table below. However, the power and affect size will remain constant as is the ceiling of treatable adults (not to exceed 45,000 eligible adults).

Total clusters needed	Total children eligible per cluster	Non-consenting	Included	LFU	Final size	Total children in clusters	Total children enrolled	Total children completing trial
144	35	5	30	6	24	5040	4284	3427
153	30	5	26	5	20	4590	3902	3121
162	25	4	21	4	17	4050	3443	2754
177	20	3	17	3	14	3540	3009	2407
210	15	2	13	3	10	3150	2678	2142
255	10	2	9	2	7	2550	2168	1734
465	5	1	4	1	3	2325	1976	1581

4.2.1 Preliminary data

The baseline incidence for Tanzania has been extrapolated from a recent study data that characterized malaria prevalence in a range of ages in Rufiji [14], [15], the very same district where BOHEMIA will be conducted. According to this recent data, the highest burden groups are children aged 5-15 years (prevalence of 21.5% at season's peak ranging from 9.4 to 29.7%). An incidence of 1.5 cases per child-year-at-risk was extrapolated from this prevalence using the ensemble model prediction of Cameron et al [16]. This extrapolation was corroborated against the expected incidence given climate zone by the modeling conducted to estimate the intervention's effect size.

4.2.2 Calculations

Based on the demographic data to be confirmed in the pre-dating census, the clusters are planned to include approximately 340 people, of which 250 will be above 15 years of age and potentially eligible for **treatment** and 90 are children 5-15 potentially eligible for **follow-up**. There will be 54 clusters per arm in Tanzania.

Clusters in Tanzania will be randomized in three arms as per **Figure 1**, resulting in inclusion of approximately 40,000 participants to receive treatment or control and 4,000 children to be followed for six months.

With this sample size the study has 80% power to detect a 22.5% reduction in malaria incidence infection, from 1.50 cases/child-year at risk to 1.16 for the human-only intervention, using a coefficient of variation (k_m) of 0.35 for Rufiji/Tanzania.

For the human and livestock intervention, this sample size has 80% power to detect a further 23.5% reduction in malaria incidence infection, from 1.16 cases/child-year at risk to 0.88.

The total number of clusters needed per site has been increased by one for all scenarios to account for potential LFU of a whole cluster (withdrawal of community consent, displacement, etc.)

The Tanzania site has been powered to detect a slightly larger difference between arms (22.5-23.5%) in order to harmonize the number of clusters among sites.

4.3 Sample size scenarios

4.3.1 Drought

In this scenario the incidence at baseline is 50% lower than expected.

With the current sample size, the Mozambique site has 80% power to detect a 22% difference in incidence from 2.10 to 1.64 infections per child-year-at-risk. The Tanzania site has 80% power to detect a 26.5% difference in incidence from 0.75 to 0.55 infections per child-year-at-risk.

4.3.2 Flooding

In this scenario the incidence at baseline is 50% higher than expected and the coefficient of variation is set at 0.5 to account for displaced populations.

With the current sample size, the Mozambique site has 80% power to detect a 25.5% difference in incidence from 6.3 to 4.69 infections per child-year-at-risk. The Tanzania site has 80% power to detect a 26.5% difference in incidence from 2.25 to 1.65 infections per child-year-at-risk.

4.3.3 Conflict

In this scenario 20% of the total clusters are LFU due to population moving out or withdrawing community consent.

With 42 clusters per arm, the Mozambique site has 80% power to detect a 22.5% difference in incidence from 4.2 to 3.26 infections child-year-at-risk.

With 43 clusters per arm, the Tanzania site has 80% power to detect a 25% difference in incidence from 1.5 to 1.13 infections child-year-at-risk.

4.3.4 Rumors

In this scenario 50% of the children in every cluster withdraw consent or are LFU.

With cluster size 7, the Mozambique site has 80% power to detect a 24.5% difference in incidence from 4.2 to 3.17 infections child-year-at-risk.

With cluster size 9, the Tanzania site has 76% power to detect a 25% difference in incidence from 1.5 to 1.139 infections child-year-at-risk.

4.3.5 Weak ivermectin effect

In this scenario the effect size is 15% instead of the 20% required by WHO to consider as public health value, K_m remains unchanged at 0.35.

With the current sample size, the Mozambique site has 54% power to detect a 15% difference in incidence from 4.2 to 3.57 infections per child-year-at-risk. The Tanzania site would have a 45% power to detect a 15% difference in incidence from 1.5 to 1.28 infections per child-year-at-risk.

The susceptibility of the sample size to changes in the coefficient of variation are presented in **Figure 5**.

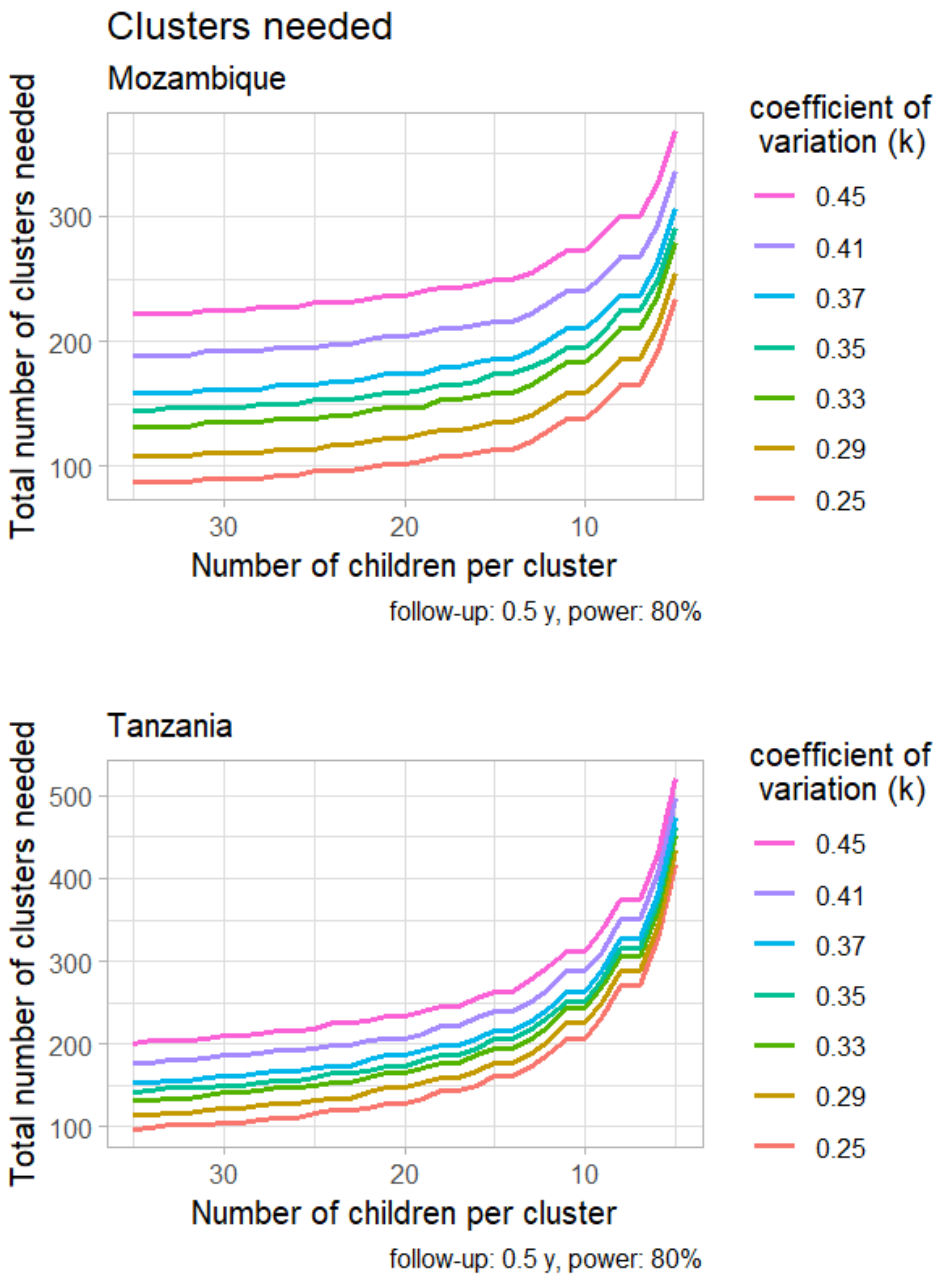

Figure 5 Susceptibility of the sample size to changes in the coefficent of variation (K_m)

4.3.6 Probability of success with each sample size scenario

The probability of success (PoS) gives an overall estimate of the probability a trial is likely to succeed. The PoS is calculated by computing the statistical power of each scenario, multiplying this by the estimated probability of each scenario, which is then summed up. For the scenarios outlined below, the PoS for Mozambique and Tanzania are 79.2% and 78.6%, respectively **(Figure 6)**.

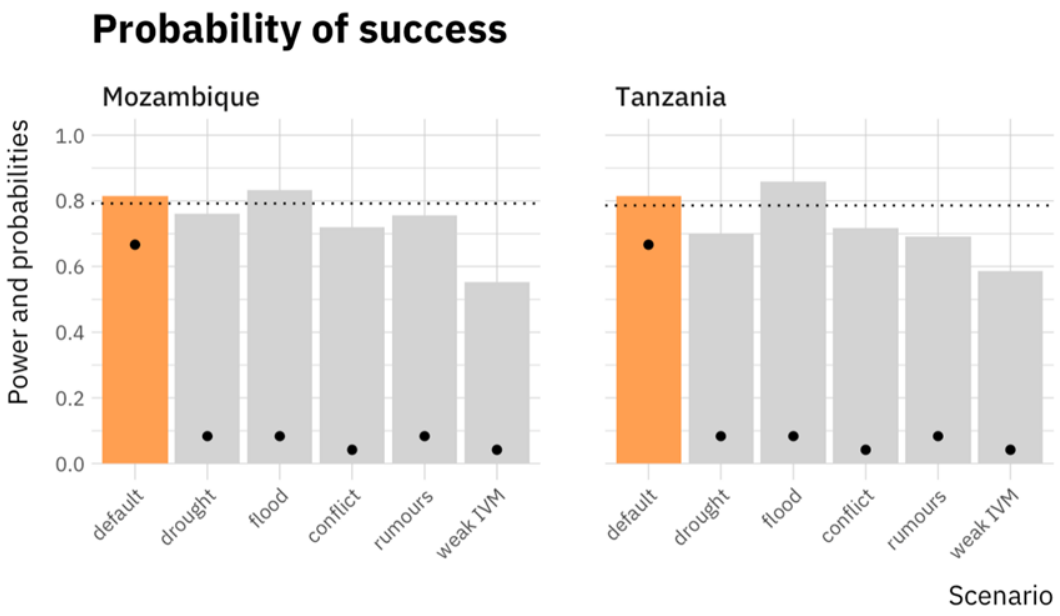

Figure 6. Probability of success by trial sites (dotted lines).

The grey bars indicate the statistical power the intervention would achieve for different scenarios compared to the default scenario (orange bar), for which the trials are powered. The dots show the assigned probabilities for each scenario.

4.4 Cross sectional

4.4.1 Mozambique

Accounting for cluster effect, a sample of 1590 participants (530 individuals per arm, 10 individuals per cluster), has 80% power to detect a 26.5% difference in overall prevalence from 45% to 33% using a K_m of 0.35 in Mozambique. The same sample can detect a further 30% reduction from 33 to 23% in the human + livestock arm.

4.4.2 Tanzania

Accounting for cluster effect, a sample of 3240 participants (1080 individuals per arm, 20 individuals per cluster), has 80% power to detect a 30% difference in overall prevalence from 20% to 14% using a K_m of 0.35 in Tanzania. The same sample can detect a further 34% reduction from 14 to 9.2% in the human + livestock arm.

4.5 Whole blood PK of ivermectin

The PK of ivermectin will be assessed in a subset of the treated population using dried blood spot capillary sampling.

4.5.1 Randomization procedures for Population PK

106 clusters in Mozambique and 108 clusters in Tanzania will be randomized to one of the treatment arms to receive ivermectin (either with or without co-treatment of livestock). Approximately one fifth of these clusters will be included in the PK assessment, i.e. 20 clusters in Mozambique and 20 clusters in Tanzania, totaling 40 clusters. Note that an equal number of clusters will come from either ivermectin treatment arm.

Within each cluster where PK sampling is done, 14 adult participants will be selected.

In order to achieve the most informative coverage over the concentration time profile and capture differences in time of maximum concentration, AUC, and elimination, individual participants will be randomized to one of two sampling schedules (A or B). **Table 5**. Sampling times are given with windows of tolerance for optimal pharmacometric analysis. We will aim to include any samples taken outside these time windows in the analysis.

	Sample Number						
	1	**2**	**3**	**4**	**5**	**6**	**7**
Time point	0.5 - 1h	2 - 3h	4 +/- 1h	8 +/- 1h	12 +/- 2h	24 +/- 4h	72 +/- 6h

Table 5. PK sampling times.

4.5.1.1 Association of CYP 3A5 and ABCB1 pharmacogenetics with CNS AEs

The first 100 participants to report CNS AEs judged to be drug-related by the investigator will be asked to supply a blood sample for pharmacogenetic testing for CYP 3A5 and ABCB1 SNPs by finger prick and transfer to a DBS filter card (4 drops, 10-20 uL each). The frequency of the SNPs in this cohort will be compared to the prevalence within a subset of the PK sub study population. This subset will be selected by availability of unused filter cards with whole blood samples, in total n=400 blood samples.

4.5.1.2 Impact of ivermectin against selected ectoparasites and NTDs

Scabies is the condition used to calculate sample size of this outcome. The baseline prevalence of scabies will be determined more accurately during the census. For the purposes of this calculation, it is assumed to be 6% in both sites [17]. Sampling four random adults per cluster (approximate n: 600), the assessment would be powered to detect a 90% reduction [18] from 6 to 0.6% using a Km of 0.35 in one year. All children in the active pediatric cohort will be assessed for NTDs at enrollment and in visits 1-4 and 6. NTDs will be assessed in the safety cohort at enrollment and at visit 3 (see section 3.4).

5 General Analysis Considerations

Independent analysis for the primary endpoints will be conducted at each site; the trials implement the same design, with sample size adapted to local epidemiology. There will be subsequent cross-trial analysis to explore variations in efficacy across the sites, in the context of varying endemicity, vectors and other variables, as well as site-specific safety issues should these exist.

5.1 Timing of Analyses

The final analysis will be performed on data meeting the cleaning and approval requirements and after

the finalization and approval of this SAP document.

5.2 Analysis Populations

5.2.1 Human treatment/safety cohort

All subjects who received any study treatment (including control) but excluding subjects who drop out prior to receiving any treatment. For these excluded subjects, their characteristics and drop out reasons will be described.

Per protocol (PP) analyses as well as subgroups according to total dose received will be carried out as sensitivity analyses. Only subjects taking three MDA doses will be considered in this case.

5.2.2 Active pediatric cohort

Analyses will be performed in an intention to treat (ITT) approach for this cohort. This is, considering children (under 5 years of age in Mozambique or 5-15 in Tanzania) under the effects of the assigned intervention without regards of treatment compliance.

5.2.3 General study population

All study population (i.e. those living in the study clusters) will be considered in the analyses of passive surveillance data, with an ITT approach. Subjects will be considered under the effects of the intervention assigned to their cluster of residence.

5.2.4 Cross sectional

This population will be also analyzed in an ITT manner. Subjects will be considered under the effects of the intervention assigned to their cluster of residence.

5.3 Covariates and Subgroups

For the selection of covariates in multivariable models, a stepwise procedure will be followed. Those variables with p-values lower than 0.20 in the univariate analysis and those considered significant from literature will be considered. The procedure will start with an empty model and will consider at each iteration entering (with a Wald test p-value lower than 0.05) or removing (with a Wald test p-value higher than 0.10) variables from the selected set.

5.4 Missing Data

All the available data on safety and efficacy shall be included in the data lists and tables. Initially, no values will be allocated for unavailable data, we will assume that missing values occur at random (MAR). To confirm this randomness, primary outcomes (malaria incidence and AE occurrence) will be compared between those with and without missing information.

However, if the proportion of missing values exceeds 5% in any of the adjusting variables used in the models responding to the primary objectives, multiple imputation assuming MAR will be used to impute missing observations.

5.5 Interim Analyses and Data Monitoring

There are no interim analyses planned.

5.6 Multiple Testing

Correcting for multiple comparisons reduces the chance of making type I error but it increases the chance of type II error. Therefore and although this study includes multiple outcome measures, no adjustment will be applied to correct for multiple comparisons [19]. Results interpretation will not focus on p-values, effect sizes will play a central role.

6 Summary of Study Data

Descriptive analyses will use frequency and percentage (based on the non-missing sample size) for qualitative variables and mean, standard deviation and n (non-missing sample size) for quantitative variables. For quantitative variables that typically present skewed distributions (i.e. times), median and interquartile ranges will be presented instead. Summary tables will be structured using one column per study arm and overall in the order: Albendazole (C), Ivermectin (H), Ivermectin (H+L), All subjects.

6.1 Subject Disposition

A flow diagram will be drawn to show the flow (randomization, treatment reception and analysis inclusion) of clusters and individuals by study arm for each cohort and study site.

6.2 Derived variables

The list of derived variables is provided in Annex B.

6.3 Concurrent Illnesses and Medical Conditions

BOHEMIA will use MedDRA coding and CIOMS forms to ensure standardization of terminology across the trial.

6.4 Prior and Concurrent Medications

Medications will be grouped based on their therapeutic use as detailed in derived variables section. Also, as standard practice in pharmacovigilance, those medications concomitant with severe adverse events will be coded using the WHO drug dictionary.

6.5 Treatment Compliance

All treatment will be administered under direct observation by the field worker. Immediate tolerance will be observed for 30 minutes after dosing. If the participant vomits within 30 minutes of taking the dose, the dose will be repeated. Participant dosing will be recorded by the fieldworker on the electronic visit template.

Treatment compliance will be summarized by frequency counts and percentages for each study arm.

7 Primary Analyses

7.1 Efficacy

Incidence Rates

Crude incidence rates (IR) will be calculated by dividing the number of positive RDTs recorded by the appropriate number of at-risk months of follow up. For any given unit (i.e. cohort, study arm, or cluster), a monthly incidence rate per child-month at risk equals:

(+RDTs that month)

[(Total RDTs performed that month) - (1/2*Total number of AL treated in the previous month)] months

Note that those treated with AL in the previous month will be considered at risk only for 14 days (i.e. half month) as explained in section 2.4.1.1. Assuming that the incidence rate follows a Poisson distribution, the 95% confidence interval will be calculated by means of the approximation to the Normal distribution:

$$IR \pm 1.96 * \sqrt{\frac{\text{IR}}{(\text{RDTs performed}) - (1/2 * \text{Number of AL treated in the previous month})}}$$

Overall incidences will be expressed in cases per child per year.

Cumulative incidence

Cumulative incidence will be based on the sum of all the cumulative incident cases observed through a given month in a given cohort, study arm, or cluster. For example, the cumulative incidence through the first six months in a given cluster will be the sum of all the positive RDTs observed each month in that cluster for the first six study months divided by the baseline population size.

Incidence rate ratio

A Poisson regression model using generalized estimated equations (GEE) with exchangeable correlation structure that considers the cluster design effect and includes adjustment for potential confounders identified in the univariate analysis will be used to estimate the differences in malaria incidence rates across study arms. Based on previous vector-control trials, the variables to be considered can be classified in the following categories: demographics (age and gender), socio-economics (socio-economic index, head of household formal education, head of household occupied as a subsistence farmer, electricity in the household, house wall material, house ceiling material, livestock-human ratio, number of nets owned and distance to the nearest health facility), clinical (having experienced fever in the last month, having slept under a bed net the previous night and infection of a sibling in the same household) and entomological (distance to and type of water bodies). A step-wise approach will be applied for building the final multivariable model, more details on the process are explained in section 5.3. Additionally, treatment contamination will be estimated and considered as an adjusting variable [20, 21].

7.2 Safety

Occurrence

For safety co-primary objective, AEs will be described in total and by body system. Tables will show the number of AE observed and the number and percentage of participants experiencing them within a system organ class or within preferred term category by severity or by relationship to study product.

Rate

For each study arm, the rate of AEs and SAEs will be computed by dividing the number of events occurred during the study by the number of treated subjects.

Total AEs (or SAEs)
population

95% confidence intervals will be calculated by means of the approximation to the Normal distribution:

$$AE\ rate \pm 1.96 * \sqrt{\frac{AE\ rate}{\text{population}}}$$

Incidence rate ratio

Differences between AE (and SAE) rates in the intervention groups will be assessed by means of Poisson regression models using GEE with exchangeable correlation structure to account for the cluster design.

8 Secondary Analyses

The summary statistics will be produced in accordance with section 6.

8.1 Efficacy

- Time to first positive RDT in children in the cohort

Study arms will be compared using competing-risks survival regression models accounting for the cluster design. Time at risk will be calculated from the date of recruitment to date of first positive RDT, last contact, death from any cause or end of follow up, whatever occurs first. Death will be considered as a competing event.

- Molecular force of infection in a subset of children in the cohort

Molecular force of infection, defined as the number of new *P falciparum* clones acquired during follow up, will be compared between study arms by means of the Poisson model using GEE with exchangeable correlation structure.

- Malaria case incidence in all ages presenting at health facility

Incidence rates in study arms will be compared by means of the Poisson model using GEE with exchangeable correlation structure.

- Malaria prevalence in all ages one month after the last dose

Prevalence will be compared between study arms estimating a logistic model using GEE.

- Multiplicity of infection in all ages one month after the last dose

Multiplicity of infection, defined as the number of concurrent parasite clones per host, will be described by study arm. Differences between arms will be assessed by means of the Poisson model using GEE.

- Spatial heterogeneity of malaria transmission

The heterogeneity of the intervention effect within and between clusters will be analyzed. Spatial statistical models will be estimated and used to generate the corresponding maps.

- Effect of livestock presence in malaria incidence

Livestock presence (by type and number) will be considered in the malaria incidence models. Apart from that, the relationship between livestock presence and malaria incidence will be displayed graphically. Distance from the household to livestock enclosure will be also considered.

- Effect of entomological measures in malaria incidence

Considering a subset of 15 clusters where entomological measures are collected, malaria incidence models will be estimated. These models will assess the relationship between entomological measures (mosquito densities, mosquito parity, sporozoite rate, human blood index, pig blood index, mosquito mean survival, human biting rate and entomological inoculation rate) and malaria incidence. Entomological measures will be given by the entomology sub-study. These measures consist of mean monthly values obtained from generalized negative binomial mixed-effects models.

- Relationship of malaria incidences with changes in predominant mosquito species over time

Considering a subset of 15 clusters where entomological measures are collected, malaria incidences will be plotted together with mosquito densities per specie.

- Relationship between ivermectin coverage in the community and mosquito survival

Considering a subset of 15 clusters where entomological measures are collected, the relationship between ivermectin coverage (none, less than 60% population, more than 60% population) and mean mosquito survival will be explored graphically.

8.2 Safety

- Observed tolerability of the dose

Frequencies of dose tolerability (not vomiting after administration) will be described as explained in section 6.

- Rate of SUSARs

These rates will be calculated in the same manner than those of AEs and SAEs (see section 7.2).

- AEs and SAEs by organ system

Frequencies will be described as explained in section 6.

8.3 Pharmacokinetics

A non-compartmental analysis (NCA) approach will be used for initial descriptive analysis of PK samples (e.g. peak concentration (C_{max}), time to peak concentration (T_{max}), terminal elimination half-life ($t_{1/2}$), and area under the curve for the all observed time points (AUC_{all}) and extrapolated AUC ($AUC_{0\text{-}inf}$). Quality of the profiles obtained will be judged by the extrapolated ratio of AUCs ($AUC_{extrap\%}$) for inclusion in the final descriptive analysis. Results from NCA will inform further pharmacometric analyses.

Covariate analysis will be performed using non-linear mixed effects modeling (nlme) with a step-wise covariate modeling approach. Models obtained from nlme will be also be to estimate primary and secondary pharmacokinetic parameters (volumes of distribution, clearance, elimination half-lives,

etc.) and descriptive parameters (e.g. C_{max}, $AUC_{0\text{-}inf}$) as well as secondary determinant of efficacy (e.g. fraction of time above LC_{50}). Goodness-of-fit will be assessed with predictive checks with numerical (bootstrapping) and visual methodology (e.g. visual predictive checks, basic goodness-of-fit plots).

8.4 Impact of ivermectin against selected ectoparasites and NTDs in the dosage regimen chosen

Description of the prevalence of each NTD at the specific timepoints when they are assessed. Prevalences will be compared between study arms by means of the logistic model using GEE.

8.5 Prevalence - incidence correlation

The cross-correlation function relating both time series (malaria incidence in the pediatric active cohort and malaria prevalence at all ages) will be estimated and presented graphically by means of a correlogram.

8.6 Relationship between active and passive surveillance

The cross-correlation function relating both time series (malaria incidence in the pediatric active cohort and malaria incidence in children at the health facility) will be estimated and presented graphically by means of a correlogram.

8.7 Performance of RDTs vs PCR

Cross tabulation of each pair (HRP2 RDT result vs. pLDH-based RDT and RDT vs. PCR) of diagnostic tools will be presented. Their classification performance will be summarized by means of sensitivity, specificity, positive predictive value and negative predictive value. In the comparison between RDTs, HRP2 RDT will be considered as the gold standard. RDT positivity will be defined as explained in **Table 1**. Classification performance measures and their 95% confidence intervals will be calculated by means of logistic regression models using GEE [22].

Monthly proportion and 95% confidence interval of RDT negative but PCR positive infections will be calculated.

9 Exploratory Analyses

The summary statistics will be produced in accordance with section 6.

9.1 Accuracy of self-reported pregnancy status and LMP

Sensitivity and specificity with their 95% confidence intervals will be given by study arm. Pregnancy test result will be considered as the gold standard and compared separately with self-reported pregnancy status and LMP. Classification performance measures and their 95% confidence intervals will be calculated by means of logistic regression models using GEE [22].

9.2 All-cause mortality

Frequencies in human treatment/safety cohort and active pediatric cohort will be presented as explained in section 6. Study arms will be compared by means of mixed-effects Cox proportional hazards models. Cluster will be included in the models as a random effect.

9.3 Pharmacogenomics

Associations of genetic variants in *CYP3A5* and *ABCB1* with central nervous system adverse effects will be assessed using logistic regression. Association analyses will be performed using an additive genetic

model for individual SNPs, as well as for *CYP3A5* drug metabolizer phenotype groups (extensive, intermediate, poor metabolizer; using both additive coding and by grouping extensive vs. intermediate/poor as well as poor vs. extensive/intermediate). Additionally, for *ABCB1*, associations with CNS AEs will be assessed for individual haplotypes inferred using gametic phase estimation. Logistic regression analyses will be performed both univariable as well as adjusting for any clinical or demographic covariates identified to be associated with neurological adverse effects.

10 Reporting Conventions

P-values greater than or equal to 0.001 will be reported to 3 decimal places. P-values less than 0.001 will be reported as '<0.001'. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data.

11 Technical Details

The analyses will be conducted using Stata [23]. Graphs will be produced using the package ggplot2 [24] for R [25]. Software versions will be the most recent available when the analysis starts. The operating system of the computer will be Windows 10. Additional pharmacometric analyses will be performed using NONMEM (Icon Development Solutions, Ellicott City, MD, USA) and Monolix Suite (Lixoft SAS, Antony, France), and may include runs on Apple Macintosh computers and Linux based clusters.

12 Summary of Changes to the Protocol

This document has been written based on information contained in the study protocol version 4.2.

13 References

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14 Listing of Tables and Figures

All results will be produced twice, one for each site. Tables corresponding to primary analyses will be duplicated in accordance to the sensitivity analyses planned.

14.1 Tables

14.1.1 Efficacy

Table E-1. Baseline study characteristics of active pediatric cohort by study arm

	Study arm			p-value
	Albendazole (C)	Ivermectin (H)	Ivermectin (H+L)	
Cluster characteristics (N=)				
Km to nearest health facility [1]				
Household characteristics (N=)				
Number of people				
Presence of water bodies				
Number of water bodies				
Distance to water bodies				
Type of water bodies				
Permanent water				
Semi-permanent water				
Transient water				
LLIN ownership				
LLIN effective coverage				
Number of LLINs in the household [1]				
Socio-economic status tercile				
Lower				
Medium				
High				
Head's formal education				
Head occupied as a subsistence farmer				
Electricity				
Livestock presence				
Livestock-human ratio [1]				
Children at enrollment (N=)				
Gender: female				
Age [1, 2]				
Slept under a LLIN the previous night				
Fever in the previous month				
RDT positive				
RDT positive sibling				

Cell content: n/N (%), 1: mean (SD), 2: For Mozambique, age at enrollment in months. For Tanzania, in years.
LLIN: Long Lasting Insecticidal Nets, RDT: Rapid Diagnostic Test

Table E-2. Incidences in active pediatric cohort by study arm

Study Visit	Albendazole (C)			Ivermectin (H)			Ivermectin (H+L)			IRR (95% CI)	
	RDT+	Cohort months at risk	Cummulative cases	RDT+	Cohort months at risk	Cummulative cases	RDT+	Cohort months at risk	Cummulative cases	H vs C	HL vs H
1											
2											
3											
4											
5											
6											
7											

RDT: Rapid Diagnostic Test, IRR: Incidence Rate Ratio, CI: Confidence Interval

Table E-3. Estimated intervention effect in active pediatric cohort

Variable	H vs C IRR (95% CI)		HL vs H IRR (95% CI)	
	Crude	Adjusted	Crude	Adjusted
Intervention				
Km to nearest health facility				
Presence of water bodies				
Distance to water bodies				
Type of water bodies				
Permanent water				
Semi-permanent water				
Transient water				
LLIN ownership				
LLIN effective coverage				
LLIN usage				
Number of LLINs in the household				
Head's formal education				
Head occupied as a subsistence farmer				
Electricity				
House wall material				
House ceiling material				
Socio-economic status tercile				
Lower				
Medium				
High				
Livestock-human ratio				
Gender: female				
Age				
Slept under a LLIN the previous night				
Fever in the last month				
RDT positive				
RDT positive sibling				

IRR: Incidence Rate Ratio, CI: Confidence Interval

Table E-4. Time (in days) to first positive RDT in active pediatric cohort

Study arm	Time (in days) to first +RDT		
	Median (IQR)	HR (95% CI)	p-value
Albendazole (C)		-	-
Ivermectin (H)			
Ivermectin (H+L)			

HR comparing H vs C and H+L vs H. IQR: Interquartile Range, HR: Hazard Ratio, CI: Confidence Interval

Table E-5. Molecular force of infection in a subset of children in the cohort

Study arm	Molecular force of infection		
	Median (IQR)	RR (95% CI)	p-value
Albendazole (C)		-	-
Ivermectin (H)			
Ivermectin (H+L)			

RR comparing H vs C and H+L vs H. IQR: Interquartile Range, RR: Risk Ratio, CI: Confidence Interval

Table E-6. Incidences in the general population (passive surveillance) by study arm

Study Month	Albendazole (C)			Ivermectin (H)			Ivermectin (H+L)			IRR (95% CI)	
	RDT+	Cohort months at risk	Cumulative cases	RDT+	Cohort months at risk	Cumulative cases	RDT+	Cohort months at risk	Cumulative cases	H vs C	HL vs H
1											
2											
3											
4											
5											
6											
7											

RDT: Rapid Diagnostic Test, IRR: Incidence Rate Ratio, CI: Confidence Interval

Table E-7. Estimated intervention effect in the general population (passive surveillance)

Variable	H vs C IRR (95% CI)		HL vs H IRR (95% CI)	
	Crude	Adjusted	Crude	Adjusted
Intervention				
Gender: female				
Age				

IRR: Incidence Rate Ratio, CI: Confidence Interval

Table E-8. Malaria prevalence in all ages one month after the last dose

Study arm	Malaria prevalence		
	n/N (%)	OR (95% CI)	p-value
Albendazole (C)		-	-
Ivermectin (H)			
Ivermectin (H+L)			

OR comparing H vs C and H+L vs H. OR: Odds Ratio, CI: Confidence Interval

Table E-9. Multiplicity of infection in all ages one month after the last dose by study arm

Study arm	Multiplicity of infection (number of concurrent parasite clones)		
	Median (IQR)	RR (95% CI)	p-value
Albendazole (C)		-	-
Ivermectin (H)			
Ivermectin (H+L)			

RR comparing H vs C and H+L vs H. IQR: Interquartile Range, RR: Risk Ratio, CI: Confidence Interval

14.1.2 Safety

Table S-1. Baseline study characteristics of treatment/safety cohort by study arm

	Study arm			p-value
	Albendazole (C)	Ivermectin (H)	Ivermectin (H+L)	
Cluster characteristics (N=)				
Km to nearest health facility [1]				
Household characteristics (N=)				
Presence of water bodies				
Number of water bodies				
Distance to water bodies				
Type of water bodies				
Permanent water				
Semi-permanent water				
Transient water				
LLIN ownership				
LLIN effective coverage				
LLIN usage				
Number of LLINs in the household [1]				
Socio-economic status tercile				
Lower				
Medium				
High				
Head's formal education				
Head occupied as a subsistence farmer				
Electricity				
House wall material				
House ceiling material				
Livestock presence				

Livestock-human ratio [1]				
Subjects enrolled (N=) Gender: female Age at enrolment Slept under a LLIN the previous night Fever in the last month Had malaria in the last month				

Cell content: n/N (%), 1: mean (SD). LLIN: Long Lasting Insecticidal Nets

Table S-2. General description of the adverse events in treatment/safety cohort by study arm

	Albendazole (C) (N=)	**Ivermectin (H) (N=)**	**Ivermectin (H+L) (N=)**	**ALL (N=)**
Number of AEs observed[1]				
Number of AEs observed[2] None 1-2 3 or more				
Number of SAEs observed[1]				
Number of SAEs observed[2] None 1-2 3 or more				
Number of SUSARs observed[1]				
Number of SUSARs observed[2] None 1-2 3 or more				
Number of treatment-related AEs observed[1]				
Number of treatment-related AEs observed[2] None 1-2 3 or more				

1: Median (IQR) [n], 2: n/N (Percentage)

AEs: adverse events, SAEs: serious adverse events, SUSARs: suspected unexpected serious adverse reactions, treatment-related: corresponds to possibly, probably or definitely related.

Table S-3. General description of subjects suffering any adverse events in treatment/safety cohort by study arm

Table S-1 considering only subjects with AEs.

Table S-4. Observed adverse events in treatment/safety cohort by study arm

System Organ Class Preferred Term [1]	**Albendazole (C) (N=)**	**Ivermectin (H) (N=)**	**Ivermectin (H+L) (N=)**	**ALL (N=)**

Any AE				
System organ class 1				
Preferred term 1				
Preferred term 2				
……				
System organ class 2				
Preferred term 1				
Preferred term 2				
……				

Cell content: number of patients (percent of patients) [number of events]. Dashes indicate absence of events.
1: Preferred terms reported only in SAEs and SUSARs tables. Coding dictionary: MedDRA version xx.x

The same structure will be used to describe:

- SAEs
- SUSARs
- AEs judged related (possibly, probably and definitely) to study treatment

Table S-5. Observed severe adverse events in treatment/safety cohort by severity

System organ class Preferred term [1]	Mild (N=)		Moderate (N=)		Severe (N=)		All grades (N=)		ALL (N=)
	NR	R	NR	R	NR	R	NR	R	
Any AE									
System organ class 1									
Preferred term 1									
Preferred term 2									
……									
System organ class 2									
Preferred term 1									
Preferred term 2									
……									

Cell content: number of patients (percent of patients) [number of events]. Dashes indicate absence of events.
NR=Not related, R=Related
Coding dictionary: MedDRA version xx.x

Table S-6. Withdrawal reasons in treatment/safety cohort by study arm

Variable		Study arm			All Subjects
		Albendazole (C)	Ivermectin (H)	Ivermectin (H+L)	
Main reason of patient withdrawal	Migration				
	Consent withdrawal				
	Pregnancy or intention to become pregnant				
	Protocol violation				

	Loss of follow-up				
	Safety				
	Death				
	Others				

Cell content: n (Column percentage)

Table S-7. Observed tolerability of the dose

Variable		Study arm			All Subjects
		Albendazole (C)	Ivermectin (H)	Ivermectin (H+L)	
Dose tolerability (not vomiting)	Round 1				
	Round 2				
	Round 3				

Cell content: n/N (%)

14.1.3 Others

Table O-1. Monthly prevalence of NTDs in active pediatric cohort by study arm

Study Visit	Scabies			Head lice			*Tunga penetrans*			Bed bug infestation		
	C	H	H+L	C	H	H+L	C	H	H+L	C	H	H+L
1												
2												
3												
4												
5												
6												
7												

Cell content: n/N (%)

Table O-2. Intervention effect in the prevalence of NTDs in active pediatric cohort.

Outcome	H vs C OR (95% CI)		HL vs H OR (95% CI)	
	Crude	Adjusted	Crude	Adjusted
Scabies				
Head lice				
Tunga penetrans				
Bed bug infestation				

OR: Odds Ratio, CI: Confidence Interval

Table O-3. RDT performance in a subset of children in the cohort.

Classification performance	Comparison		
	pLDH-based RDT vs HRP2 RDT *	pLDH-based RDT vs PCR *	HRP2 RDT vs PCR *
Sensitivity			
Specificity			

Positive predictive value			
Negative predictive value			

*: gold standard, Cell content: % (95%CI)

Table O-4. Monthly proportion of RDT negative but PCR positive individuals

Study visit	Study arm			All Subjects
	Albendazole (C)	Ivermectin (H)	Ivermectin (H+L)	
1				
2				
3				
4				
5				
6				
7				

Cell content: % (95%CI)

14.1.4 Exploratory

Table Ex-1. Self-reported pregnancy status and LMP vs pregnancy test

Classification performance	Self-reported pregnancy status vs pregnancy test	LMP vs pregnancy test
Sensitivity		
Specificity		
Positive predictive value		
Negative predictive value		

Cell content: % (95%CI)

Table Ex-2. Accuracy of self-reported pregnancy status and LMP

Variable		Study arm			All Subjects
		Albendazole (C)	Ivermectin (H)	Ivermectin (H+L)	
Proportion of pregnant women among those self-reporting as non-pregnant	Round 1				
	Round 2				
	Round 3				
	Final safety visit				
Proportion of pregnant women among those reporting LMP more than 2 weeks before the test	Round 1				
	Round 2				
	Round 3				
	Final safety visit				

Cell content: n/N (%, 95%CI)

Table Ex-3. All-cause mortality

Variable	Cohort	
	Active pediatric	Treatment/ safety

All-cause mortality		
Malaria-related mortality		

Cell content: n/N (%)

14.2 Figures

14.2.1 Efficacy

Figure E-1. Monthly incidence in active pediatric cohort by study arm

Line graph showing the monthly incidence of malaria cases per child-month for each study arm. MDA rounds will be highlighted.

Figure E-2. Monthly cumulative incidence in active pediatric cohort by study arm

Line graph showing the monthly cumulative incidence of malaria cases per child-year for each study arm. MDA rounds will be highlighted.

Figure E-3. Monthly IRR (H vs C) in active pediatric cohort

Graphical display of monthly IRR and their 95% CI. MDA rounds will be highlighted.

Figure E-4. Monthly IRR (HL vs H) in active pediatric cohort

Graphical display of monthly IRR and their 95% CI. MDA rounds will be highlighted.

Figure E-5. Time to first positive RDT in active pediatric cohort by study arm

Kaplan-Meier curves showing the time to first positive RDT by study arm.

Figure E-6. Monthly incidence in the general population (passive surveillance) by study arm

Line graph showing the monthly incidence of malaria cases per person-month for each study arm. MDA rounds will be highlighted.

Figure E-7. Monthly cumulative incidence in the general population (passive surveillance) by study arm

Line graph showing the monthly cumulative incidence of malaria cases per person-year for each study arm. MDA rounds will be highlighted.

Figure E-8. Monthly IRR (H vs C) in the general population (passive surveillance)

Graphical display of monthly IRR and their 95% CI. MDA rounds will be highlighted.

Figure E-9. Monthly IRR (HL vs H) in the general population (passive surveillance)

Graphical display of monthly IRR and their 95% CI. MDA rounds will be highlighted.

Figure E-10. Spatial heterogeneity of malaria transmission

Maps showing the results of the corresponding spatial statistical models.

Figure E-11. Effect of livestock presence in malaria incidence

Combined plot consisting of three graphs (one for each study arm). These graphs will show a boxplot with total malaria incidence for each livestock quartile.

Figure E-12. Relationship of malaria incidences with changes in predominant mosquito species over time

Line plot showing malaria incidences and mosquito densities (per specie).

Figure E-13. Relationship between ivermectin coverage in the community and mosquito survival

Line graph with mosquito survival over study time. With different lines per coverage level (none, less than 60% population, more than 60% population).

14.2.2 Safety

Bar plots summarizing AE frequencies presented in Tables S-2, S-4, S-6 and S-7 will be provided.

14.2.3 Others

Figure O-1. Cross-correlation function relating malaria prevalence and incidence

A correlogram presenting the correlation between both time series (malaria incidence in the pediatric active cohort and malaria prevalence at all ages) at different lags.

Figure O-2. Cross-correlation function relating malaria incidence in the studied cohorts

A correlogram presenting the correlation between both time series (malaria incidence in the pediatric active cohort and malaria incidence in children at the health facility) at different lags.