AIM-Skin

Impact of Single-Dose Azithromycin in Impetigo and Skin Microbiology

ISRCTN
NCT *(clinicaltrials.gov)*

V1.0
17th February 2016

SPONSOR: London School of Hygiene & Tropical Medicine
FUNDERS: Wellcome Trust
STUDY COORDINATION CENTRE: LSHTM

LSHTM ethics reference: Pending

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Sponsor

London School of Hygiene & Tropical Medicine is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Research Governance and Integrity Office:

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Funder
This study is funded as part of a Wellcome Trust Research Fellowship held by Michael Marks.

This protocol describes the AIM-Skin study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version.

Problems relating to this trial should be referred, in the first instance, to the study coordination centre.

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, protocol and all applicable local regulations.

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GLOSSARY OF ABBREVIATIONS

AAH	Atoifi Adeventist Hospital
AE	Adverse Event
MDA	Mass Drug Administration
SAE	Serious Adverse Event
SUSAR	Serious Unexepected Event

KEYWORDS

Yaws
Scabies
Azithromycin
Ivermectin
Impetigo
MDA

STUDY SUMMARY

TITLE	Impact of Single-Dose Azithromycin in Impetigo and Skin Microbiology
DESIGN	A prospective community intervention trial to assess the impact of community mass treatment with azithromycin for yaws and ivermectin for scabie, on non-yaws bacterial skin infections.
AIMS	Assess the impact of single dose azithromycin, given for yaws, on other prevalent bacterial skin infections. Assess the impact of single dose azithromycin on antimicrobial resistance patterns in isolates of S.pyogenes and S.aureus.
OUTCOME MEASURES	Primary Outcome a) Difference in the change in prevalence of impetigo between baseline and 12-months between the parallel and the sequential treatment arms. Secondary Outcomes b) Change in the proportion of swab samples from which S. pyogenes is cultured between baseline and follow-up in the two arms c) The proportion of samples from which a drug-resistant isolate of S.pyogenes is cultured in the two arms
POPULATION	Parallel Treatment Arm: Sample size of 637 Sequential Treatment Arm: Sample size of 637
ELIGIBILITY	All residents of selected communities are eligible to participate in the study
TREATMENT	*Treatment of yaws:* Single dose of Azithromycin (30mg/kg, max 2G). *Treatment of scabies:* Either an oral dose of Ivermectin (200µg/kg) or permethrin cream for those with a contraindication to Ivermectin (WT<15kg, pregnant or breastfeeding women) given in 2 doses 7-14 days apart.
DURATION	12 months

1. INTRODUCTION

1.1 BACKGROUND

Both trachoma, caused by *Chalmydia trachomatis*, and yaws, caused by *Treponema pallidum* subsp. *pertenue*, are endemic in many Pacific countries including the Solomon Islands[1,2]. Mass treatment with azithromycin is the cornerstone of the WHO strategy for the elimination and eradication of these two diseases resepectively[3,4]. Mass treatment with azithromycin has been shown to have beneficial off-target effects including decreased malaria transmission and some evidence to support a reduction in infant mortality [5,6]. Conversely, mass treatment with azithromycin has been associated with changes in the resistance patterns of nasopharyngeal isolates of *Streptococcus pneumoniae*[7].

Scabies is also a significant public health problems in the Pacific[8]. Scabies is associated with secondary bacterial infections (impetigo) which are most commonly caused by *Streptococcus pyogenes* and *Staphylococcus aureus*[9]. Recently community mass treatment with Ivermectin has been shown to be an effective strategy for reducing the prevalence of both scabies and associated bacterial complications[10]. Recent surveys conducted in the Solomon Islands have shown that the prevalence of scabies is between 18-25% and the prevalence of impetigo between 25-40% (A Steer, personal communication).

1.2 RATIONALE FOR CURRENT STUDY

Current WHO recommendations for yaws are for community mass treatment with single dose azithromycin[3]. The impact of this treatment on other bacterial skin diseases is unknown.

Azithromycin has activity against both *S. pyogenes* and *S. aureus* and mass treatment with azithromycin, for either yaws or trachoma control, might have additional impacts on both the prevalence of impetigo and the potential emergence of resistant organisms. These issues may be of particular relevance in the Pacific where mass treatment for yaws or trachoma is likely to be conducted in the near future and where scabies and impetigo are also both common.

Understanding the impact of azithromycin mass treatment on impetigo will inform whether integrated control programmes for yaws, trachoma and scabies could be considered in the Pacific where all three diseases are endemic.

2. STUDY OBJECTIVES

Study Aims:

Assess the impact of single dose azithromycin, given for yaws, on other prevalent bacterial skin infections.
Assess the impact of single dose azithromycin on antimicrobial resistance patterns in isolates of *S.pyogenes* and *S.aureus*.

Primary Objective:

The primary objective is to see whether a single dose of azithromycin, given as treatment for yaws, has an additional impact on impetigo.

Secondary Objectives:

The secondary objective is to assess whether treatment with a single dose of azithromycin results in change in the anti-microbial susceptibility of clinical skin swab isolates .

3. STUDY DESIGN

This is an open-label prospective community intervention trial to assess the impact of community mass treatment with azithromycin for yaws and ivermectin for scabies, on non-yaws bacterial skin infections.

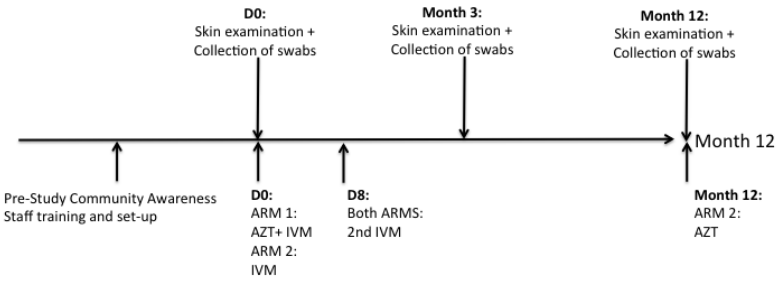
Study Site

This study will be conducted within communities residing in the catchment area of Atoifi Adventist Hospital (AAH), Malaita Province, Solomon Islands. Both yaws and scabies are known to be endemic across the whole of the Solomon Islands[1].

Duration

The duration of the study is 12 months. For all participants, there will be a 15 day on-study period which will include two visits by the study team

- Day 1 for baseline medical assessment and delivery of azithromycin/tetracycline and ivermectin/permethrin
- Day 8-15 for delivery of second dose of ivermectin/permethrin



Treatment

No investigational medications or indications are being assessed. Both study sites will receive standard treatment for both yaws and scabies either in parallel (site 1) or in sequence (site 2).

Treatment of yaws:
Single dose of Azithromycin (30mg/kg, max 2G).

Treatment of scabies:
Either an oral dose of Ivermectin (200µg/kg) or permethrin cream for those with a contraindication to Ivermectin (WT<15kg, pregnant or breastfeeding women) given in 2 doses 7-14 days apart.

Site 1- Parallel Treatment Arm
Single dose azithromycin (for yaws) and Ivermectin/Permethrin (for scabies) will be offered on D1. A second dose of Ivermectin/Permethrin will be offered 7-14 days later.

Site 2- Serial Treatment Arm
Ivermectin/Permethrin (for scabies) will be offered on D1 with a second dose of Ivermectin/Permethrin offered 7-14 days later..
Single dose azithromycin (for yaws) will be offered at the twelve month follow-up visit.

3.1 STUDY OUTCOME MEASURES

Primary Outcome
a) Difference in the change in prevalence of impetigo between baseline and 12-months between the parallel and the sequential treatment arms.

Secondary Outcomes
b) Change in the proportion of swab samples from which *S. pyogenes* is cultured between baseline and follow-up in the two arms
c) The proportion of samples from which a drug-resistant isolate of *S.pyogenes* is cultured in the two arms

3.2 RISKS AND BENEFITS

Mass treatment with azithromycin is the standard of care for yaws endemic communities. Several studies have demonstrated a reduction in both active and latent cases of infection[11,12]. Mass treatment for scabies with both Ivermectin and Permethrin has been shown to be an effective intervention at reducing the prevalence of scabies at a community level[10,13].

The safety profile of single dose azithromycin is well known. Azithromycin is considered the standard treatment for trachoma and yaws, both as therapy and in MDAs, and has been employed for over 10 years in trachoma control programs. An active population-based surveillance of multiple communities in Ethiopia found a low prevalence of AEs after mass azithromycin distribution. The most frequently observed AEs (between 1 and 10%) were nausea, vomiting and diarrhea.

The safety profile of ivermectin is also very well known. Safety has been well studied through its usage therapeutically and in large scale MDA programs. In the past 21 years, more than 1 billion doses of ivermectin tablets have been distributed for both onchocerciasis and lymphatic filariasis, at doses of 100-200 □g/kg with excellent safety. A review of women accidentally given ivermectin while pregnant showed no evidence of teratogenicity.

Co-Administration of Azithromycin and Ivermectin was shown to be safe in the Azival study[14]. There was no difference in the number of adverse events in individuals who received combined treatment compared to those who received treatment one week apart. The safety of co-administration has recently been confirmed in the AIM study in which the rate of adverse events following combined Azithromycin and Ivermectin treatment was <5% and no SAEs were noted (A Steer, Personal Communication).

Benefits to Communities

Communities will benefit from receiving treatment for both scabies and yaws as part of these studies. These are both major public health problems in the Solomon Islands and participating communities will therefore gain benefit from receiving the best available treatment for these two conditions which it is believed will result in improvements in their health and well being.

4. SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1 PRE-RANDOMISATION OR PRE-REGISTRATION EVALUATIONS

Mass treatment of the whole community with azithromycin is recommended for the purpose of yaws control. Mass treatment of the whole community with Ivermectin and Permethrin is the best available treatment for the purpose of scabies control. Both treatment are offered to all individuals regardless of the presence/absence of clinical features of either disease – which is in line with the best evidence on how community mass treatment for these diseases should be conducted.

4.2 INCLUSION CRITERIA

All consenting individuals in the participating communities will eligible to participate

4.3 EXCLUSION CRITERIA.

Individuals not consenting to participate in the study.

Individuals who are unwell on the day that study medications are administered.

4.4 WITHDRAWAL CRITERIA

Study participation is voluntary and study participants can withdraw at any time. The number of withdrawals will be recorded and only data collected prior to withdrawal will be included in the analysis. Only data collected prior to withdrawal will be included in the analysis.

5. RANDOMISATION AND ENROLMENT PROCEDURE

5.1 RANDOMISATION OR REGISTRATION PRACTICALITIES

Randomisation will be done at the level of the community by drawing sealed envelopes.
All individuals within a community will be offered treatment in line with the randomisation of that community. All residents of the selected communities will be invited to participate in the study.

Community Awareness

Prior to the study commencing we will engage community leaders and local health staff from communities in the catchment area of AAH. A research training workshop will be held at AAH and which will be attended by AAH and other study staff as well as key community leaders. This meeting will provide an opportunity for explanation of the study aims and methodologies and for study staff to answer questions about the study design and implementation.

Eligibility Criteria:

All individuals within a community will be offered treatment in line with the randomisation of that community. All residents of the selected communities will be invited to participate in the study.

Inclusion Criteria:

All residents of the selected communities will be invited to participate in the study.

Exclusion Criteria:

Individuals with a contra-indication to treatment.
Individuals not consenting to participate.

5.2 BLINDING

This is an open-label study

6. TRIAL MEDICATION

6.1 Name and description of investigational medicinal product(s)

Azithromycin

Azithromycin is an azalide antibiotic, a subclass of the macrolides. After oral administration, peak plasma concentration is reached in 2 to 3 hours. Tissue levels of azithromycin are greater than plasma levels (up to 50 times the maximum plasma concentration). Biotransformation occurs mainly in the liver, with elimination mainly by the bile and partly by urine. The plasma terminal half-life is 2-4 days. Azithromycin is indicated for mild to moderate infections such as respiratory-tract infections, otitis media, skin and soft-tissue infections and genital chlamydial infections Azithromycin is the treatment of choice for mass treatment of both yaws and trachoma. The recommended dose for the mass treatment of yaws is a single- dose of azithromycin 30mg/kg up to a maximum of 2g. Azithromycin is available as 250 mg or 500 mg tablets and as oral suspension.

Ivermectin

Ivermectin is an anthelminthic. Ivermectin is metabolized in the liver, and ivermectin and/or its metabolites are excreted almost exclusively in the feces over an estimated 12 days, with less than 1% of the administered dose excreted in the urine. After oral administration, the apparent plasma half-life of ivermectin is approximately 16 hours. Ivermectin is indicated for the treatment of onchocerciasis or river blindness caused by Onchocerca volvulus and for strongyloidiasis caused by Strongyloides stercoralis. The recommended dosage for treatment of scabies is two oral doses designed to provide approximately 200µg of ivermectin per kg of body weight. The same dose is recommended in the Solomon Islands. Ivermectin is available in 3mg tablets.

Topical 5% permethrin cream (Lyclear®)

Topical 5% permethrin (Lyclear ®) cream for scabies is supplied in a 30g tube. The cream is applied all over the body including from neck to toe and washed off after a minimum of 8 hrs. For children aged 2 months or less permethrin should be washed off after 4 hours.

6.2 Legal status of drug

Azithromycin is licensed for use in the UK. It is listed on the essential medicines list of the Solomon Islands and is the WHO recommended drug for community mass treatment for yaws eradication.

Permethrin is licenced in the UK for the treatment of scabies. It is listed as on the essential medicines list for the Solomon Islands and recommended as a potential treatment for scabies.

Ivermectin is not licenced for the treatment of scabies in the UK although NICE has provided guidance on its use (https://www.nice.org.uk/advice/esuom29/resources/ivermectin-for-difficulttotreat-scabies-17546902981). Ivermectin is widely used in control programmes for both Onchocerciasis and Lymphatic Filariasis. Ivermectin is listed as on the essential medicines list for the Solomon Islands and recommended as a potential treatment for scabies.

6.3 Summary of Product Characteristics (SmPC) or Investigator Brochure (IB)
Product Characteristics Sheets are attached in the Appendix.

6.4 Drug Storage and Supply
Medications will arrive by plane and will reach the islands by boat at the provincial pharmacy / medical store. The order request will be checked with the supplies delivered. The delivery notice number, delivery date and the medications batch number will be recorded in a log book. Medications will be taken out of the pharmacy in bulk by the study teams for dispensing in the community. Study teams will maintain a log of all medicines dispensed that can be cross-checked against participants study records.

6.5 Preparation and labelling of IMP
For participants receiving ivermectin and azithromycin, the dose will be determined according to body weight and treatment will be administered under direct supervision of the study team. Drug administration will be recorded in a standardized record form.

Participants assigned to permethrin (due to contra-indication to ivermectin) will receive a tube of cream and will be asked apply the cream from neck to toes before they leave the clinic and under supervision of a study nurse, and leave it on for a minimum of 8 hours, maximum 24 hours if possible. For children aged 2 months or less, cream will applied for a maximum of 4 hours.

6.6 Dosage schedules/modifications
In line with standard treatment the dosing of both Azithromycin and Ivermectin will use the following weight bands

WEIGHT	AZITHROMYCIN TABLETS (250mg Tabs)	IVERMECTIN TABLETS (3mg Tabs)
<15KG~~12.5KG~~	1	PERMETHRIN CREAM
~~12.5~~15 – 25 KG	1	1
25 – 37.5 KG	2	2
37.5 – 50 KG	3	3
50-75 KG	4	4
>75 KG	4	5

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Permethrin will be used instead of Ivermecitn in the following circumstances

- Pregnancy
- Breastfeeding
- Child <6 months age
- Child <~~12.5kg~~15kg

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Where permethrin is indicated the following standard dosing protocol will be used:

- Full tube for adults.
- Half tube for children.
- Apply to whole body and leave on for 1 day before washing off

6.7 Known drug reactions and interaction with other therapies

The safety profile of both azithromycin and ivermecitn is well established from large mass treatment campagins where >100 million doseases have been adminsted. The most commonly reported side effects are for Ivermectin are headache, dizziness, itch. For Azithromycin the most commonly reported side effects are abdominal pain, nausea, vomiting and diarrhoea. For both drugs adverse events are normally mild and self-limiting with no specific therapy required.

Results from a pharmacovigilance study involving more than 3,000 participants on the adverse events associated with the triple, co-administered combination therapy of azithromycin, ivermectin and albendazole (AZIVAL, AZithromycin, IVermectin, ALbendazole) in Mali found that triple combination therapy appears to be safe[14]. There were no serious adverse events in this study. Overall the rate of adverse events was similar in the triple combination therapy group (18.7%) compared to the standard therapy group (16.0%). Taken together these studies support expert opinion that the combination of azithromycin and ivermectin is safe.

6.8 Concomitant medication

Individuals receiving Warfarin may not receive treatment with Ivermectin due to potential interactions.

No individuals outside of the capital of the Solomon Islands (Honiara) are receiving Warfarin due to a lack of INR monitoring facilities and therefore it is not anticipated that nay individuals in the study will be receiving a contra-indicated concomitant medication.

6.9 Trial restrictions

There are no trial restrictions.

As noted above pregnant and breast feeding women and children <15kg will be offered permethrin rather than ivermecitn but will still be allowed to participate in the study.

6.10 Assessment of compliance

Drugs will be delivered as a single observed treatment and therefore compliance will be assessed at the time of drug distribution.

7. SAFETY REPORTING FOR DRUG TRIALS

7.1 DEFINITIONS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death • Is life-threatening • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • In the case of any other investigational medicinal product, in the investigator brochure (IB) relating to the trial in question.

7.2 CAUSALITY

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related side effects due to the drugs used in this study. The assignment of causality should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, both points of view are to be reported.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

7.3 REPORTING PROCEDURES

Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance.

7.3.1 Non serious Adverse Reactions (ARs)/Adverse Events (AEs)

Given the established safety profile of the drugs being used in this study and the fact that they are being used for established indications we will only collect data on SAEs and SUSARs.

7.3.2 Serious Adverse Reactions (SARs)/Serious Adverse Events (SAEs)

Serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs) should be reported to the study coordination centre within 24 hours of the local site being made aware of the event.

An SAE form should be completed and submitted to the study coordination centre with as much detail of the event that is available at that time. If awaiting further details, a follow up SAE report should be submitted promptly upon receipt of any outstanding information. The CI (for a single-centre trial) or PI (for a multi-centre trial) must record the event with an assessment of seriousness, causality and expectedness.

Any events relating to a pre-existing condition or any planned hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

7.3.3 SUSARs

All SAEs assigned by the PI or delegate as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Regulatory Authority, in the UK: Medicines and Healthcare Products Regulatory Agency (MHRA). The Sponsor (or delegate) will inform the MHRA, and the ethics committee of UK-relevant SUSARs within the required expedited reporting timescales (as per LSHTM Standard Operating Procedure for recording, managing and reporting of adverse events for IMP studies).

For blinded trials, all SUSARs must be reported assuming the active compound is involved.

In the case of a suspected, unexpected, serious adverse reactions (SUSAR), the staff at the site should:

1. Contact the study coordination centre immediately by phone or email to inform them of the event.
2. Submit a completed SAE form (signed and dated) within 24 hours, together with relevant treatment forms and anonymised copies of all relevant investigations.
3. Submit any additional information promptly upon request.

Contact details for reporting SAEs and SUSARs
Telephone: +677 7738438 / +44 7984 643424
Email: michael.marks@lshtm.ac.uk

8. ASSESSMENT AND FOLLOW-UP

Baseline Data Collection

At baseline (D1) all individuals will undergo a standardized examination to collect data on the presence of skin lesions consistent with yaws, scabies and impetigo. Following examination a finger-prick sample will be obtained from all individuals on to filter paper. In individuals with skin lesions consistent with yaws the same finger prick sample will be used for a rapid diagnostic test for yaws. In individuals with skin lesions consistent with yaws or impetigo two sterile lesion swabs will be obtained.

Following examination individuals will be weighed and directly observed treatment will be dispensed in line with standard treatment guidelines (see above). On D8 study teams will return to each community and offer a second dose of medication for scabies.

Interim Visit

At Month 3 an interim visit will be made. Individuals will be re-examined and swabs collected from those with clinical evidence of impetigo. Data from previous studies indicates that scabies and impetigo continue to decline between month 3 to month 12 following community mass treatment for scabies therefore treatment will not routinely be offered at this time point.

Follow-Up Data Collection

At follow-up all individuals will undergo again undergo a standardized examination to collect data on the presence of skin lesions consistent with yaws, scabies and impetigo. Following examination a finger-prick sample will be obtained from all individuals on to filter paper. In individuals with skin lesions consistent with yaws the same finger prick sample will be used for a rapid diagnostic test for yaws. In individuals with skin lesions consistent with yaws the same finger prick sample will be used for a rapid diagnostic test for yaws. In individuals with skin lesions consistent with yaws or impetigo two sterile lesion swabs will be obtained.

In communities where azithromcycin mass treatment was not conducted at baseline (sequential treatment arm 2) this will be offered at the follow-up visit.

Laboratory Work

- Dried blood spots will be eluted at tested using the Treponema Pallidum Haemagglutination Assays.
- From each pair of lesion swabs, one swab will be tested using culture and anti-microbial sensitivity testing for *S. pyogenes* and *S. aureus..*

- The second lesion swab will tested using molecular techniques to assess the microbiological flora of the lesions.

8.1 LOSS TO FOLLOW-UP

This is not an individually randomised clinical trial but allowance has been made for loss to follow-up in the sample size calculation.

8.2 TRIAL CLOSURE

The trial is planned to run over a 12 month period. The trial will be complete at the end of this 12 month period.

9. STATISTICS AND DATA ANALYSIS

Sample Size

The sample size required for our primary outcome was estimated as follows:

- Pre-MDA prevalence of impetigo of 25-30%
- Impetigo prevalence to fall to about 10% in the Ivermectin only arm
- Impetigo prevalence to fall to about 5% in the combined arm
- Enrolment 80%
- Loss to follow-up 10%
- 90% power to detect a difference between the two arms

Primary Outcome:

a) Prevalence of impetigo at months 12 months in parallel treatment communities compared to sequential treatment communities.

Secondary outcomes:

b) Change in the proportion of swab samples from which *S. pyogenes* is cultured between baseline and follow-up in the two arms

c) Proportion of samples from which a drug-resistant isolate is cultured.

Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

10. MONITORING

10.1 RISK ASSESSMENT

This is considered a low risk study.

All the drugs being used are being prescribed for routine indications and have well established safety profiles. As such only passive monitoring for adverse events will be undertaken during the study.

10.2 MONITORING AT STUDY COORDINATION CENTRE

Data will be entered directly into an electronic database at the time of the study.

10.3 MONITORING AT LOCAL SITE

Site visits will take place at D1 (treatment for yaws and scabies), D8 (second treatment for scabies) and month 12 (assessment of outcome).

11. REGULATORY ISSUES

11.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the LSHTM Research Ethics Committee, as well as the Atoifi Adventist Hospital Ethics Committee.

Substantial protocol amendments will not be implemented until a favourable opinion has been granted from both the LSHTM and AAH ethics committee.
Correspondence from both ethics committees will be maintained in the trial master file.
As the duration of the study is 1 year the annual progress report will accompany the notification of the end of the study.

11.2 CONSENT

Prior to the study commencing a research training workshop will be held at AAH and which will be attended by AAH and other study staff as well as key community leaders. This meeting will provide an opportunity for explanation of the study aims and methodologies and for study staff to answer questions about the study design and implementation.

Prior to performing any study specific procedure, written informed consent will be obtained for each subject. Information sheets explaining the study will be distributed to community nurses who will be trained in explaining the study. These information sheets will also be available to study participants. For subjects below the legal age, a parent or legal guardian must provide consent. Written consent will be obtained in local dialect on all occasions.

11.4 CONFIDENTIALITY

Subject confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples and the clinical information relating to participating subjects. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsoring institution. Authorized representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records. All evaluation forms, reports and other records that leave the site will be identified only by the Subject Identification Number (SID) to maintain subject confidentiality. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by HREC or regulatory agencies.

11.5 INDEMNITY

London School of Hygiene & Tropical Medicine holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

11.6 SPONSOR

London School of Hygiene & Tropical Medicine will act as the main sponsor for this study. Delegated responsibilities will be assigned locally.

11.7 FUNDING

This study is funded as part of a Wellcome Trust Research Fellowship held by Michael Marks.
No payments will be made to patients participating in this study.

11.8 AUDITS AND INSPECTIONS

The study may be subject audit by the London School of Hygiene & Tropical Medicine under their remit as sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

12. TRIAL MANAGEMENT

A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be co-ordinated by Michael Marks and Jason Diau.

All treatments in the study are being given for standard indications and the drugs have known safety profiles including in the setting of co-administration. A DSMB will therefore not be appointed.

All data will be held jointly by LSHTM and AAH. Data will be stored on an encrypted password protected server at both LSHTM and AAH.

13. PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. If there are named authors, these will include at least the trial's Chief Investigator, Statistician and Trial Coordinator. Members of the TMG and the Data Monitoring Committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

14. REFERENCES

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APPENDICES

1. Informed Consent Form
2. Assent Form
3. Study Information Sheet
4. MDA Record Form
5. Skin Examination Record Form
6. SAE Report Form
7. Summary of Product Characteristics for Azithromycin
8. Summary of Product Characteristics for Ivermectin
9. Summary of Product Characteristics for Permethrin