SCHOOL OF PUBLIC HEALTH, COLLEGE OF
HEALTH SCIENCES, UNIVERSITY OF GHANA,
LEGON

A SINGLE DOSE ORAL AZITHROMYCIN VERSUS
INTRAMUSCULAR BENZATHINE
BENZYLPEICILLIN FOR THE TREATMENT OF
YAWS- A RANDOMISED NON INFERIORITY TRIAL
IN GHANA
BY
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THIS THESIS IS SUBMITTED TO THE UNIVERSITY
OF GHANA, LEGON IN PARTIAL FULFILMENT OF
THE REQUIREMENT FOR THE AWARD OF PhD
EPIDEMIOLOGY AND DISEASE CONTROL DEGREE
MARCH 2015
DECLARATION

I hereby declare that with the exception of references cited to other people’s work which has been duly acknowledged, this work is a result of my own research work done under supervision and has neither in part or whole been presented elsewhere for another degree.

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DEDICATION

I dedicate this work to my dear brother Richard, my husband Mac and my children Koby, Aku and Allan and to my dear Bijou.
ACKNOWLEDGEMENT

I wish to express my sincere gratitude to my academic supervisors, Professor Fred Binka of the University of Health & Allied Sciences, Professor John Gyapong, Pro-Vice Chancellor of the University of Ghana, Dr. Priscillia Nortey of the University of Ghana School of Public Health. I also thank Dr Nsiire Agana former Program manager of the National Yaws Eradication Program, Ghana, Dr. Kingsley Asiedu Bampoe of the WHO, Geneva, and Professor Yaw Adu-Sarkodie, Dean, School of Medical Sciences, KNUST.

My sincere thanks also go to the WHO and the University Of Ghana School Of Public Health for their support of this study. I also express my sincere appreciation to Mrs. Esther Aryee, Mr Micheal Amakyi, Mr Roland Adukpo of the National Public Health Reference Laboratory Korle Bu, and Mr. Albert Dompreh of the Komfo Anokye Teaching Hospital Serology Laboratory.

I thank the DHMT members of the Awutu Senya, Ga South and West Akim districts, and all teachers and pupils involved in the study.

Finally special thanks to Mr Opoku Gyan, Mrs Mary Asamoah Bonsu, Mrs Stella Edith Tsar, Mrs Love Yaa Boadu, Mr Martin Oppong, Mr Nana Yaw Yeboa and Mr Johnston Amofah of the Ga West Municipal Health Administration office, and all the laboratory staff of the Ga West Municipal Hospital for their tremendous contributions to this study.
ABSTRACT

Background: Yaws is a treponemal infection that was almost eradicated fifty years ago has re-emerged in a number of countries including Ghana. Single dose intramuscular benzathine benzylpenicillin was the recommended treatment. However treatment by intramuscular injection poses several operational and logistical constraints in poor communities where yaws occurs. Results of a randomized clinical trial in Tanzania showed that azithromycin was effective against syphilis a venereal treponemal infection, however little is known about its effect on yaws. This study describes the epidemiological characteristics of yaws including its prevalence and risk factors, and compares the efficacy of a single dose oral azithromycin as an alternative to intramuscular benzathine benzylpenicillin for the treatment of yaws in three selected yaws endemic districts in Southern Ghana namely: Awutu Senya, Ga South and West Akim districts.

Methods: To describe the epidemiology of yaws we conducted a cross sectional survey that described the prevalence of the disease among various socio-demographic groups in the study area, and a case control study to determine various risk factors associated with the disease. In the clinical trial we set out to test the hypothesis that azithromycin was inferior to injection benzathine benzylpenicillin by 10% in the treatment of yaws. We conducted an open-label, randomized non-inferiority trial in the three selected yaws endemic districts. Children aged 1-15 with yaws lesions were assigned to receive either 30mg/kg of oral azithromycin or benzathine benzylpenicillin at a dosage of 0.6 million units for children below 10 years and 1.2 million units for those 10 years and above. The primary end point was clinical cure rate, defined as a complete or partial resolution of lesions 3 weeks after treatment. The secondary endpoint was serological cure, defined as at least a four-fold decline in baseline RPR titre 6 months after treatment. Non-inferiority of azithromycin was determined if the upper bound limit of a 2 sided 95% CI was less than 10%.

The trial was registered with Pan African Clinical Trials Registry number PACTR 2013030005181.

Results: The overall prevalence of yaws in the study area was 1.95%; however district prevalence ranged from 0.96% in the West Akim district to 2.77% in the Awutu Senya district. Yaws prevalence among female participants was 1.76% compared to 2.05% among male participants. Participants below 5 years had the lowest prevalence of 1.77%; the age
group with the highest prevalence of 2.02% was 11-15 years. Results of the univariate analysis showed several risk factors associated with yaws: Males were 1.8 times more likely to have yaws compared to females (OR: 1.8, CI: 1.0-3.2, p-value=0.032). Persons who do not bath daily were 3 times more likely to have yaws compared to those who bathed daily, (OR=3.0, CI: 1.0-5.4, p-value=0.000). The results also showed that persons living in a compound house were 1.8 times more likely to have the disease compared to those who lived in single houses (OR=1.8, CI: 1.0-3.4, p-value=0.048). Persons sleeping in a bedroom with more than 7 occupants were 4.4 times more likely to get yaws than those sleeping in a room with fewer people (OR= 4.4, CI: 1.4-16.8, p-value =0.004). However in the multivariate analysis the risk factors with significant association with yaws were living in a compound house (OR= 2.0, CI 1.0 – 3.8, p-value=0.047) and not bathing daily (OR= 2.4, CI: 1.3-4.4, p value=0.005).

The mean age of trial participants was 9.5 years (S.D.3.1, range 1-15 years), 247(70%) were males. The clinical cure rates were 98.2 % in the azithromycin group and 96.9 % in the penicillin group (risk difference:-1.3%,-4.7 to 2.0). The serological cure rates at 6 months were 57.4% in the azithromycin group and 49.1 % in the penicillin group (risk difference:-8.3%,-19.1 to 2.4), achieving the specified criteria for non-inferiority.

Conclusion: Yaws was shown to be still present in some rural communities in Ghana; risk factors are related to hygiene and overcrowding. A single oral dose of azithromycin, at a dosage of 30mg/kg, is non inferior to intramuscular benzathine benzylpenicillin for the treatment of early yaws hence the hypothesis of inferiority of azithromycin compared to penicillin is rejected. This finding is particularly useful in developing countries in removing the requirement for trained health personnel required to administer treatment by intramuscular injection during mass campaigns.
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LIST OF ABBREVIATIONS

AEs                      Adverse Events
AFR                      Africa Region
AIDS                    Acquired Immune Deficiency Syndrome
CDC                     Centers for Disease Control and Prevention
CHN                     Community Health Nurse
CHPS                   Community Based Health Planning and Services
CNS                     Central Nervous System
CSF                      Cerebro -Spinal Fluid
CHPS                   Community Based Health Planning and Services
DDCO                  District Disease Control Officer
DFM                   Dark Field Microscopy
DHMT                 District Health Management Team
DNA                   Deoxyribonucleic Acid
FTA-ABS            Flourescent Treponema Antibody Absorption tests
GHS                   Ghana Health Service
HIV                     Human Immunodefiency Virus
ICH                    International Conference on Harmonization
IgG                      Immunoglobulin G
IgM                     Immunoglobulin M
ITT                    Intention-to-treat
MFU                   Medical Field Unit
MIC                     Minimum Inhibitory Concentration
MOH                   Ministry of Health
NPHRL                National Public Health Reference Laboratory
NTDs                 Neglected Tropical Diseases
NYEP                  National Yaws Eradication Program
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>PAHO</td>
<td>Pan American Health Organisation</td>
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<tr>
<td>PAM</td>
<td>Procaine penicillin G in oil with 2% Aluminium Monostearate</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>PNG</td>
<td>Papua New Guinea</td>
</tr>
<tr>
<td>POC</td>
<td>Point –of-Care</td>
</tr>
<tr>
<td>PP</td>
<td>Per Protocol</td>
</tr>
<tr>
<td>RCH</td>
<td>Reproductive and Child Health</td>
</tr>
<tr>
<td>RPR</td>
<td>Rapid Plasma Reagin</td>
</tr>
<tr>
<td>SAEs</td>
<td>Severe Adverse Events</td>
</tr>
<tr>
<td>SEAR</td>
<td>South East Asia Region</td>
</tr>
<tr>
<td>SSI</td>
<td>Scientific Software International</td>
</tr>
<tr>
<td>STD</td>
<td>Sexually Transmitted Disease</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TPHA</td>
<td>Treponema Pallidum Haemagglutination Assay Test</td>
</tr>
<tr>
<td>TPPA</td>
<td>Treponema Pallidum Particle Agglutination</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
</tr>
<tr>
<td>VDRL</td>
<td>Venereal Disease Research Laboratory</td>
</tr>
<tr>
<td>WHA</td>
<td>World Health Assembly</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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<td>WPC</td>
<td>West Pacific Countries</td>
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CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

In 1949 the second World Health Assembly (WHA) passed resolution WHA 2.36 recognizing the public health importance of the endemic treponemal infections including yaws. The resolution eventually led to the World Health Organisation (WHO) and the United Nations Children’s Emergency Funds (UNICEF) global treponema campaign between 1952 and 1964. The goal of the campaign was to control and eventually eradicate the treponemal diseases in 46 endemic countries. The strategy for the campaign was to screen at least 90% of the target population and conduct periodic resurveys to treat missed, new and latent cases and contacts. Mobile treatment teams were involved in mass examination and treatment of entire populations of children in affected areas irrespective of their infection status. Three million people in 46 countries were examined and 50 million were treated (1).

Procaine penicillin G in oil with 2% aluminum monostearate (PAM) a long acting penicillin was the drug of choice for treatment in the campaign, the results were massive reduction by 95% in prevalence of treponemal diseases by 1964. The campaign went down in the annals of medicine as one of public health’s most successful stories (2, 3).

With the success of the campaign a vertical yaws control program which entailed continuous surveys and re surveys, treatment of cases and their contacts based on the WHO guideline for treatment, and the putting in place of strong surveillance systems to track cases and their contacts was put in place in yaws endemic countries. However the 1970s saw a change in
strategy from a vertical yaws program to a premature integration of yaws control activities including surveillance into already existing weak public health surveillance systems (4).

The integration led to the eroding of the gains of the successful campaign. The 1970s saw the re-emergence of yaws in areas in which the disease was almost eradicated, and led to the adoption of WHA resolution 31.58 in 1978. The resolution recognized the public health implication of the resurgence of yaws and the other endemic treponematoses, its devastating consequences on children and the danger of further extension and entrenchment of the disease. Affected member states were requested to update WHO on the current epidemiological situation on the treponematoses and formulate control programmes for interruption of transmission (5).

Resolution WHA 31.58 led to renewed control efforts in affected countries especially in West Africa; however these efforts failed because of poor financial capacities of affected countries and lack of political commitment in these countries who gave priority to other diseases such as malaria, TB and HIV/AIDS. Yaws became the most neglected of the Neglected Tropical Diseases (NTDs). Logistical and operational resources needed to control yaws which had almost been eradicated a decade earlier were not made available in endemic countries and when available were diverted for the management of more ‘important’ conditions (4). In 1995 the WHO estimated that there were 460,000 infectious cases of yaws throughout the world, with 400,000 in western and central Africa, 50,000 in Southeast Asia, and the remainder in other tropical areas (6).

In the context of a new global effort to prevent, control, eliminate or eradicate NTDs the WHO in 2007 launched a new global initiative to eliminate yaws and the other treponematoses with the aim of reaching a large section of the neglected and marginalized populations who are the people mostly affected (1).
1.2 Yaws Disease

Yaws is an endemic relapsing non-venereal treponemal infection which occurs in humans; it affects mainly the skin but can also affect the bones, joints and cartilages and may persist for many years as a chronic infection. If left untreated, yaws may lead to crippling and disfigurement (7). The disease is characterized by contagious primary and secondary skin lesions and non-contagious tertiary lesions that affect bones and cartilages. Yaws may become latent for several years although 10% of latent cases may reactivate and lead to deformities and disabilities. Transmission of yaws is from person to person through direct skin contact with infectious exudates from early skin lesions of infected individuals, the yaws treponemes are located in the epidermis of the skin and enters the body through breaks in the skin due to trauma, bites or excoriations (4). Fleas may be involved in transmission from clothing and dressing that have become contaminated by fluid from sores (8).

1.2.1 Clinical Stages of Yaws

The primary, secondary and tertiary stages of yaws are interspersed with asymptomatic latent periods. Hackett in 1957 also classified yaws into early and late yaws. Early yaws includes the primary and secondary stages of the disease and is characterized by the presence of contagious skin lesions. Late yaws includes the tertiary stage, when lesions are not contagious (9).

Primary yaws is made up of a single papule or a vesicle usually on the lower extremities of the body that enlarges to become a macule and later a papilloma; it may be accompanied with pain and swelling, lymphadenopathy, fever, and joint pains.

Secondary yaws lesion appears as a result of the treponemes entering the circulatory system and setting up in various parts of the body including skin, bone and joints. Secondary yaws may present as ulcers, papilloma, macules, papules, nodules, or hyperkeratotic lesions. The
type and number of lesions depend on climatic conditions; macules appear more in the dry season and are usually fewer in number, in the wet season more cases of ulcerative lesions occur. Secondary lesions may heal spontaneously and may reoccur 5 years after infection. The disease then enters a non-infectious latent stage during which patients do not show any signs and symptoms, the latent period may last a lifetime (9).

Tertiary yaws appears in about 5% of cases after 5-15 years of latency and involves the destruction of tissues which leads to permanent scars, contractures, and bone and cartilage deformities. Sabre tibia develops from chronic inflammation of the tibia bone, 1% of cases will develop bilateral hypertrophic osteitis of the external aspects of the nasal processes of the maxillae with persistent swelling known as goundou, this slowly progresses over 5-20 years and eventually lead to the destruction of the nose and palate known as gangosa (9, 10).

1.2.2 Prognosis of Yaws

Twenty four hours after treatment of yaws the lesion becomes noninfectious, joint pains if present disappears in 1-2 days, skin lesions will heal in 2-4 weeks. Yaws can become a chronic relapsing disease of the skin, bones and joints after 5-15 years if left untreated or is partially treated. Secondary bacterial infection of the yaws lesion can lead to scaring. Late yaws is characterized by irreversible destructive skin, bone and joint lesions with neurological and ophthalmologic involvement (11).

1.3 Epidemiology of Yaws

Yaws is caused by *Treponema pallidum* sub species *pertenue*, and is the most prevalent of the endemic treponematoses. Seventy five percent of people affected with yaws are children below 15 years with a peak incidence between 6-10 years old. Males and females are equally affected. High temperatures of above 27°C, heavy rainfall and high humidity favor the
survival of the treponemes in exudates and increases infectiousness and transmission of the
disease, however the bacteria does not thrive in cold climates or extreme temperatures (12).

Incidence of yaws lesions is higher in the rainy season than in the wet season, the highest
incidence of yaws in the tropics occurs in areas with an average rainfall above 1300mm per
year (13, 14). Yaws is often endemic in areas with low standard of living, where there is
overcrowding and where there is lack of proper sanitation and facilities for personal hygiene
(12). Studies by Saunders showed that yaws incidence increases as sanitary conditions in the
home decreases (15). Currently yaws is reported in Africa, Asia and in the South Pacific
region and 12 countries are known to harbor yaws. WHO estimates that 21-40 million people
live in yaws endemic areas, more than 300,000 new cases of yaws were reported to the
WHO from 2008 to 2012 (11).

1.4 Yaws in Ghana

Yaws is a common disease in rural communities of Ghana, and has been endemic in the
country for generations. The disease is among the first diseases to be identified and treated
with conventional Western treatment in the Gold Coast (present day Ghana) (16). In Ghana
yaws is an important Public Health problem, routine data over the years have indicated that
yaws is reported in all the 10 regions of Ghana and nearly all the districts in the country, the
severity of the disease varies from region to region depending on sanitation and
overcrowding conditions (17). Yaws turns to be more prevalent in the humid forest region of
southern Ghana compared to the northern savannah zone. Prevalence studies in three
purposively selected districts in southern Ghana in 2008 showed a prevalence of 1.92%
among children in basic schools (18). The disease is found mainly among people in deprived
rural communities.
1.5 Treatment of Yaws

The treatment of yaws involves treatment of persons with the disease and their contacts namely; schools, households or whole communities. The recommended dosage for the standard treatment injection benzathine benzylpenicillin is 1.2 million units for adults and 0.6 million units for children below 10 years (19). Studies have shown that penicillin levels of over 0.03 units per 1 ml of serum maintained over 7 days are treponemacidal (20). These high levels of penicillin in serum could be achieved by repeated doses of short acting penicillin or a single intramuscular injection of repository penicillin preparations such as benzathine benzylpenicillin or penicillin in aluminum monostearate (21).

The advantages of treatment by injection penicillin are its low cost, the absence of any problem with adherence over an extended treatment course, and the apparent absence of resistance despite extensive use (22). However there are several challenges associated with the use of penicillin injection namely: Penicillin allergy, pain and infection associated with injection use, the risk of blood borne infections if sterile protocols are not followed and the unavailability of refrigeration needed to store benzathine benzylpenicillin in poor resourced areas where yaws is found (23). Treatment by injection penicillin also poses constraints in mass treatment campaigns, in particular the need for trained staff and more complex logistics to deliver the treatment.

The use of oral penicillin V in multiple doses over 10 days have been documented in treatment of whole communities with yaws (24). In patients with penicillin allergy tetracycline, doxycycline and erythromycin given over a period of 15 days are likely to be effective against yaws, however this is based on clinical efficacy in a few patients and not in clinical trials (25-27). The disadvantages of these oral treatments is that they are given over several days in multiple doses and adherence to a multi-day treatment regimen poses a problem of compliance and are not practical in mass yaws eradication campaigns.
Tetracycline is contraindicated in children below 8 years due to its association with dental staining and interference with bone growth (28).

1.5.1 Current Treatment of Yaws in Ghana

Treatment of yaws in Ghana involves the treatment of cases and their contacts with injection benzathine benzylpenicillin. The extent of contact treatment is based on the level of endemicity. In hyper endemic areas (prevalence of active yaws cases >10%) the entire population is treated (Total Mass Treatment). In meso endemic areas (prevalence of active yaws cases of 5-10%) all children and obvious contacts are treated (Juvenile Mass Treatment). In hypo endemic areas (prevalence is <5%) treatment is given to persons with active case, their households, contacts and other obvious contacts (Selective Mass Treatment).

Yaws treatment in Ghana faces several challenges including frequent shortage of injection penicillin or logistics that accompany its use (needles, syringes, water for injection, cotton swabs etc.) and inadequate numbers of trained health staff needed to administer treatment by injection especially in remote areas where yaws occurs.

Azithromycin is a macrolide antibiotic with a long tissue half-life, it has previously been shown to be an effective agent in the treatment of venereal syphilis a treponemal infection. In Ghana oral azithromycin has been used to treat HIV/AIDS patients with syphilis. Azithromycin is also the cornerstone of the strategy for the elimination of blinding trachoma (29) and the drug has been distributed by community health volunteers during mass drug administration for the treatment and prevention of trachoma in the Upper West region of Ghana. The conclusion of a clinical trial among commercial sex workers in Tanzania involving the use of a single oral dose of azithromycin in the treatment of syphilis was that the drug can be as effective as injection penicillin in the prevention and treatment of syphilis.
Azithromycin offers a number of advantages as an agent in the treatment of yaws, including oral route of administration, excellent safety profile and negligible risk of anaphylaxis. As such the drug is well suited for use in community mass treatment programmes for yaws eradication. However the efficiency of the drug in the treatment of yaws has not been explored in Ghana.

1.6 Rationale and Justification of Study

1.6.1 Problem Statement

Although the mass treponemal campaigns in the 1950s and 1960s led to a massive reduction of yaws prevalence worldwide, the disease has reemerged in countries where it was almost eradicated including Ghana. Routine data in Ghana shows a significant increase in notified cases of yaws since 1970. From 2009 to 2013, between 8000 and 36,000 cases of clinical yaws were reported annually in Ghana. However the current epidemiological characteristics of the disease including the prevalence among the various socio demographic groups and risk factors associated with the disease are not well documented in the country.

For the goal of eradication of yaws to be achieved there is the need to explore the use of an accessible and acceptable treatment that will facilitate interruption of transmission. Injection benzathine benzylpenicillin the standard treatment for yaws poses several challenges that limit its access and acceptability. These challenges include improper sterilization of injection equipments in poor areas where yaws occurs that puts persons with yaws at risk of blood borne infections like HIV/ AIDS and hepatitis, unavailability of refrigeration needed for the storage of penicillin in poor areas where yaws occurs, and penicillin allergy in certain settings. Yaws affects mainly children below 15 years; however treatment by injection poses a problem of acceptability among children due to their aversion parenteral treatment.
Treatment of yaws involves treatment of cases and their contacts, this often involves the treatment of whole communities, however areas where yaws occurs often lack adequate numbers of trained health personnel needed to administer treatment by injection during mass campaigns in often remote rural communities.

1.6.2 Justification

The challenges associated with the use of injection benzathine penicillin, the current treatment for yaws have resulted in the need to explore an alternate treatment with a single dose oral antibiotic such as azithromycin that avoids the complications posed by the standard treatment. Several studies have shown that a single dose of oral azithromycin is effective against several infections including syphilis, a treponemal infection. The drug has also been successfully used in mass drug treatment campaigns in areas with ocular infection with Chlamydia trachomatis (30). However there is little information on its effectiveness in the treatment of yaws. Azithromycin has a good safety profile and side effects include mild gastrointestinal upset, nausea and vomiting, although in large clinical trials few side effects have been reported (31, 32). If Azithromycin were shown to be effective in the treatment of yaws, its replacement as the standard treatment would be beneficial for a number of reasons: There would be no need for trained health workers to administer treatment as the drug can be administered by community volunteers, this would mean reduced cost for eradication efforts compared with the complications of treatment by injection. Reduced side effect would also improve community acceptability of this treatment.

Knowledge on yaws prevalence and risk factors will enable policymakers target the appropriate groups in resources allocation for disease management and prevention, and enable the formulation of health messages that will educate the public on yaws disease prevention.
1.7 Research Questions

1. What is the prevalence of yaws in the Awutu Senya, Ga South and West Akim Districts?

2. What are the risk factors for yaws in the Awutu Senya, Ga South and West Akim Districts?

3. Will a single dose oral azithromycin be as effective as a single dose intramuscular injection of benzathine benzylpenicillin in the treatment of yaws?

1.8 Objectives

1.8.1 General Objective

To describe the epidemiological characteristics of yaws in the study area, and determine whether a single oral dose of azithromycin can be as effective as the current WHO recommended treatment of single intramuscular injection of benzathine benzylpenicillin in the treatment of yaws.

1.8.1 Specific Objectives

1. To describe the prevalence of yaws among children 1-15 years in the Awutu Senya, Ga South and West Akim districts.

2. To describe risk factors associated with yaws among children 1-15 years in the Awutu Senya, Ga South and West Akim districts.

3. To compare clinical cure rates between subjects treated with a single dose of oral azithromycin and those treated with a single injection of benzathine benzylpenicillin.

4. To compare serological cure rates between subjects treated with a single dose of oral azithromycin and those treated with a single injection of benzathine benzylpenicillin.

5. To compare clinical cure rates based on age, sex, clinical stage, baseline RPR titre and household exposure to yaws between subjects treated with a single dose of azithromycin and those treated with a single injection of benzathine benzylpenicillin.
1.9 Hypotheses

The null hypotheses tested in this study were:

1. There is no difference in the characteristics of people who contract yaws and those who do not.

2. Clinical cure rate, (defined as total or partial resolution of primary and secondary yaws skin lesion 3 weeks after treatment) in subjects treated with a single dose of oral azithromycin is inferior to clinical cure rates in subjects treated with a single injection of benzathine benzylpenicillin by more than 10%.
CHAPTER TWO

2.0 REVIEW OF LITERATURE

2.1 History and Origin of Yaws

Yaws is the most prevalent of the endemic treponematoses and is caused by *Treponema pallidum* subspecies *pertenue*, the other endemic treponematoses are bejel caused by *T. pallidum* subspecies *endemicum* and pinta caused by *T. pallidum* subspecies *carateum*. These organisms are similar to *Treponema pallidum* subspecies *pallidum* the organism that causes syphilis. Yaws is known as Pian in French, Fraemboesis in German, Buba in Spanish and Parangi in Malay (33).

The name yaws could have originated from the Carib word for sore ‘yaya’ or the African word for berry ‘yaw’. The Dutch physician Willem Piso provided one of the earliest recorded clinical descriptions of yaws in South America in the 17th century. The disease was given the name framboesia tropica because of the resemblance of the cutaneous yaws lesion to raspberries known in Dutch as framboos (34). Yaws was also described as a disease among African slaves by Thomas Sydenham in 1679 and at the time was thought to be the same disease as syphilis (35). In 1905 Castellani discovered the presence of spirochetes in the lesions of patients suffering from yaws in Ceylon (36).

Yaws is theorized to have appeared in humans around 10,000 BC in the Afro-Asian landmass as a mutant of pinta. Hackett on the origins of the treponematoses suggests that the four treponemas have a common pathogenic ancestor in animals (37). Studies by Hudson in 1963 also suggest a unitary theory in which the four clinical forms of *Treponema. pallidum* existing today are one disease with different epidemiological patterns due to changing environmental conditions (38).
2.2 Causative Organism of Yaws

*Treponema pallidum* subspecies *pertenue* is a gram negative motile spirochete that belongs to the order spirochaetales, family treponemataceae and genus treponema (39). *Treponema pallidum* subspecies *pertenue* is morphologically and serologically indistinguishable from the organisms that cause the other endemic treponematoses and syphilis (40). Differentiation of the subspecies of *T. pallidum* is by their clinical manifestations and mode of transmission, although recent studies have discovered an antigenic difference between subspecies *pertenue* and subspecies *pallidum* due to a single amino acid residue at position 40 in the proteins namely: glutamine in TpF1 in subspecies *pallidum* and arginine in TyF1 in subspecies *pertenue* (41).

2.2.1 Structure of *Treponema pallidum*

![Structure of Treponema pallidum](image)

*Figure 1: Structure of Treponema pallidum*

*Treponema pallidum* is not visible under the light microscope but is visible under dark field illumination. The organism is a slender, unicellular, tightly coiled helical spiral shaped organism (figure 1.), 10-15µm in length and 0.2µm in diameter (42). The organism is made up of an outer membrane and a cytoplasmic membrane. The periplasmic space is made up
of flagyl-like filaments known as endoflagyls that have a coiled motility due to their expansion from both ends towards the middle of the organism (43, 44). The organism’s ability to swim in gel-like medium like connective tissues gives yaws its chronic and infectious nature (45). T. pallidum contains at least 8 major membranes associated lipoproteins whose function is unknown but appears to be linked to the cytoplasmic membrane (44). The outer membrane particles are uniformly sized and sparsely distributed indicating that the difference in protein in the outer membrane is few. This low concentration of surface exposed antigen leads to a reduced immune response by reducing antibody and immune cells reactivity, this is also the cause of its pathogenesis (44). Treponema pallidum cannot be grown in vitro and does not survive outside the mammalian host, hence the transmission from man to man (46).

2.2.2 Genome

Treponema pallidum subspecies pertenue was sequenced and compared to subspecies pallidum by Milkalova in 2010, the genome size for both subspecies is about 1139 kilobases and both had identical structures. The close relationship between the 2 subspecies was demonstrated by a 99.8% sequence identity (47). The study hypothesized though it was not proven that the difference in pathogenicity in humans between the two pathogens could be due to differences localized in 6 genetic regions (48). These include a one base pair difference in the regions of the tpp15 gene encoding lipoproteins (49), a base pair deletion in the tp92 gene encoding surface proteins (50), one nucleotide substitution in the gpd gene encoding hydrolase enzyme, variation in alleles in members of the tpr gene family encoding outer membrane protein, sequence variation in the arp gene, and sequence variation in intergenic spacer IGR19 (41, 50, 51).
2.3 Histopathogenesis

*T. pallidum* subspecies *pertenue* has the tendency to affect the upper layers of the skin, but unlike subspecies *pallidum* there is very little evidence of it affecting the cardiovascular and central nervous systems (52). The spirochettes enter the human body through breaks on the skin and attach to the extracellular matrix of the host cells in the upper region of the epidermis, they then enter the lymph nodes and disseminate within hours (43, 53, 54). Early yaws lesions are made up of epidermal hyperplasia and papillomatosis with focal spongiosis and intradermal collection of neutrophils. The infiltration of the epidermis with neutrophils and the dermal perivascular infiltrates of plasma cells lead to the formation of epidermal micro abscesses. Skin biopsies from infected patients show many plasma cells and few T and B cells (52, 55).

2.4 Transmission of Yaws

Transmission of yaws is by direct skin to skin contact with infectious lesions through a cut, scratch, bite, trauma and excoriations, these lesions act as entry for the treponemes. Overcrowding, lack of protective clothing and humid conditions favor transmission of yaws (34). Although not proved in humans, studies have shown that flies have produced infection in experimental animals after being fed with scrapings from yaws lesions (56). Studies have shown the evidence of infection with *T. pallidum* subspecies *pertenue* in wild gorilla populations in the Democratic Republic of Congo (57). Friedmann-Blanc also describes a reservoir of yaws-like treponemes in West African baboons in the early 1960s (58). However the significance of these reservoir to man is uncertain although studies have shown that after experimental inoculation with simian isolates human beings have shown yaws like lesions (34, 59). A recent study by Knauf revealed *T. pallidum* antibodies in Guinea baboons, there is however no evidence of cross transmission between humans and infected primates or from mother to fetus (60).
2.5 Immune Response of *Treponema Pallidum* Subspecies *Pertenue*

Clinical manifestations of yaws results from the immune response from the host to the treponemes. Immune response is both humoral and cellular. Studies of the immune response of *T. pallidum* using the Western blot and Immunoprecipitation techniques have shown that antibody response in yaws is similar to that of syphilis and pinta. IgM and IgG are present during active primary and secondary infection, however IgM decreases during the latter part of the disease and after treatment (61, 62). The immune response is the basis for treponemal serological tests in which host antibodies bind with antigens.

2.6 Classification of Yaws

Yaws is classified in 4 stages namely primary, secondary, tertiary and latent stages.

2.6.1 Primary Yaws

The primary stage involves the initial yaws lesion which develops at the site of entry of the treponeme through a scratch or bite and is often found on the buttocks or lower extremities (63). The lesion is known as ‘mother yaws’ and initially appears as a papule that later crusts and ulcerate or become a papillomata (9). The mother yaws may last for weeks or months and may persist into the secondary stage of the disease although on some rare occasions the primary lesion is not identified. The primary lesion may undergo condillomatous changes and regress into depigmented scars with dark margins. During the primary stage there is regional lymphadenopathy, fever and arthralgia (14, 64).

2.6.2 Secondary Yaws

In weeks or months after the primary yaws, secondary yaws lesions results from widespread dissemination and is associated to more morbidity. The lesions resembles the primary lesion but are more in number and bigger in size (34). The lesions diffuse and often ulcerate and
secret infectious treponemes, secondary yaws lesions occur more around orifices like nose and mouth, the lesions may take different forms (14).

2.6.3 Tertiary Yaws
Approximately 5-10 years after inoculation 10% of cases will go on to develop tertiary yaws, which involves deformities of skin, bones and cartilages. Skin lesions in tertiary yaws are made up of subcutaneous gumatous nodules which suppurate and break out into ulcers with necrosis of tissue followed by debilitating scaring and contractures (64).

Bone and cartilage changes are gangosa which is a rhinopharyntis obliterans, destructive osteitis that results in saddle nose and the bowing of the tibia known as sabre tibia. Hypertrophic periostitis leads to exostosis of paranasal maxilla known as gondou (65-67).

Although it is generally known that the central nervous system (CNS) and viscera are not affected in tertiary yaws recent studies isolated treponemes in aqueous humor and cerebrospinal fluid, these abnormalities were in 24.0% of 902 patients with yaws indicating CNS involvement (68).

2.6.4 Early and Late Yaws
In the International Nomenclature of Yaws Lesions, yaws is classified as an early yaws stage comprising the primary and secondary stages during which skin lesions are contagious and a late yaws stage made up of the tertiary stage (9).

2.6.4.1 Early Yaws
This stage is made up of the primary and secondary stages, the initial yaws lesion after an incubation of 9-90 days appears as a pruritic lesions that later develops into crusted ulcers or papilomatas (69). The initial lesion may disappear and during this period relapses or disseminated lesions known as daughter yaws may appear, this period may be accompanied
by general malaise, fever and generalized lymphadenopathy. Early yaws may also present in the form of macules, papules and nodules. Crab yaws is the manifestation of early yaws in the form of hyperkeratosis of palms or soles. Bony manifestation of early yaws is in the form of osteitis and periostitis (10). Early yaws lesions are subject to climatic conditions, in the dry season lesions are atypical and scanty, whilst in the warm rainy season lesions are florid and abundant (34).

2.6.4.2 Late Yaws

Late yaws involves irreversible destruction of the bones, cartilages, soft tissue and the skin. The lesions of late yaws are gangosa, sabre tibia, gumatta, contractures, and gondou. Although late yaws does not exist with early yaws reports from some studies suggests that gangosa and gondou can occur early in yaws infection and be stopped with appropriate treatment or progress to permanent deformities (70).

2.6.5 Attenuated yaws

Several studies have suggested that the varying syndromes of endemic treponematoses depend on the frequency of the infection in a certain community (71). Attenuated yaws is the milder forms of yaws that occurs in areas with low endemicity, because of the influence of climate, or after a mass campaign in a highly endemic area. It is characterized by scanty or small papillomas of a few days’ duration and long periods of latency and low reagin levels. Attenuated yaws is of public health significance because of the potential to revert to classic yaws with high rates of transmission (71). In a survey that described the presence of attenuated yaws amongst children examined clinically and serologically for yaws in Northern Surinam, of the 969 children examined 212 (22%) had reactive VDRL test. Of these 29 (13.6%) had clinical yaws lesions of either solitary papilloma or macular lesions consistent with the classic picture of attenuated yaws (72).
2.6.6 Latent Yaws

The clinical skin manifestation of early yaws subsides after a period and is followed by a latent period of varied duration; this period is usually interrupted by one or more episodes of relapse. Diagnosis during this period is by positive serology test, latency lasts for a lifetime in majority of cases but 10% of cases will after 5-10 or more years proceed to a destructive late yaws stage (34).

2. 7 Clinical Manifestations of Yaws

![Figure 2: Papillomatous Lesion](image1.png)  ![Figure 3: Ulcerative Lesion](image2.png)

**2.7.1 Papillomas**

Appear as firm, painless skin lesions 1-3cm in diameter which are yellowish in color with dark tips, (Figure 2.) there may be inflammation of adjoining skin, secondary bacterial infection accentuates inflammation.

**2.7.2 Ulcers**

Yaws ulcers are characterized by raised edges with dirty and crusty bases but may be also be soggy and filled with treponema containing exudates (Figure 3).
2.7.3 Papules

Papules are firm discrete painless lesions described as small raised bumps the size of rice grains; they are smaller than papilomas (Figure 4).

2.7.4 Macules

Macular lesions are described as patchy erythematous rash on any part of the body that may be mixed with other yaws lesions (Figure 5).

2.7.5 Plantar and Palmer Hyperkeratosis

Plantar yaws are painful lesions that appear as cracks or fissures, erosions, pitting or hyperkeratotic thickenings on the soles and palms, the palmar lesions are less painful and appear as yellowish hyperkeratosis (Figure 6 & 7).
2.7.6 Sabre Tibia

Late yaws can present as swelling of the bones and joints, sabre tibia is the bowing of the tibia bone with or without ulcerated lesions on the shin (Figures 8 & 9).

2.7.7 Polycactilitis

Polycactilitis is swelling and tenderness that affects mostly the bones and joints of the forearm and wrists (Figure 10) and can also involve multiple fingers and joints in the legs.

2.7.8 Gondou and Gangosa

Late yaws can affect the bones of the face and the nose, gangosa is a deformity of the nose caused by yaws (Figure 11) and gondou is caused by the enlargement of facial bones.
2. 8 Laboratory Diagnosis of Yaws

*Treponema pallidum* is a fragile spirochete and cannot be cultured in a clinical laboratory setting; diagnosis is by direct observation of the organism and indirect evidence of the infection. Direct diagnostic methods are limited by the fact that treponemes cannot be cultured on synthetic media. The rabbit infectivity test (RIT) is the gold standard for demonstrating *T. pallidum* infection; it is impractical for clinical use because of high costs and delayed test results (73). Direct fluorescent antibody tests using anti *T. pallidum* antibodies can distinguish pathogenic treponemal infections from saprophyte treponemes (74, 75). Other tests are Dark Field Microscopy (DFM) tests, histopathological examination of skin lesions and molecular assay that detects *T. pallidum* DNA. Indirect evidence of infection involves serological testing of blood to demonstrate host antibody to either endogenous antigens (non-specific tests) or to antigen of T.pallidum (specific test).

### 2.8.1 Dark Field Microscopy

In Dark Field Microscopy (DFM) live treponemes obtained from exudates of yaws lesions can be visualized using indirect light. In the test, exudate from lesion is transferred to a glass slide which is examined under the microscope. *T. pallidum* spirochetes are observed by their characteristic morphology and motility. DFM of exudates can reveal the presence of treponemes from early stage skin lesions however this test has a limited sensitivity and requires skill for specimen collection and microscopy (52).

### 2.8.2 Polymerase Chain Reaction (PCR)

PCR is a technique in molecular genetics that permits the analysis of any short sequence of DNA (or RNA) in samples containing only minute quantities of DNA or RNA. PCR is used to reproduce (amplify) selected sections of DNA or RNA for analysis. In the last two decades there has been an increasing effort to apply PCR techniques for direct diagnosis of
treponematoses (73), the test detects treponemal DNA using a direct method with detection thresholds as low as a few copies of the treponemal chromosome per PCR reaction (73).

Although genetic signatures of *T. pallidum pertenue* have been identified (76), DNA sequencing to confirm yaws in a patient with active skin lesions has been described only once in a 10-year-old boy from Democratic Republic of the Congo (77). Real-time PCR is useful to identify *T. pallidum pertenue*, and would be a good test to differentiate between the *T. pallidum* subspecies in one assay. However, such methods are expensive, and are unlikely to be available outside reference laboratories.

### 2.8.3 Serological Tests for Yaws

Serological tests used for syphilis is the same as those used for the endemic treponematoses including yaws, and cannot distinguish yaws from the other treponematosis (78). These tests rely on testing for the presence of treponema and non treponema antibodies. The tests consist of non-specific treponema tests and a confirmatory test by a more specific treponema test.

The non-specific agglutination tests are Rapid Plasma Reagin (RPR) and Venereal Disease Laboratory (VDRL) tests, both tests are positive in untreated cases.

The treponema specific tests are *Treponema Pallidum Hemaglutination Assay* (TPHA) test, *Treponema Pallidum Particle Agglutination Assay* (TPPA) test, *Flourescent Treponemal Antibody Absortion Tests* (FTA-ABS tests) and *Treponema Pallidum Immobilisation* (TPI) test, these tests remain positive for life (79).

These serology tests are not practical for community screening as they require trained personnel to conduct and interpret results. Equipment such as refrigerators, centrifuges for serum separation and electric rotators for flocculation tests are usually not available in poor urban settings where yaws occurs.
2.8.3.1 Rapid Plasma Reagin Test

The RPR antigen is a modified form of the VDRL antigen, which contains delicately divided carbon particles that enables the flocculation that occurs when reagins come in contact with antibodies to be seen with the naked eyes. RPR test measures non-specific IgM and IgG antibodies to lipoidal material released from damaged host cells (80) and lipoprotein-like material and cardiolipins released by treponemes. These can also be released in response to chronic or acute non treponemal diseases in which tissue damage occurs (7). The test can be done in both qualitative and quantitative evaluations and can give false positive results in viral infection, malaria, pregnancy, and the elderly and in autoimmune diseases.

The RPR test is also able to detect asymptomatic cases of treponema infections, positive RPR test requires confirmation with specific treponema tests because of the possibility of a false positive results (81). The RPR test reverses to sero negativity within 3-6 months of treatment and is used to measure success of drug treatment.

In studies to evaluate the VDRL and RPR non treponemal tests in patients with syphilis, the specificity and sensitivity of the 2 tests were similar, the study concluded that RPR could be an alternative to VDRL in the diagnosis of neuro syphilis (82).

2.8.3.2 Treponema Pallidum Haemagglutination Assay Test

The specific treponema tests do not distinguish between syphilis and the other treponema infections and could give false positive results in communities with high prevalence of syphilis (83). Persons infected with any of the treponemes remain positive for these specific tests for life. The TPHA test is the main treponemal test used in treponemal infection, and has a high specificity. The test involves indirect haemagglutination that detects and titrates specific antigen to treponema pallidum. In the test sensitized avian erythrocytes coated with cell surface antigens is mixed with serum of patient, if serum contains T. pallidum antibodies
there is binding with antigens on erythrocytes, which leads to agglutination. There is no agglutination if serum does not contain *T. pallidum* antibodies. TPHA is performed both qualitatively and quantitatively and its main use is often for screening and confirmation of treponemal infections. Although not used often in monitoring treatment outcome, a 4 fold increase in titre indicates re infection.

2.8.3.3 Treponema Pallidum Particle Agglutination Test

In the TPPA test patients serum is mixed with gelatin particles sensitized with *T. Pallidum* antigens, the particles aggregate and form clumps if there are Treponema antibodies in the host serum.

2.8.3.4 Rapid Point- of –Care Treponemal Tests

A combined point-of-care (POC) test, which detects both treponemal and non-treponemal antibodies, has recently been evaluated for the diagnosis of syphilis, and appears promising for yaws diagnosis. The use of the dual POC test would result in the ability to both screen and confirm the serological status of patients with suspected yaws within 15 minutes and give a better indication of active disease. The POC test involves the use of immunochromatographic strips on whole blood. The test can be used in screening and is conducive for use in resource limited settings where yaws often occur. Studies have shown that these Rapid POC treponema tests reported sensitivity and specificity estimates that were comparable to laboratory based treponema tests (84). These tests are not able to distinguish between treated cases and active cases of yaws and may lead to re- treatment of already treated cases that may ultimately lead to the development of resistance strains.

The limitation of these serology tests are that they cannot distinguish between an infection with the endemic treponematoses and a syphilitic infection (83), also during the first 1-3 weeks of infection treponema antibodies are not detectible in serum (85).
2.9 Epidemiology

The causative organism of yaws, *T. pallidum* subspecies *pertenue* is similar to *T. pallidum* subspecies *pallidum* the organism that causes syphilis although *T. pertenue* is less virulent (86). Yaws disease is found in areas characterized by hot temperatures, high humidity and heavy rainfall. Incidence of yaws is higher in the rainy season than in the dry season, the highest incidence occurs where the average rainfall is above 1300mm per year (8). Yaws occurs in clusters and its prevalence varies between communities. Prevalence studies in some villages in the Democratic Republic of Congo using the Lots Quality Assurance sampling method showed that whilst the overall prevalence was 4.7%, some Lots had a high prevalence of over 10%. (7).

2.9.1 Global Burden and Incidence of Yaws

The WHO/UNICEF campaign resulted in a 95% reduction of cases however the gains were not sustained and the result is the re-emergence of yaws in areas that saw remarkable reduction of cases after the 1950s campaign (4, 87).

In 1995, the WHO estimated that there were 460,000 infectious cases of yaws throughout the world, with 400,000 in western and central Africa, 50,000 in Southeast Asia, and the remainder in other tropical areas (7, 88). Due to a strong surveillance and treatment of whole communities, India has not reported new cases of yaws since 2004. Papua New Guinea, Solomon Islands and Vanuatu remain endemic in the Pacific region.

The current global burden is not fully known, as reporting of yaws is not mandatory in most endemic countries. Recent information and data on yaws from 2008-2011 from routine surveillance is shown in Table 1, Ghana, Papua New Guinea and Vanuatu reported the highest number of cases of yaws between the period (89).
### Table 1: Reported Cases of Yaws 2008-2011

**African Region (AFR)**

<table>
<thead>
<tr>
<th>Country</th>
<th>Year of Reporting</th>
<th>No. of Reported Yaws Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRC</td>
<td>2011</td>
<td>167</td>
</tr>
<tr>
<td>Ghana</td>
<td>2010</td>
<td>20525</td>
</tr>
<tr>
<td>Togo</td>
<td>2010</td>
<td>15</td>
</tr>
<tr>
<td>Democratic Republic of Congo</td>
<td>2009</td>
<td>387</td>
</tr>
<tr>
<td>CAR</td>
<td>2008</td>
<td>243</td>
</tr>
<tr>
<td>Cameroon</td>
<td>2010</td>
<td>789</td>
</tr>
<tr>
<td>Benin</td>
<td>2010</td>
<td>Data Not Available</td>
</tr>
</tbody>
</table>

**South-East Asia Region (SEAR)**

<table>
<thead>
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<th>Country</th>
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<th>No. of Reported Yaws Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
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<td>0</td>
</tr>
<tr>
<td>Indonesia</td>
<td>2011</td>
<td>5319</td>
</tr>
<tr>
<td>Timor-Leste</td>
<td></td>
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</table>

**Western Pacific Region (WPR)**

<table>
<thead>
<tr>
<th>Country</th>
<th>Year of Reporting</th>
<th>No. of Reported Yaws Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papua New Guinea</td>
<td>2011</td>
<td>34628</td>
</tr>
<tr>
<td>Solomon Islands</td>
<td>2010</td>
<td>20635</td>
</tr>
<tr>
<td>Vanuatu</td>
<td>2010</td>
<td>1574</td>
</tr>
</tbody>
</table>

Data Source: WHO 2012

Some authors have suggested that after the mass campaign in the 1950s a low level of transmission had persisted. Currently the main reservoir of yaws can be found throughout Africa (90).
2.9.2 Global Distribution of Yaws

In Ghana, Togo, and the Central African Republic the incidence of yaws is on the increase, with the current situation resembling the pre campaign era. Increasing number of cases have also been reported in the Ivory Coast, Nigeria and Mali (91). In South America, Surinam, Guyana, Haiti, Brazil and Venezuela have reported sporadic cases of yaws (92). The South East Asia region and Oceania have also reported dispersed foci of infection in Papua New Guinea, Indonesia, Solomon islands and Vanuatu(93-95).

2.9.3 Age Distribution

The age groups most affected by yaws are children below 15 years old; the peak incidence is between 6-10 years. Several studies have demonstrated a higher prevalence of yaws among children aged below 15 years. The earliest studies on yaws among children was by Thorpe in 1898 that observed skin lesions among children in the South Pacific islands and described
lesions as being identical to African yaws (96). A survey in the Central African Republic in 1987 observed a 15% prevalence of serologically confirmed yaws among pigmy children (97), another survey carried out in the Democratic Republic of Congo to estimate the village-level prevalence of yaws in the Equator region showed that of the 383 persons with cutaneous lesions clinically suggestive of yaws, 37.6% were children less than 15 years (7). The overall prevalence of confirmed yaws in this study was 4.7% but when separated in age groups the overall prevalence of confirmed yaws among persons less than 15 years was 6.1% (7). A survey in the Santiago basin area in Ecuador in 1988 showed a yaws prevalence rate of 11.3% with half of the cases being children (63).

In studies conducted in Papua New Guinea between 2000 and 2001 the number of reported yaws cases were 494, with a median affected age of 9 years (98). Another study on Karkar island in PNG which looked at Penicillin injection for the treatment of yaws showed that out of 632 children examined 39 (6%) were found with active yaws (21).

In a survey consisting of history taking, physical examination and VDRL and TPHA serology tests undertaken in a village and schools with an outbreak of yaws in Southern Thailand in 1990, half of cases (53.7%) were children younger than 15 years, the survey in 105 primary schools students found an attack rate of 32% and a higher prevalence in the lower classes (99).

### 2.9.4 Sex Distribution

Prevalence of yaws is described as equal between males and females. Some authors have described a higher prevalence in males. A survey on yaws in Thailand found a male to female ratio of 1.5:1 (99). The dominance of yaws among males can be explained by the fact that after 2 years of age boys are more active and are more susceptible to trauma than girls. Also at school going age girls are better clothed than boys and clothing protects skin from
trauma therefore reducing the incidence of yaws among females (12, 100). Another reason for the higher prevalence among males could be due to the fact that male children tend to sleep in rooms with many occupants leading to more body contacts.

2.9.5 Risk Factors Associated with Yaws

Risk factors are factors that do not directly cause a disease condition but are associated to the disease, although these factors increase the chances of getting the disease, they do not always lead to the disease. Yaws is known to affect populations living in the tropics; warm humid and moist climates are favorable conditions that enable the disease to spread. There is a higher incidence of the disease where there is rainfall of over 1300mm per year. The disease does not thrive in areas with extreme temperatures. Saunders notes a striking difference in the clinical yaws lesion during the wet and the dry seasons. Infectious yaws namely ulcers and papillomas are common in the rainy season whilst dry maculopapular lesions are common in the dry season (12).

The age group most at risk of yaws are children aged 2-15 years who are also considered as a reservoir for the disease, the peak age of infection is 6-10 years (70). The disease is not transmitted congenitally from an affected mother to an unborn child (101). Although both males and females are equally affected some authors have described a higher prevalence among males (99). Yaws is usually seen clustered in households but there can also be transmission within communities, schools and public places (102). The disease occurs in rural communities amongst people with poor hygiene and lack of clothing, overcrowding and poor access to health care have been documented as contributing factors to the spread of yaws (14). These conditions together with poor water supply, lack of sanitation and good hygiene practices and poor public health surveillance allows yaws to thrive in these areas (103).
2.9.6 Reported Cases of Yaws in Ghana

Since the WHO assisted campaigns in the 1960s no nationwide active surveillance has been carried out in Ghana, data from health facilities shows gross under reporting of yaws cases.

Routine data over the years have indicated that yaws is reported in all the 10 regions of Ghana.

Table: 2. Yaws Case Notification Rate Per 100,000 Population in Ghana 2002-2008

<table>
<thead>
<tr>
<th>Region</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western</td>
<td>157</td>
<td>293</td>
<td>581</td>
<td>224</td>
<td>153</td>
<td>153</td>
<td>136</td>
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<tr>
<td>Central</td>
<td>628</td>
<td>501</td>
<td>665</td>
<td>172</td>
<td>211</td>
<td>194</td>
<td>145</td>
</tr>
<tr>
<td>GAR</td>
<td>-</td>
<td>12</td>
<td>169</td>
<td>13</td>
<td>7</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Eastern</td>
<td>931</td>
<td>516</td>
<td>393</td>
<td>141</td>
<td>228</td>
<td>415</td>
<td>610</td>
</tr>
<tr>
<td>Volta</td>
<td>67</td>
<td>360</td>
<td>-</td>
<td>584</td>
<td>88</td>
<td>283</td>
<td>33</td>
</tr>
<tr>
<td>Ashanti</td>
<td>71</td>
<td>71</td>
<td>134</td>
<td>55</td>
<td>55</td>
<td>47</td>
<td>50</td>
</tr>
<tr>
<td>Brong Ahafo</td>
<td>205</td>
<td>133</td>
<td>202</td>
<td>69</td>
<td>84</td>
<td>63</td>
<td>92</td>
</tr>
<tr>
<td>Northern</td>
<td>-</td>
<td>-</td>
<td>60</td>
<td>55</td>
<td>4</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>Upper West</td>
<td>24</td>
<td>5</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>7</td>
<td>34</td>
</tr>
<tr>
<td>Upper East</td>
<td>517</td>
<td>14</td>
<td>30</td>
<td>10</td>
<td>60</td>
<td>41</td>
<td>68</td>
</tr>
<tr>
<td>Total</td>
<td>241</td>
<td>189</td>
<td>229</td>
<td>120</td>
<td>87</td>
<td>113</td>
<td>118</td>
</tr>
</tbody>
</table>

Source: Ministry of Health Ghana, 2008

Prevalence of the disease varies from region to region depending on geographical conditions (17), and the Ashanti, Eastern and Central regions have the highest infection rates. Yaws turns to be more prevalent in the humid forest regions of southern Ghana mainly among people in deprived rural communities. From 2009 to 2013 between 8000 and 36,000 cases of clinical yaws were reported annually although the actual figures may be higher.

A yaws survey in 2008 carried out in communities gave a prevalence of 0.68% with some rural communities having prevalence as high as 20 %(104). In 2009 a rapid assessment
survey gave a prevalence of 150/100,000 in the general population, suggesting that 10% of the 30,000 communities in Ghana are endemic with yaws.

Figure 13: Map of Ghana Showing Reported Cases of Yaws by Region, 2009-2013
Currently the estimated national clinical prevalence of yaws is 700/100,000 among children less than 15 years old. Based on routine reports of passive cases and a few active case searches in schools the case notification rate is 87-241 per 100,000 people (105).

2.10 Global Yaws Treatment Campaigns

2.10.1 Yaws Treatment Campaigns in the 1920s and 1930s
In the 1920s and 1930s before the introduction of antibiotics in the treatment of infections, the main treatment for yaws and the other treponema infections was by multiple arsenical and bismuth injections. The treatment strategy was a combination of mass treatment by mobile
teams and treatment at health facilities. Early yaws treatment involved the treatment of both clinical and latent cases (106).

Yaws control campaigns in Africa began in the 1920s and 1930s, the strategies for these early campaigns were by mobile health teams that moved within communities to examine skin lesions and treat cases and their contacts. The drug of choice used in the treatment in these campaigns was injections of arsenic preparations and bismuth given in multiple doses. The result of this treatment was a rapid and dramatic resolution of yaws lesions (6, 107, 108).

The yaws treatment campaigns in Malay between 1921 and 1930 involved treatment of 13,000 to 31,000 cases of yaws annually with Novarsenobillon. The result of the campaign was reductions in yaws prevalence in four Federated Malay States, leaving a reservoir of the disease in the unfederated states. The onset of the second world war led to reappearance of yaws in the region (109).

2.10.2 Yaws Campaigns in the 1950s

In the aftermath of World War II there was an increase in disease rates especially infectious diseases in an already weakened world population (106). Diseases that were otherwise thought to have been eradicated or eliminated began to reappear. Yaws was the first disease that was targeted for eradication after the WWII.

In Africa the prevalence of active yaws ranged from 5.6% in Cameroon to 30% in Liberia. In Central and South America prevalence ranged from 2.5% in. In South East Asia the range was 3.1% in Thailand to 17.2% in Indonesia (110).

On the establishment of the WHO in 1948 the endemic treponematosis, malaria, tuberculosis and venereal infections were among the first public health problems to be addressed by the new agency. The World Health Assembly passed resolution WHA2.36 in 1949 as part of its
efforts to address increased numbers of yaws cases during the 1940s. The resolution recognized the importance of the endemic treponematoses including yaws and targeted them for eradication (3).

At the beginning of the campaign it was estimated that there were 50 million cases of yaws worldwide although other reports estimates up to 150 million cases (6). The high number of yaws cases was considered public health problems due to its economic impact in terms of loss of manpower as the disease was associated with disability in agricultural countries. The resolution was followed by a worldwide campaign from 1952 to 1964 by UNICEF and WHO and sponsored by PAHO that targeted yaws and the endemic treponematoses for control and eventual eradication (111). Forty-six countries were involved in the campaign and the strategy was the creation of vertical yaws programs with the goal of screening at least 90% of targeted populations and treating both active and latent cases, families and contacts with long acting penicillin. This was followed up with identification and treatment of new and recurrent or missed cases, conducting periodic resurveys, treating entire reservoir, and the use of adequate doses of penicillin. Between 1952 and 1964, 160 million people were screened and 50 million were treated, this was followed by a resurvey involving the reexamination of 300 million people (2).

The drug of choice during the campaign was procaine penicillin with aluminum monostearate injection given as a single dose of 1.2 million units for adults and a lower dose for children, dosage for contacts was half of the dosage for an adult active case (3). The campaign resulted in a massive reduction in yaws prevalence in many endemic areas, with complete disappearance in certain endemic countries. Globally there was a 95% reduction in the burden of endemic treponematoses. Primary health care systems were strengthened in most countries.
The campaign in Ghana was between 1954 and 1967 and led to a reduction in prevalence from 10% -15% in most regions to 0.5%. The campaign took place at different times in each region. Between 1963 and 1968 medical team unis (MFU) of the ministry of health the executing body was used for active surveillance. In 1968 and 1969, active cases of yaws were reduced to 6593 and 3343 respectively, however after 5 years the MFU was disbanded and staffs were integrated into the general health service. Surveillance changed from active to passive surveillance, this was ineffective, yaws cases increased from 3343 in 1969 to 71,763 in 1976 (17).

In Nigeria the Nssuka region in the eastern part of the country was selected as the starting point for the campaign due to the high endemicity of yaws in that region, total mass treatment was the strategy adopted for the campaign. Of the 383,769 persons examined 12,221 were infectious cases, 42,553 were late cases and 328,995 were latent cases and contacts. The strategy also involved resurveys at six month intervals which resulted in a dramatic fall in the reservoir of infectious cases (112).

The campaign in the Ivory Coast was conducted between 1956 and 1970 at the end of the campaign the number of cases had been reduced to less than 30,000 (113).

In South America the yaws eradication campaign in the 1950s and 1960s was one of Pan American Health Organisation’s (PAHO) most successful stories. After the campaign, yaws which was highly endemic in nearly all of the Latin American countries in the 1950s had been reduced to a minor public health problem in a few countries (114, 115).

The successful yaws campaigns of the 1950s led to a shift in yaws control programs in endemic countries. The vertical yaws program was integrated into the primary health care systems. Although there was 95% reduction in cases, the lack of public health surveillance and insufficient treatment facilities in endemic communities made efforts to trace the
remaining 5% difficult. The integration also made it difficult to trace subclinical cases and contacts (111). These lapses coupled with lack of commitment by endemic countries and the dwindling resources available for yaws control activities led to a resurgence of yaws and the other endemic treponematosis in the 1970s in countries that had earlier seen dramatic reductions during the campaign (116, 117).

2.10.3 Resurgence of Yaws

The mass campaigns in the 1950s did not result in the expected eradication of yaws and the other endemic treponematoses due to several obstacles to control namely: The misconception that yaws was under control after the 1950s campaign had led to complacency in endemic countries. The fact that the people affected by yaws are the poor people living in remote rural areas whose plight doesn’t make an impact on decision makers. The mode of treatment which requires accompanying logistics equipment such as syringes, needles, cotton wool and rubbing alcohol which are not always available in rural settings. Inadequate numbers of experienced health staff to administer treatment by injection in mass treatment campaigns. Storage of injection penicillin at temperatures of 2°C-8°C also poses a challenge in rural settings where there is lack of electricity (24). These factors coupled with lack of proper sanitation and poor surveillance activities have led to the resurgence of yaws in areas in which it was almost eradicated during the campaign.

Studies have shown resurgence of yaws in parts of West Africa, Central Africa, South East Asia and the West Pacific Islands (2, 99, 117). A clinical survey on the extent and nature of skin diseases among 10,224 Melanesians in the Western Province of the Solomon Islands in 1985 determined that yaws which had reappeared for the first time in 20 years had a prevalence of 8.5% among children below 15 years. Studies conducted in Togo in 1981 showed a resurgence of yaws in many areas of Togo, the study showed a prevalence of
clinical yaws among examined persons varying between 1%-3.9% and confirmed the underreporting of the disease due to weak surveillance (118).

A survey in a village in Southern Thailand in 1990 involving physical examination and TPHA and VDRL serology tests showed an attack rate of 23% between persons 2-79 years, 53.7% of the confirmed cases of yaws were children below 15 years old (99).

2.10.4 Yaws Control Efforts in the 1980s and 1990s

Following the resurgence of yaws in areas whose prevalence rate had been drastically reduced through the 1950s campaign, the UN in 1978 passed resolution WHA 31.58. The resolution recognized the resurgence of the endemic treponematoses particularly yaws as a public health problem in countries in which yaws was once controlled through the collaborative effort of WHO and UNICEF. The resolution addressed the implementation of an integrated treponema control program with emphasis on active surveillance to interrupt transmission at the earliest possible time and to prevent recurrence in areas in which the diseases had been eliminated or never occurred (5).

In the 1980s yaws control efforts were renewed in West Africa namely in Ghana, Mali, Niger, Togo, Benin, Burkina Faso and the Ivory Coast, these renewed efforts involved treatment with long acting penicillin in the form of injection benzathine benzylpenicillin.

A summary of a 3 year yaws campaign introduced in Ghana between 1981 and 1983 to reduce an unusually high prevalence rate showed that financial and technical constraints slowed the progress of the campaign in the first year and reduced the population targeted to be covered in the campaign. Despite these constraints 77,818 people (4.04%) of those examined during the campaign were diagnosed as active yaws cases and 1,556,360 contacts were treated with injection benzathine benzylpenicillin (119). The strategy of the campaign was to integrate yaws and yellow fever control programmess and also involved
measles, TB and tetanus vaccinations. Results from the evaluation of the first three years showed that the multidisciplinary approach used in this campaign resulted in improved access to medical care by the targeted population (120).

In the 1990s there were renewed yaws eradication efforts in endemic countries. Integration of yaws activities into primary healthcare which were not strong enough, coupled with lack of commitment by authorities in these countries resulted in the campaign of the 1990s having little impact on yaws eradication (6).

2.10.5 Yaws Control in Ghana

Yaws has been endemic in Ghana for generations and is among the first diseases to be identified and treated with conventional Western treatment in the Gold Coast (present day Ghana). In 1956 Scott described the epidemiology of yaws in Ghana after a yaws control campaign program in Northern Ghana, the prevalence of infectious yaws was 1.5% and reduced to 0.19% after the treatment campaign (17). Between 1957 and 1961 the WHO and UNICEF assisted Ghana in its mass yaws campaigns that led to a reduction of prevalence rates from 10% -15% in most regions to 0.5% (121).

The executing agency of the treatment campaigns were the Medical Field Units (MFU). The strategy for the mass yaws treatment was based on the WHO strategy, which focused on the disease prevalence in a given area: In areas where yaws is hyper endemic there is total mass treatment, in meso endemic communities the strategy is Juvenile Mass Treatment and in hypo endemic areas Selective Mass Treatment is the strategy.

Between 1963 and 1968 the MFU was used for active surveillance. In 1968 and 1969, 6593 and 5343 active cases of yaws were reported respectively. The apparent success of the yaws campaign in the 1950s and 1960s led to a false perception that yaws had been eradicated and resulted in lack of vigilance and a weakened surveillance system. Yaws was no more
considered a priority by national policymakers and its control activities was changed from a vertical program to its integration into the primary health care system that emerged after the 1960s campaigns.

The integration resulted in a number of challenges namely: inadequate funding, shortage of penicillin and its accompanying logistics due to the diversion of drug for the treatment of other conditions and the unavailability of health staff who could administer treatment by intramuscular injection during mass treatment campaigns.

The first cholera outbreak in Ghana occurred during the same period with the result of the diverging of resources for yaws control activities to cholera management and control. This took a toll on yaws control activities as focus was shifted from active case search and mass treatments to sporadic case findings and treatments (17).

The MFU continued work on the field treating any skin lesions including yaws with benzathine benzylpenicillin. The integration of a weakened yaws control program resulted in the gradual increase in yaws cases in the early 1970s with a peak in 1976 that reached pre campaign levels.

In 1980 Ghana reported 71,765 cases of yaws; this led to the 1981 anti yaws campaign which involved active case search and treatment of cases and contacts with a single dose of injection benzathine benzylpenicillin. The campaign resulted in a reduction to 45,568. In 1983 there was another campaign which further reduced to cases to 4375 and almost resulted in the elimination of yaws. This success further led to a weakening of the yaws surveillance leading to a gradual rise in the number of reported cases from 4375 to 58,519 from 1983 to 1997 (122).
Over the years the general picture for yaws control in Ghana has been a drop of incidence with each campaign followed by a rise; this is due to the health systems inability to commit to sustained control measures through strengthened surveillance systems, and provision of logistics, drugs and personnel for continuous targeted and mass treatments.

2.10.5. 1 National Yaws Eradication Programme

The National Yaws Eradication Programme (NYEP) was put in place by the government in 2008. The objective of the programme is to eliminate yaws from Ghana by 2017 and subsequently eradicate the disease by 2020. The NYEP is a unit under the disease control and prevention department of the Public health division in the Ghana Health Service.

The programme is headed by a Manager who reports directly to the Head of the Disease Control Department, and is assisted by two technical officers and a secretary. The functions of the NYEP includes planning and coordinating yaws activities at the national, regional and district levels, and mobilization of resources for yaws activities. Yaws data are collated at the districts and sub districts and entered on the GHS DHIMS 2 software which is accessible at all levels.

At the regional level yaws activities involve surveillance, case management, mobilization and distribution of resources. The focal person for yaws at the region is also in charge of all Neglected Tropical Diseases and is supervised by the Regional Director of Health. Cases of yaws in the communities are recorded in community registers by the Community-Based Surveillance Volunteers, who report to the facility heads. Treatment of cases and contacts is organized by health facilities in collaboration with the district health management teams.

The NYEP faces several challenges namely lack of financial support for programme activities at all levels, inadequate logistics for case detection and management, and lack of transportation for monitoring and supervision (105).
2.10.5.2. Yaws Surveillance in Ghana

Yaws is one of the diseases conditions that are reported monthly in Ghana, through the Integrated Disease Surveillance and Response (IDSR) program which adopts the integration of all surveillance activities and avoids vertical programs.

Yaws surveillance is passive, community surveillance data is captured from community registers by community based surveillance volunteers who send data to sub district health authorities. Data from sub district is transferred to the district health administration data base. At the health facilities data on yaws is captured through review of facility registers and records and sent to the DHMTs.

Periodic active case search for yaws is conducted by DHMTs during periodic surveys in yaws endemic areas and sometimes during national programs such as National Immunization Days (NIDs).

2.11. Treatment and Management of Yaws

At the beginning of the 20th century cases of yaws were treated with mercury, arsenic and potassium iodide. These treatments were given over a long period to achieve permanent results. While some yaws lesions would disappear with the administration of these treatments fresh lesions would appear. In 1910 Strong documented the results of yaws treatment with arsenobenzol (Salvasan) after the drug had proven successful for the treatment of syphilis. The mode of treatment was by intramuscular injection in the gluteal region. Of the 25 yaws patients treated, all were cured and there were no cases of relapse four months after treatment (123).

The early yaws campaigns in the 1920s and 1930s used multiple dose injections of arsenical preparations and bismuth. MacBride writes that the treatment drugs used in the yaws campaigns by the American health mission in Haiti in the 1920s and 1930s were arsenic-
bismuth injections, this mode of administration was not received well by most of the affected people who were mainly children due to the pain associated with the injections, the arsenical and bismuth preparations also had toxic manifestations (12). Sulpharsphenamine or acetasone tablets were suggested as replacements as they were proved to be more effective, however treatment with these drugs were not able to break the cycle of yaws epidemics in Haiti, although the severity of symptoms were reduced, relapse rates was 15% in one year and 20% in two years (124).

Oral antibiotics were introduced in the treatment of the treponematoses including yaws and syphilis during the 1950s. Studies in 1951 documented the results of the use of Aureomycin in clinical trials in the treatment of yaws in Haiti (26). The results showed that clinically the healing of yaws lesions was slower in patients treated with Aureomycin as compared with those treated with injection penicillin (125). Other studies conducted in 1953 showed that 69 cases of infectious yaws treated with oral chloramphenicol showed a cure rate of 79% 9-12 months after of treatment (27).

Studies done by Hendricks in syphilitic mice were the first studies to demonstrate that Terramycin had anti treponemal actions (27). The curative effect of Terramycin was found to be close to that of injection penicillin in the outcome of the use of the 2 drugs in yaws treatment. The results included the rapid disappearance of the treponemes from the lesions, the healing of lesions and sterilization of blood and lymph nodes (27).

A clinical trial in Haiti which involved the treatment of 150 persons with yaws in the primary, secondary and tertiary stages with oral terramycin resulted in impressive results. There were remarkable improvements in lesions and a low incidence of relapse. The side effects of the antibiotic were very minimal and involved a few cases of nausea. The study
concluded that terramycin was much more efficacious than procaine penicillin in the treatment of yaws (126).

Hill observed in studies involving oral treatment for yaws that the disadvantages of multi dose therapy were compliance, this was due to the 14 day treatment regimen which proved to have both administrative and supervisory constraints, especially their use in mass campaigns (12).

2.11.1 Treatment of Yaws with Penicillin

Treatment of yaws with penicillin an antibiotic with bactericidal effects was first documented by Finlay in West Africa in 1943 (127), the rationale for the use and dose of penicillin was based on the fact that investigations had proved that yaws responds the same way as syphilis in treponemacidal therapy (128). The yaws eradication campaign by UNICEF and WHO in the 1950s involved the use of procaine penicillin G in oil with 2% aluminum monostearate (PAM) as the drug of choice.

Penicillin has a high plasma level after 72 hours of treatment due to the fact that the drug deposits in the tissues and is absorbed slowly over a period of 12 hours to several days (129). PAM was given at a dosage of 1.2 million units for adults given as a single injection and a lower dose for children, dosage for contacts was half of the dosage for an adult active case (3).

From the early 1970s PAM was replaced with benzathine benzylpenicillin as the choice of penicillin in the treatment of yaws in most yaws endemic countries. In 1980 the WHO scientific group formally recommended benzathine benzylpenicillin as the standard for the treatment of yaws cases and their contacts. The recommended dosage was 0.6 million units for patients less than 10 years and 1.2 million units for patients aged 10 years and above. The mode of administration was by a single intramuscular injection, the dosage for latent yaws
and contacts is the same as for active yaws. In cases of penicillin allergy tetracycline or erythromycin have been given (130).

The advantages of treatment with injection benzathine benzylpenicillin is that it is cost effective and the problem of poor adherence is minimum. However it has several disadvantages including inadequate supply of accompanying logistics in often poor resourced environment where yaws is found, pain and infection associated with of intramuscular injection.

Unavailability of qualified health staff needed to administer injection during mass treatment campaigns poses operational challenge in penicillin use in mass campaigns. Unsafe injection practices such as re use of injection equipments may lead to the transmission of blood borne infections like HIV/AIDS and hepatitis. Storage of Benzathine benzylpenicillin at temperatures of 2-8°C is a challenge in tropical areas or areas with no electricity. In high penicillin allergy settings treatment with penicillin is impossible (23).

Oral penicillin has been used and has proved to be efficient in the treatment of yaws. In a study on the effectiveness of targeted oral penicillin V treatment in children with active yaws skin lesions in rural Guyana, study subjects with yaws were given oral penicillin V at a dosage of 50mg/kg in 4 divided doses for 7-10 days. The results was a success rate of 94% and the study concluded that a targeted oral penicillin V based treatment regimen can reduce the prevalence of yaws in the community and can also be used to treat individual cases effectively, however, adherence to a multi-day treatment regimen could be a problem (24).

Although treatment of yaws with penicillin has yielded good results some studies have shown failure of penicillin in the treatment of yaws. Studies in Papua New Guinea showed that among 39 children with yaws, dark field microscopy (DFM) was positive in 91% of the cases including 5 who had received treatment with penicillin within the past 2-12 weeks (21),
although spirochetes are not detectable in DFM in yaws lesion within 8-10 hours after
treatment (131). The study showed that by the end of follow up 11 (28%) of cases had
developed clinical or serological evidence of relapse. When given further treatment with
penicillin, response was slow in all 11 cases, in 3 cases evidence of recurrence or active
infection persisted despite repeated treatment with penicillin. The study concluded that
reduced susceptibility to penicillin of *T. pallidum* subspecies *pertenue* was the most likely
dause of treatment failure (21).

The constraints related to the use of injection penicillin in treatment of yaws stands in the
way of the achievement of the WHO target of eradication by the year 2020, hence the need to
explore the possibility of the use of an equally effective single dose oral treatment that avoids
the challenges and constraints of penicillin and can effectively be used in mass treatment
campaigns. Azithromycin has previously been shown to be an effective agent in the treatment
of venereal syphilis (23), and it is the cornerstone of the strategy for the elimination of
blinding trachoma.

### 2.12 Pharmacokinetics of Azithromycin

Azithromycin is a macrolide antibiotic which belongs to the azalide subclass. Its mechanism
of action is through the prevention of the growth of bacteria by interfering with its protein
synthesis. It is an acid stable antibiotic that can be taken orally, its absorption is greater on an
empty stomach. Azithromycin has a long tissue half-life and its slow elimination from the
body allows a once daily treatment for 3-5 days in many bacterial infections, compared to 3-4
times a day for up to two weeks for erythromycin. A study that examined the
pharmacokinetics of Azithromycin in man showed that approximately 37% of a single oral
dose of 500mg was bioavailable and produced peak serum concentration of 0.4mg/l. Multi
dose regimen produced only a slight increase in serum concentration (132).
Adverse events following treatment with azithromycin is minimal and consists of mild cases of gastrointestinal discomfort, vomiting and diarrhoea. Studies by Ayele on adverse events after a mass azithromycin treatment for trachoma in 2011 found that the common adverse events were abdominal pains, nausea, vomiting and skin rash. However the prevalence of adverse events varied in the various age groups, with a higher prevalence in older persons. Within 1-9 years age group the prevalence of adverse events ranged from 4.9% to 7.0 %, whilst the prevalence ranged from 17% to 18.7 % in people 10 years and above (133).

Azithromycin is effective against respiratory and soft tissue infections. In pilot studies undertaken to explore the potential of oral single dose therapy against several disorders azithromycin appeared to be effective against Chlamydia trachomatis, Neisseria gonorrhea and Haemophilus ducreyi infections (23) and appears promising in the treatment of the treponematosis.

2.13 Efficacy of Azithromycin in the Treatment of Syphilis

Several studies have proven the successful use of azithromycin in the treatment of syphilis. A randomized trial by Hook among patients attending a STD clinic who had recently been exposed to sexual partners with infective syphilis, explored the possibility of a single dose of azithromycin as an alternative to benzathine penicillin G in the treatment of incubating syphilis. Forty study participants were treated with azithromycin and 23 were treated with penicillin. The outcome was post exposure syphilis prevention indicated by non-reactive RPR and FTA-abs tests throughout the 3 months follow up. None of the study participants developed evidence of syphilis and the study concluded that a single 1.0g dose of azithromycin seemed to be efficacious for the prevention of syphilis in persons exposed (134).
In an equivalent trial in Tanzania by Riedner, 328 subjects with primary and latent syphilis were randomly assigned to receive 2g of oral azithromycin or 2.4 million units of intramuscular injection of Penicillin G Benzathine. The primary outcome for this study was treatment efficacy defined as serological cure which was a drop in baseline RPR titre by 2 dilutions at 9 months post treatment, and the epithelization of ulcer 2 weeks after treatment in primary syphilis. The study concluded that a single dose of azithromycin given as 2g was effective in treating syphilis(23).

In another randomized comparative pilot study of intramuscular injection of benzathine penicillin G and two oral azithromycin regimens for the treatment of syphilis, patients were randomly assigned to either 2.4 million units benzathine penicillin G or 2.0g oral azithromycin given as a single dose or as two 2.0g doses given one week apart. The study followed the serological response to therapy at 3months, 6months, 9months and 12months post treatment. Patients whose post treatment RPR titre became non-reactive or decreased by 2 dilutions or more were classified as responding to therapy. Results of this study showed 86% response from patients treated with benzathine penicillin, 94% response for treatment with a single dose azithromycin and 83% for azithromycin given in 2 doses one week apart. The study concluded that oral Azithromycin given as a single or divided doses is a promising alternative therapy to benzathine penicillin G for the treatment of syphilis(135).

In a multicentre randomized clinical trial, 517 HIV negative patients with syphilis attending an STD clinic were assigned to treatment with either 2.0g of a single dose oral azithromycin or to intramuscular injection of 2.4 million units benzathine benzylpenicillin. The serological cure rates of the 2 groups were compared and results showed that serological cure among the azithromycin group was 77.6% compared to 78.5% among the penicillin group.
Another study evaluated the efficacy and safety of azithromycin versus benzathine benzylpenicillin for early syphilis and a meta-analysis to compare the antibiotics for early syphilis. Four randomized controlled trials met the inclusion criteria. Cure rates were 95.0% for azithromycin and 84.0% for penicillin G benzathine. After the data was pooled to compute the difference in efficacy cure rate (OR = 1.37), (95% CI, 1.05 to 1.77) the risk difference for cure rate between the two drugs were statistically significant. The study concluded that azithromycin achieved a higher cure rate than penicillin G benzathine in a long follow-up. Although the gastrointestinal adverse effects was five times higher in patients treated with Azithromycin the differences were not significant (136).

In a review of 3 clinical trials involving treatment with oral azithromycin and injection benzathine penicillin using meta-analysis to compare absence of healing rates at nine months follow up between azithromycin and penicillin among in-patients with syphilis, a single dose of azithromycin given orally was found to be as effective as the 2.4 million units of benzathine penicillin for treating syphilis (137, 138).

2.14 Clinical Trials Involving the Use of Single Dose of Azithromycin in Children

Three clinical trials looked at the use of a single dose of azithromycin for the treatment of acute otitis media in children (139). The first was a pilot study that found that the clinical and microbiological efficacy of a single dose (30 mg/kg) azithromycin was comparable to that of a 3 day azithromycin or a single dose of ceftriaxone (140). The second was a non-comparative trial that confirmed the clinical and microbiologic efficacy of a single dose of azithromycin (141). The third study was a large double blind trial that demonstrated comparable clinical success rates between single dose azithromycin and 10 day standard amoxicillin/clavulanate (142).
Incidence of adverse events in patients treated with single dose azithromycin (30mg/kg) was low in all 3 trials. Compliance with azithromycin was significantly better than amoxicillin/clavulanate (p<0.001). Conclusions in the analysis of the 3 studies was that a single dose of azithromycin (30mg/kg) was safe and effective in uncomplicated acute otitis in children (139).

2.15 Non Inferiority Trials

Randomized non inferiority trials were introduced in clinical trials in the 1990s, the trial design attempts to show that the treatment effect of an experimental drug is not worse than that of the standard by an acceptable margin. Non-inferiority trials are performed when there is already an existing effective therapy for a disease but a new treatment has extra benefits such as lower cost, less invasiveness and convenience compared to the standard treatment. In non-inferiority trials the standard treatment is the active control (143).

The aim of a non-inferiority trial is to demonstrate that an experimental drug is not worse than an active treatment drug by more than a pre specified margin (non-inferiority margin). The non-inferiority margin is the maximum difference between the active treatment and the experimental drug for which the study is prepared to accept in a given direction that the new treatment is not to be considered clinically inferior to the active control. Non-inferiority is said to be established if a 95% confidence interval for the difference between treatment means lies above or below the boundary value of non-inferiority margin (in a favorable direction). In non-inferiority trials it is assumed that the active control drug has been proved to have a significant clinical effect against a placebo, non-inferiority trials are used in situations where a superiority trial with a placebo as control is unethical.
2.16 Setting the Non Inferiority Margin

A non-inferiority margin is selected prior to the trial and is based on both statistical reasoning and clinical judgments. The non-inferiority margin is the degree of inferiority of the test treatment to the control which the trial will attempt to exclude statistically. If the confidence interval of the difference between the test treatment and the control can exclude that the degree of inferiority of the test treatment is not greater than the non-inferiority margin then the test treatment can be declared non-inferior (144). The ICH E10 guideline states that the margin chosen for non-inferiority trial cannot be greater than the smallest effect size that the active drug would be expected to have compared to a placebo (145).
CHAPTER THREE

3.0. METHODOLOGY

3.1. Study Area

The study was conducted in three neighbouring yaws endemic districts in southern Ghana namely: Awutu Senya (AS) district in the Central Region, Ga South (GS) district in Greater Accra Region and West Akim (WAK) district in Eastern Region (Figure 14).

Figure 14: The Awutu Senya, Ga South and West Akim Districts of Ghana

The three study districts have a total population of 787,747, with a distribution of 274,584, 316,091, and 197,072 respectively. Children under the age of 15 years, known to bear the bulk of yaws infections, represent an estimated 38.3% of these populations. The study area is made up of 912 communities, 405 of which are rural. These rural communities are very deprived and lack potable water, access to healthcare is also limited. Roads in the study area
are mainly untarred roads, and more than 70% are unmotorable. The average distance from community to nearest health facility is more than 10km.

3.1.1 Rationale for Selecting Study Districts

The three neighboring study districts report high incidence of yaws throughout the year. Between 2010 and 2013 more than 2000 cases of suspected yaws were reported in the 3 districts through routine reporting and active case search, majority of persons affected were children below 15 years. However this number may not reflect incidence of the disease in the districts due to the fact that in Ghana persons with yaws do not routinely report to health facilities; data on the disease comes from occasional surveys, active case search, school screenings by community health nurses and the few cases that report to health facilities. Head teachers of basic schools in these districts have also reported high incidence of suspected yaws lesions among school children to their various health directorates.

3.1.2 Awutu Senya District

The Awutu Senya District is in the south eastern part of the Central region. It has a population of 274,584 and is made up of over 300 communities’ 70% of which are periurban and 30% rural.

The administrative capital of the district is Awutu Breku. The district is bordered by the Ga South district to the east, Efutu district and the Gulf of Guinea to the south, the West Akim district to the north, Birim south district to the north-west, Agona West district to the west and the Gomoa East district separating the southern part of the district from the main land. The Awutu Senya district is divided into 9 health sub districts, the district has 5 public health centers and 12 CHPS zones. There are 31 registered private health facilities providing
clinical, RCH and eye services in the district. Major ethnic groups in the district are the Brekus and Fantes.

### 3.1.3 Ga South District

The Ga South district occupies an area of 517 square kilometers and lies in the south western part of the Greater Accra region. The district has a population of 316,091 made up of 362 communities, 76% of which is urban and 24% rural. The Ga South district shares boundaries with the Accra metropolis to the south east, Akwapim South district to the north east, Ga West district to the east, West Akim district to the north, Awutu Senya to the west, Gomoa district to the south west and the Gulf of Guinea to the South. The district is divided into 6 health sub districts, and has 1 government hospital, 3 health centers, 1 Reproductive and Child Health clinic and 2 functioning CHPS compounds; the private health sector is made up of 6 hospitals, 16 clinics and 29 maternity homes. The main ethnic groups in the district are Gas, Ewes and Akans.

![Figure 15: A Rural Settlement and a Borehole in Ga South District](image)

### 3.1.4 The West Akim District

The West Akim District is located in the southern part of the Eastern region of Ghana; the district covers an area of 1018 square kilometers and has a population of 197,072 and of 250 communities. Asamankese is the district capital and is the only urban community in the
district. West Akim district shares boundaries to the north with the Kwaebibirem and Atiwa districts, south with the Ga South and Awutu Senya districts, east with Suhum Kraboa Coaltar and Akwapim South districts and west with Birim South and Agona East districts.

The district is divided into 8 health sub districts, and has 15 health facilities made up of 1 government hospital, 2 Health Centres, 2 functioning CHPS compounds, 3 clinics and 7 privately owned clinics and maternity homes.

**Figure 16: Untarred Road and Wooden Bridge in the West Akim District**

**3.1.5. Climate, Topography and Vegetation of Study Area**

The study area falls under the semi-equatorial climatic zone and is marked by a dry and rainy seasons. The major rainy season is from the end of March to August with the heaviest rainfall in June. The minor rainy season is from September to October. The mean annual rainfall is between 1,238 mm and 1,660 mm. The dry season begins in November through to the middle of March with a peak between January and February. The climate in the study area is characterized by high relative humidities of 55% in the rainy season and 90% in the dry season. Annual mean temperatures are between 22.2°C in August and 28.4°C in February.

The landscape in the Ga South district is made up of gentle slopes interspersed with plains; in the western edge of the district are the Akwapim range which runs into the Weija hills with a vegetation of coastal Savannah and shrub-land in most parts of the Densu River basin and thin remnants of forests towards their northern section. The West Akim and Awutu Senya districts lie in the forest belt and the vegetation is principally semi-deciduous forest. The
vegetation has undergone degradation due to sand weaning, tree felling and slush and burn method of farming.

The natural climatic conditions of high temperatures and high humidity coupled with the high rainfall and semi deciduous forest vegetation are favorable for yaws infection.

3.1.6 Water and Sanitation

Water Supply

The Densu and Ayensu rivers and their tributaries are the main source of water in the rural parts of the study area; however both of these rivers are highly polluted. Despite the fact that the Weija water reservoir and treatment plant the largest water treatment plant in Ghana is located in the Ga South district, majority of residents do not have access to portable water. In the GS district the urban communities depend on water supplied by water tankers, wells and harvested rainwater. In the rural communities only 33% of the population have access to boreholes and hand dug wells, the rest access water from unsafe water sources such as the Densu River and its tributaries, streams and ponds.

In the West Akim district only 48% of the population has access to portable water; the remaining depends on unsafe water sources such as ponds, rivers and streams. In the Awutu Senya district although a majority of the district is connected to a main water pipeline, most often water does not flow resulting in inadequate water supply to households. The peri urban communities depend on dug wells and water tankers whilst most rural communities depend on hand dug wells, boreholes, rivers, streams and ponds.

Sanitation

Only a small fraction of the population of the study area has access to acceptable standards of sanitation. In several instances, households depend on over loaded and run-down public toilets, whilst others practice open defecation. There are only 36 public toilets utilized by
64% of the population in the West Akim district and only 23.7% of the people in peri urban settlements have improved toilet facilities (West Akim district annual report 2012). In the rural parts of the AS district there are few public toilets constructed through community initiative with the assistance of some donor agencies, few people in the district have access to sanitary facilities. (Source: Water and Sanitation Department, Awutu Breku). Drainage is non-existent in most parts of the study area.

Inadequate supply of portable water coupled with unavailability or inadequate toilet facilities and open defecation in most communities in the study area has resulted in high prevalence of water related diseases like Buruli Ulcer, diarrhea, Bilharzia and yaws.

3.1.7 Occupation

Subsistence farming is the main economic activity in the rural parts of the study districts; peasant farmers grow cassava, maize, pepper, okra and tomatoes. The youth in the 3 districts are employed by large commercial plantations that grow and export pineapples, mangoes, pawpaw, watermelons and coconuts.

In the West Akim district cocoa farming, palm oil extraction, and brewing of local gin is common among the men whilst the youth are engaged in surface mining known as ‘galamsey’. Sand weaning is a major occupation of the youth in the GS district and fishing is the main occupation along the coast in the AS and GS districts.

Most women in the study districts engage in trading and small-scale industries i.e. agro and garri processing. The urban and peri urban communities are made up of civil servants, industrial workers, artisans, traders and tradesmen who are mostly engaged in carpentry, automobile repair, carving and basket weaving.
3.1.8 Health Services

The 3 study districts are each divided into a number of health sub districts; the District Health Management Team (DHMT) provides technical and administrative support including resource mobilization and distribution, training and implementation of programmes to health service providers. The DHMT also ensures that services provided are in line with the national policies.

Service delivery is at community, sub district and district levels and is in both curative and preventive medicine. The rural communities have limited access to health care and the sub district health teams organize weekly or monthly health outreaches to ensure that communities have access to healthcare. The commonest diseases reported in the study area are malaria, respiratory infections and hypertension. The rural communities have high prevalence of infectious diseases e.g. bilharzia, dracunculiasis and yaws. The rural part of the Ga South district lies in the Densu river basin and has a high prevalence of Buruli Ulcer.

Community Based Surveillance Volunteers (CBSVs) are selected by opinion leaders of their respective communities to assist health workers in health delivery within the communities. All health events within the communities are recorded by the CBSVs. Data from the CBSVs records are sent to the health units for onward transmission to the sub district office and DHMTs.

3.1.9 Education

The study area has a total of 1750 basic schools and kindergartens which are mainly government owned, with a few owned by the private sector and missions. The total number of children enrolled in school is 174 536.
3.2 Study Design

The study was conducted in 2 parts; the first part was an observational study which used a cross sectional and case control study designs to describe the epidemiological characteristics of yaws including its prevalence in the various socio-demographic groups and the risk factors associated with the disease.

The second part of study was an interventional study that sought to explore the efficacy of a single dose of oral azithromycin (experimental drug) compared to benzathine benzylpenicillin (active control) through a randomized controlled, open label non-inferiority phase III single-centre trial. Considering that the efficacy of the standard treatment a single intramuscular injection of benzathine benzylpenicillin is as high as 95%, a non-inferiority trial design was chosen to estimate to what extent treatment with a single dose oral azithromycin could be inferior to the current standard treatment.

One arm of the study was treated with the experimental drug oral azithromycin and the second arm was treated with the active control a single intramuscular injection of benzathine benzylpenicillin. The study was conducted between May 2011 and December 2012.

Figure 17 describes the flow of participants in the study. Active case search for yaws was conducted in all rural communities and schools in the study districts by community health nurses and community based surveillance volunteers. All children aged 1—15 years with suspected yaws skin lesion and whose parents give consent have blood samples taken for TPHA and RPR tests.
3.2.1 Flow of participants in the study

*Randomized Clinical Trial

Figure 17: Flow of Participants in the Study
Children whose skin lesions were not suspected as yaws were treated or referred by the investigating team to the nearest health facility. Participants with Positive qualitative TPHA test and a quantitative RPR titre of 1:4 or more were enrolled in the cross sectional study. A random selection of participants recruited into the cross sectional study was done to select cases for the case control study. Eligible participants recruited into the cross sectional study were enrolled in the randomized clinical trial after photographs of yaws lesion had been taken.

3.3 Study Population

The study population comprised all children aged 1-15 years residing in the Awutu Senya, Ga South and the West Akim districts at the time of the study. Following active case search in yaws endemic communities in the 3 study districts by health workers and CBSVs, subjects suspected to have yaws were assessed for eligibility; those who met the eligibility criteria and consented to enrol in the study were recruited.

3.4 Methods for Observational Study

3.4.1 Sample Size

This was calculated using the following parameters for case control study where the exposure of interest is yaws; with a prevalence of yaws of 16 % in the control population and 36.6 % among the cases, a confidence interval (1-α) of 95%, power (1-β) of 80% and a detectable odds ratio of 3.0, a minimum of 78 cases and 156 controls were required from Epi Info software version 3.5.1. However in this study a total of 90 cases and 180 controls were used.
3.4.2 Definitions

3.4.2.1 A Case

In this study a case of yaws is defined as any person with a clinically diagnosed yaws lesion and serologically confirmed by positive Treponema Pallidum Haemaglutination Assay (TPHA) and a quantitative Rapid Plasma Reagin (RPR) titre of at least 1: 4.

3.4.2.2 Clinically Diagnosed Yaws

Primary stage yaws was defined as an ulcer with raised edges and a dirty crusty base or a papilloma that appeared as a firm yellowish skin lesion with a dark tip, on any part of the body. Secondary stage yaws was defined as any of the following skin lesions: multiple ulcerative or papillomatous skin lesions; a palmar or plantar hyperkeratosis; a macular, papular or maculopapular skin lesion.

3.4.2.3 Controls

Any person residing in the same community where the case come from but did not have any yaws skin lesion. Controls were matched to cases by a ratio of 1:2.

3.4.3 Selection of Cases and Controls

Yaws is found mainly in the rural communities of endemic districts, the disease also has a low rate of reporting in health facilities, as such a purposive sampling technique was employed in the cross sectional study. All rural communities in the study districts were purposively selected for active case search through clinical examination of skin for yaws lesions both in school and at home. All children aged 1-15 years clinically diagnosed with yaws skin lesions during the active case search were enrolled in the cross sectional study.

For the case control study all children with clinically diagnosed yaws and serologically confirmed were listed by districts. With the use of Excel Random number generator, 90
confirmed yaws cases were randomly selected, 30 from each district. Each randomly selected case was matched to 2 community controls.

The community controls were selected through the spinning of the bottle in the middle of the community; the first house in the direction of the tip of the bottle was selected and entered. Any person aged 1-15 years who did not have any skin lesion and who/parents were willing to be interviewed was selected as control. If they refused participation in study another person within the same house who met the criteria was interviewed. The next house was visited until the appropriate numbers of controls were selected.

3.4.4 Preparation for Data Collection

3.4.4.1 Community Entry

The study was conducted in close collaboration with the various District Health Management Teams (DHMTs), sub district management teams, Community Based Surveillance Volunteers (CBSVs), the National Yaws Eradication Program (NYEP), the National Public Health Reference Laboratory (NPHRL), the Komfo Anokye Teaching Hospital (KATH) serology laboratory, the Ghana Education Service (GES) and the District Assemblies of the study districts.

Several meetings were held between the stakeholders and the investigation team to explain the rationale and procedures involved in the study, its benefits to the communities and the role of the various stakeholders in the study.

Community durbars in the form of open forums were organised by sub district health staff to introduce the research team and explain rationale for the study and its benefits to the community. The community members were also educated on signs and symptoms of yaws and the need for early reporting to avoid debilitating complications. After the procedures for
the study had been explained at the durbar, the study team officially sought permission from opinion leaders and community members to conduct study.

3.4.4.2 Training of Field Team and Data Collection Personelle

The research team was made up of the Principal Investigator (physician), a representative from the National Yaws Eradication Program (NYEP), Community Health Nurses (CHNs), District Disease Control Officers (DDCOs), a laboratory technologist, a Community Based Surveillance Volunteer (CBSV), a professional photographer and National service officers trained as data collection personelle. The training was conducted in 2 sessions, the first session was held at the Ga West municipal Health Administration Office and involved health workers. Training was facilitated by the PI and staffs of the NYEP, topics discussed during the training were: The rationale for the study, diagnosis and treatment of yaws, serology tests for yaws, interview techniques and filling of questionnaires.

A second training was conducted at the DHMTs of the study districts for community based surveillance volunteers. The training was facilitated by the district disease control teams. Topics discussed were: Clinical signs and symptoms of yaws, Skin conditions that could likely be yaws and diagnosis and treatment of yaws.

3.4.4.3 Social Mobilisation

Social mobilisation for active case search for yaws was done by the CBSVs who served as the liaisons between community members, health authorities and research team. Channels of communication were announcement by community PA systems and gong-gong beating. Yaws posters were also displayed in the communities for diagnosis and referral by community members to the nearest health facility or to the CBSVs. Copies of letters containing information on study were sent to the various schools by the DHMTs for onward transmission to parents/guardians. A date for active case search in each community was
scheduled by the research team in collaboration with DHMTs and community/school. Permission to conduct study was sought and granted by the Ghana Education Service. Permission was sought from school authorities, assemblymen and parents for active case search to be conducted in the schools and the communities. Out of school children were encouraged to enrol in school by the research team and where necessary school uniforms were donated to children who did not have uniforms.

Figure 18: Donation of school uniforms to Out of School Children

3.4.5 Data Collection Methods/ Techniques and Tools

Active case search for yaws started immediately after the trainings to retain the knowledge acquired during the training. Screening of participants took place both in schools and at home. A team made up research team, health workers and CBSVs were involved in the active case search. The team moved from community to community in search of possible yaws cases. The team displayed pictures of yaws to community members and any person who had similar lesions were selected and examined. Participants were made to undress in a private area in the presence of their parents and their skin and scalp were clinically examination for signs of early yaws lesions using the WHO yaws picture guide. Skin examination was done individually by 2 persons.
All children found to have lesions suspected as yaws in school had parents/guardian invited to school, and a written consent form was administered to them. The consent form was translated to those who could not read or write. Participants who consented to the study were made to sign or thumbprint the consent form in the presence of a witness who also signed the same form. Children 12 years and above also signed consent forms. Children examined in the community had consent forms administered in the communities. To serologically confirm clinical cases of yaws diagnosed during active case search, subjects whose parents had consented to their participation in the study had 5mls of venous blood drawn by a lab technician and sent to the Ga West Municipal hospital where sample was centrifuged and transported to the National Public Health Reference Lab and Komfo Anokye teaching hospital serology Lab for TPHA and RPR serology tests respectively. All participants with positive qualitative TPHA test and an RPR titer of at least 1:4 were classified as confirmed yaws. Children confirmed as having yaws had their names, schools and community and home addresses listed in a study register. Dates for interviews were scheduled with children and parents.

Interviews were conducted by community health nurse and disease control officers who had been trained by the PI to administer questionnaires in the presence of a teacher or a parent. Semi structured questionnaires consisting of both close and open ended questions were employed to elicit information from confirmed yaws cases who agreed to participate in the study. Information on general medical condition of participants included general appearance, body temperature, and the presence of other skin lesions, pains and swelling of joints. Questions asked during interview included information on the socio-demographic background of participants: age, sex, community, education, ethnicity and religion. Questions on participants living environment including the source of drinking and bathing water, type of material used to build house, type of house (compound or single), number of people living
in participants’ house, and number of people sleeping in participants’ bedroom. For behavioural characteristics of participant questions asked included bathing daily and always bathing with soap.

Interviews were conducted either in school or at home, and each interview lasted for 20 minutes.

![Conducting Interviews at Home and in School](image)

**Figure 19: Conducting Interviews at Home and in School**

### 3.5 Statistical Analysis of Observational Study

Descriptive statistics were calculated and compared for persons who had yaws and those who did not have yaws. The results were presented using frequency tables, graphs and charts. In order to examine the association between yaws and specific risk factors the odd ratios (ORs) and corresponding 95% confidence intervals were estimated. Having yaws disease was the dependent variable and socio-demographic, behavioral and environmental factors were independent variables. Based on the results of the univariate analysis all variables that demonstrated a strong association with yaws (p-value of 0.1 or less) were retained in a multiple logistic regression module while controlling for confounding variables.
3.6 Methods for Non-Inferiority Trial

3.6.1 Eligibility Criteria

In the non-inferiority trial any subject aged between 1-15 years living in the study area at the time of the study and diagnosed clinically was eligible to enter the study if they met the following inclusion criteria.

Inclusion criteria:

1. Clinically diagnosed as early yaws (primary or secondary stage)
2. Age between 1-15 years
3. The subject or parent/guardian had signed or thumb printed written informed consent
4. Positive Treponema Pallidum Haemaglutination Assay qualitative test results
5. Baseline quantitative Rapid Plasma Reagin titer of at least 1:4
6. The parent/guardian willing to make subject available for follow up

Exclusion Criteria

1. Penicillin and/or macrolide allergy
2. Broad spectrum antibiotic in preceding 30 days
3. Judged unlikely to be available for follow up
4. Medical condition that would impair drug absorption

3.6.2 Trial Centre

The Ga West Municipal Hospital was chosen as the trial center due to its proximity to the offices of the investigation team including the PI. All data collected during the trial were entered and stored on a computer at the trial center by independent data entry clerks.
3.6.3 Assigned Interventions

There were two parallel arms in the non-inferiority trial. The first arm was treated with the experimental drug a single oral dose of azithromycin given at a dosage of 30mg/kg. The second arm was treated with the active comparator injection benzathine benzylpenicillin, at a dosage of 0.6 million units for participants below 10 years and 1.2 million units for participants aged 10-15 years.

3.6.4 Recruitment

Recruitment activities in the trial involved meeting between research team and the District Health Management teams of the study districts to introduce the various stages of the trial and discuss strategies for participants’ recruitment. The DHMTs then organised open community meetings between the research team and community members, teachers, parents and guardians during which the burden of yaws in the districts, rational and benefits of the clinical trial were discussed. The meeting was an open forum where questions were asked and all attendants made contributions. Recruitment of participants into the trial was done serially. Recruitment started on 25th May 2011 and ended on 31st December 2012. Each participant recruited and enrolled into the trial was followed up for 6 months.

Participant recruitment tools for the trial were:

1. Letters to parents and guardians to inform them about trial
2. Schedules for the various components of the trial
3. Pictorial guides to yaws diagnoses distributed within schools and communities to aid in case identification.

Informed consent forms were sent to parents/guardians of all eligible subjects. Subjects were only enrolled after signed informed consent had been received.
3.6.5 Clinical Examination of participants

Children aged 1-15 years from 62 communities were clinically examined by the field team including the PI and CBSVs for skin lesions suggestive of yaws. Screening was done both in school (Basic schools) and at home in collaboration with schoolteachers, community based surveillance volunteers and community leaders. All clinically diagnosed yaws were serologically confirmed by qualitative TPHA and quantitative RPR serology tests.

3.6.6 Blood Sample Collection

Blood samples were collected on the field by trained laboratory technicians. For both TPHA and RPR serology tests 5mls of venous blood was collected from the left arm of each study subject into a Beckton and Dickinson gel containing vacutainer tube and kept in a cold box at a temperatures of 0°C.

At the end of each day the blood samples were transported to the Ga West Municipal Hospital laboratory where samples were centrifuged at 3000 revolutions per minute for 5 minutes. The sera were aspirated into pre labeled screw capped cryotubes and frozen at a temperature of -20°C. One set of serum samples were sent to the National Public Health Reference laboratory at the Korle Bu Teaching hospital for qualitative TPHA serology tests. A second set of frozen serum samples were sent to the Komfo Anokye Teaching Hospital serology laboratory in Kumasi for baseline quantitative RPR serology tests.

3.6.6.1 Qualitative Treponema Pallidum Haemaglutination Assay Test

The Treponema Pallidum Hemagglutination test is a specific hemagglutination test used to detect T. pallidum antibodies in human serum. The TPHA test is used as screening test and in confirmation of positive reaction from a non Treponemal test. The TPHA test kit used in this study was by Debens Diagnostics Limited and was made up of: A test cell suspension made up of stabilized chicken erythrocytes coated with T.pallidum antigen, a control cell
suspension containing stabilized and uncoated chicken erythrocytes, diluent made up of buffered saline containing soluble components of T. Reiter, positive control made up of immune rabbit serum pre diluted at 1:20 and a negative control made up of animal serum pre diluted at 1:20. All reagents and specimen were brought to room temperature before the beginning of the test; dilutions were carried out in a 12 by 8 micro titration plate.

**Steps in TPHA Dilution Procedure (Debens Diagnostic TPHA Kit)**

Step 1: 25µl of diluents was dispersed into wells in rows 1, 3, 4 of the micro titration plate and 100ul dispensed in wells in row 2.

Step 2: 25ul of each sample was dispersed in wells in row 1 and mixed with a pipette

Step 3: 25ul was transferred from row 1 to row 2 and mixed

Step 4: 25ul was transferred from row 2 to row 3 and mixed

Step 5:25ul was discarded from row 3

Step 6:25ul transferred from row 2 to row 4

Step 7: 75ul of test cells was added to row 4 and left to stand at room temperature for 60minutes

Step 8:75ul of control cells was added to row 3 and left to stand at room temperature for 60 minutes

Step 9: Wells in rows 3 and 4 were macroscopically observed for agglutination pattern

**Results**

In positive results a smooth mat of agglutinated cells is formed at the bottom of micro titration plate.
3.6.6.2 Qualitative and Quantitative Rapid Plasma Reagin Test

The Immutrep RPR test kit, Lot No. 7033449 (Omega Diagnostics Ltd, United Kingdom) was used in for the rapid plasma reagin serology tests. The RPR test is a non-treponemal flocculation test meant for the qualitative and/ or quantitative determination of reagin antibodies in human serum or plasma. The reagent contains carbon antigens that bind to lecithin antibodies in the blood sample leading to the formation of black clumps that can clearly be visualized macroscopically on a test card. The test kit contains a Micropipette (20-100ul), Fine tips, Transfer pipette Gloves, Marker, Test Card, Rotator, Positive control, Negative control, Transfer pipettes and a Timer.

Steps in Qualitative RPR Serology Test (Immutrep RPR test kit)

One drop (50ul) each of sample and the control was dispensed onto the RPR test card; this was spread to cover the entire circle using the flat end of the dispenser. Using the dispensing bottle one free falling drop of antigen was dropped onto the specimen without stirring. The card was placed on a rotator and rotated at 100 rpm for 8mins. The results were visually inspected in good light.

Interpretation of Qualitative RPR Serology test results

Medium and large aggregates - Reactive

Finely dispersed aggregates – Weakly Reactive

No aggregates visible or smooth grey appearance – Non Reactive

Procedure for Quantitative RPR Tests

Serial dilutions (50ul) of participants samples (1/2, 1/4, 1/8, 1/16, 1/32, 1/64, 1/128,) were prepared using isotonic saline solutions (0.9%), one drop of each serum dilution was transferred onto the test circle on the card, one drop of shaken antigen was added to the
sample, the card was rotated for 8mins at 100 rpm, results was inspected immediately visually in good light, the RPR titer is the last dilution that produces reactive results.

### 3.6.7 Pictorial Documentation of yaws Lesions

In this trial the services of a professional photographer was engaged to take pictures of yaws skin lesions before treatment and at 3 weeks post treatment. All pictures were given ID numbers and stored on a computer at the study centre.

### 3.6.8 Drug Intervention

#### 3.6.8.1 Study Drugs

In this study azithromycin manufactured by Pfizer in the strength of 500mg was supplied by Gokals Laborex Ghana. Injection benzathine benzylpenicillin manufactured by Troge Medicals, Hamburg, in the strength of 1.2 million units per vial was supplied by Ghana Health Service Central Medical Stores.

#### 3.6.8.2 Intervention

Drug interventions were carried out by the field team in close collaboration with school authorities and community opinion leaders and parents/guardians. The treatment time schedules were planned by the field team and teachers. The average number of days between diagnosis and treatment was 5 days; the treatment allocations were generated by Health Information Officers at the study center and kept in opaque envelopes which were opened by the field teams at the point of treatment.

The study participants were divided into 2 groups according to treatment allocation and treatment for each group was given in separate areas.

There were two parallel treatment arms in this trial, the experimental arm were subjects treated with a single oral dose of azithromycin given as 30mg/kg (maximum of 2g). The
active control arm were subjects treated with a single dose of benzathine benzylpenicillin given as an intramuscular injection of 1.2 million units for subjects aged 10 years and above and 0.6 million units for subjects below 10 years.

In the experimental arm participants were directly observed to swallow azithromycin tablet with water in the presence of the field team. In the active control arm benzathine benzylpenicillin was reconstituted with sterile water according to the manufacturer’s instructions and injected deep into the left gluteal maximus muscle at slow steady rates.

To ensure maximum privacy, treatment was given one participant at a time in rooms provided by community or school heads away from the view of outsiders. All participants who received treatment were observed for 2 hours after treatment for adverse events. Treatment with both oral azithromycin and injection benzathine benzylpenicillin were free.

3.6.9 Adverse Events Monitoring and Management

To ensure safety the research teams remained in the communities 2 hours after treatment to observe and manage any adverse events following treatment. Adequate supplies of emergency drugs namely hydrocortisone, adrenalin and intra venous infusions were available at each treatment session to ensure effective treatment of possible cases of anaphylaxis.

Teams made up of CBSVs and Health workers were formed in each study community to monitor, document and treat any adverse effects up to 72 hours after the field team had left.

Parents and teachers were counselled on possible adverse events that could occur following the administration of treatment and the need to report these to the nearest health facility or to a CBSV. Local health facilities were on alert to manage and treat all adverse events free of charge. All adverse events following treatment in this trial were documented on Ghana
Health Service standard adverse events forms and sent to the DHMTs for onward transmission to respective regional health offices.

3.6.10 Follow-Ups

Participants were observed over a period of 6 months after treatment. Follow-ups were facilitated by the field team together with local health workers. Participants were followed up both at home and in school at 3 weeks, 3 months and 6 months post treatment.

3.6.10.1 Three Weeks Follow-Up

The 3 weeks follow-up was done by independent outcome assessors who had never come into contact with study subjects and were not privy to subjects’ treatment allocation. Yaws skin lesions were re-examined to determine if there was complete or partial healing. Lesions with complete or partial epitheliazation were classified as healed. Photographs were taken for comparison of pre-treatment and post treatment lesions. Participants whose lesion did not resolve at 3 weeks were retreated with injection benzathine benzylpenicillin.

3.6.10.2 Three and Six Months Follow-Ups

The second and third follow-up at 3 months and 6 months respectively were conducted by the field team and local health workers. Rapid plasma reagin serology tests were repeated for each subject during these follow-ups. Yaws lesions were re-examined for signs of recurrence or new lesions.

3.6.11 Treatment Outcomes

The primary outcome was clinical cure at 3 weeks defined as a total or partial resolution of yaws skin lesions 3 weeks after treatment.

Secondary outcome was serological cure defined as a 4 fold drop in baseline RPR titre within 6 months of treatment.
3.6.12 Treatment Failure

Treatment was considered to have failed if there was no resolution of yaws skin lesion (complete or partial) 3 weeks after treatment.

3.6.13 Lost to Follow-Up

Study participants who were randomized and received treatment but were not available for review at 3 weeks, 3 months or 6 months were considered as lost to follow-up.

3.6.14 Sample Size for Non- Inferiority Trial

In calculating sample size in a non-inferiority trial the non-inferiority margin, power of the test, sensitivity of the standard treatment drug and the probability of types 1 and type 2 errors must be considered. A non-inferiority margin is selected prior to the trial and is based on both statistical reasoning and clinical judgments. The non-inferiority margin is the degree of inferiority of the test treatment to the control, which the trial will attempt to exclude statistically. For this trial 10% is selected as the non-inferiority margin based on effect size of benzathine benzylpenicillin.

With an expected efficacy of penicillin of 95%, a type 1 error of 0.05, and a non-inferiority margin of 10% and assuming that 10% would be lost to follow-up, a sample size of 310 (155 per arm) would give a statistical power of 90% to test the hypothesis.

SSI–STATA software was used to calculate sample size, which was estimated based on an assumption that there is no difference in success rate between the active comparator benzathine benzylpenicillin and the experimental drug azithromycin.
3.6.15 Randomisation

Participants were randomized to the intervention drug a single dose oral azithromycin or the active control single dose of benzathine benzylpenicillin administered as an intramuscular injection of 1.2 million units for subjects 10-15 years, and 0.6 million units for subjects below 10 years.

3.6.15.1 Sequence Generation

Participants were randomly assigned to either oral azithromycin or injection penicillin with a 1:1 allocation ratio as per a computer generated randomization schedule stratified by districts, using permuted blocks of random sizes. The block sizes were not disclosed to ensure concealment.

3.6.15.2 Allocation Concealment

Treatment allocation was concealed from investigators through the use of sequentially numbered, opaque, sealed envelopes that were kept in a safe at the study center and were only opened at the point of treatment by the treatment team.

3.6.16 Implementation

All participants who fulfilled the inclusion criteria and whose parents / guardians gave consent were enrolled into the trial by the research team. Eligible participants were listed by district and by unique trial ID code on a computer at the study center. Randomizations were done by Health Information Officers at the trial center, each trial ID was given a randomization number. Treatment assignment was done using sequentially numbered sealed envelopes labeled with corresponding randomization number and containing a piece of paper with written code designating intervention or control.
3.6.17 Blinding

Owing to the obvious differences between the mode of administration of the two treatment drugs, investigators and study participants could not be blinded to the treatment received. However individuals assessing study outcomes were blinded to treatment allocation, outcome assessors were nurses trained to identify yaws and determine if lesion had healed. Serological tests were conducted in separate laboratories by laboratory technicians masked to participant’s treatment allocation and baseline RPR or TPHA test results. All data on trial participants including treatment allocations were entered on a computer at the study center by independent data entry clerks who had no contact with study participants and were not privy to the type of yaws lesion they presented.

3.7 Quality Checks

The semi structured questionnaire and Case Report Forms were designed by the PI with consistency checks to prevent errors at data collection and data entry. Each questionnaire was given a unique ID number for easy identification and retrieval. The PI ensured effective data collection through regular supervision and retraining of data collectors on the field. All filled questionnaires and CRFs were rechecked by PI to correct all errors and inconsistencies, data collectors went back to the field to fill in missing data within 24-48 hours. To ensure quality data a one- day training on case identification, participant recruitment and data collection was organized at the trial center for health workers involved in trial, field assistants and CBSVs who played various roles in the study.
3.8 Piloting

A pilot study was carried out at Baalagonno, a yaws endemic community in the Ga South district to test the study tools. All areas that needed improvement or corrections were noted during the pilot and where necessary corrections were made and retrainings were done. Interactions between the field team and study participants were observed during the pilot paying particular attention to the treatment teams’ skills in administration of tools and treatment. Time used in treatment and filling of CRFs and questionnaires were noted. Research teams’ ability to detect manages and document adverse events following treatment were observed and corrections were made.

3.9 Statistical Analysis of Clinical Trial

All statistical analyses were carried out in STATA 11.1 (Statacorp, Texas, USA). The clinical trial was designed to assess if azithromycin was non-inferior to benzathine penicillin for the treatment of yaws. With an expected efficacy of penicillin of 95%, a type 1 error of 0.05, and a non-inferiority margin of 10%, and assuming that 10% would be lost to follow-up, a sample size of 310 (155 per arm) would give a statistical power of 90% to test the hypothesis. Analysis of the primary endpoint of clinical cure was estimated by the two-sided 95% confidence interval for the difference in cure rates between the penicillin group and the azithromycin group. Secondary outcome analyses were done using similar methods. Subgroup analyses were performed with stratification by age, sex, baseline RPR titre, household exposure to yaws and stage of clinical yaws.
A two-sided test at a significance level of 0.05 was used in the comparison of baseline characteristics of the two treatment groups.

The per-protocol (PP) analysis included all subjects who completed all study procedures at 6 months. The intention-to-treat (ITT) analysis included all eligible participants who were randomised and treated. Individuals with missing data were considered treatment failures for the purposes of the intention-to-treat analysis.

3.10. Ethical Consideration

The study was approved by the Ghana Health Service Ethical Review Committee (ref: GHS-ERC: 13/11/10). The trial was conducted according to the principles of the Declaration of Helsinki.

3.10.1 Study Area Approval

All directors of health in the study districts were duly informed for their consent for the study namely: the Regional Director of Health Services of the Eastern, Greater Accra and Central Regions, the Municipal Health Director of West Akim, Municipal Health Director Ga South and District Director of Health of the Awutu Senya district. Open forums were organized by the research team to introduce the study to the DHMT members and solicit their help for their support and active case search for yaws in the communities. Permission was also sought from the District chief executives of the study areas to enable access to the communities and also enable cooperation of assemblymen and community members.

3.10.2. Subjects Involved

Written informed consent was sought from parents or guardians of all study participants. Consent forms were administered to parents and guardians on behalf of their wards and to participants above 12 years of age, and those who agreed to participate consented to the study by signing or
thumb printing. Participation in this study was voluntary and decision to participate, stay or withdraw from the study was at the discretion of participant/parents/guardians without any penalty.

3.10.3 Privacy/Confidentiality

All data related to this study was kept confidential and used only for the purpose of the study. The identity of participants was always protected and participants ‘names or identities will not be revealed in any report.

3.10.4 Proposal and Funding Information

The study proposal was developed by me and reviewed by my supervisors to make it scientifically robust. This study was jointly funded by me, the Ghana Health Service and the University Of Ghana School of Public Health.

3.10.5 Registration of Clinical Trial

This trial is registered with Pan African Clinical Trials Registry number PACTR 2013030005181

3.11 Limitations of

Cases were recruited through active case search and as such preclinical or early stage lesions that might have been serologically positive may have been excluded from the study, this may have led to bias.

In this study answers to questions being asked depended on the recall ability of respondents, cases were more likely to recall events preceding the disease compared to their respective controls, recall bias therefore is a limitation in this study. Beliefs about the disease may have also influenced response from cases. To minimize these, questionnaires were administered at
similar times and participants were given enough time to reflect and think through events before answering.

Interviewer bias may have existed in this study due to interviewers’ knowledge of yaws disease which may have influenced the way questions were presented to respondents thereby influencing response. This was minimized by using the same interviewers throughout the study, randomly assigning interviewers data collection assignments, training of interviewers to avoid probing and leading questions, quality checks and field supervision.
CHAPTER FOUR

4.0 RESULTS

4.1 Results of Observational Study

A total of 18,088 subjects aged 1-15 years residing in the study area were clinically screened for yaws from May 2011 to December 2012. Out of 403 children found with suspected clinical yaws skin lesions, 353 were serologically confirmed. There were 247 (70.0%) male subjects; the modal age group was 5-10 years (54.1%).

4.1.1 Yaws Prevalence among Socio-Demographic Groups

The overall prevalence of yaws was 1.95%, prevalence among females was 1.76% compared to 2.05% among males. Within the various age groups prevalence ranged from 1.77% among participants aged below 5 years to 2.02% among those aged 11-15 years (Table 3).

Table 3: Yaws Prevalence by Age Group and Sex: Awutu Senya, Ga South and West Akim Districts, May 2011-December 2012

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Children Examined</th>
<th>No. (%) with Yaws</th>
<th>Prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>1526</td>
<td>27(7.65)</td>
<td>1.77(1.1 to 2.4)</td>
</tr>
<tr>
<td>5-10 years</td>
<td>9874</td>
<td>191(54.1)</td>
<td>1.93(1.7 to 2.2)</td>
</tr>
<tr>
<td>11-15 years</td>
<td>6688</td>
<td>135(38.2)</td>
<td>2.02(1.7 to 2.4)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>12074</td>
<td>247(70.0)</td>
<td>2.05(1.8 to 2.3)</td>
</tr>
<tr>
<td>Females</td>
<td>6014</td>
<td>106(30.0)</td>
<td>1.76(1.4 to 2.1)</td>
</tr>
<tr>
<td>Total</td>
<td>18088</td>
<td>353(100)</td>
<td>1.95(1.8 to 2.2)</td>
</tr>
</tbody>
</table>
Table 3b: Yaws Prevalence by Sex and Age Group: Awutu Senya, Ga South and West Akim Districts, May 2011-December 2012

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>No. Ex.</th>
<th>No. with yaws</th>
<th>Prevalence (95% CI)</th>
<th>No. Ex.</th>
<th>No. with yaws</th>
<th>Prevalence (95% CI)</th>
<th>No. Ex.</th>
<th>No. with yaws</th>
<th>Prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>853</td>
<td>15</td>
<td>1.76 (0.9-2.6)</td>
<td>6553</td>
<td>131</td>
<td>2.0 (1.7-2.4)</td>
<td>4668</td>
<td>101</td>
<td>2.16 (1.7-2.6)</td>
</tr>
<tr>
<td>Female</td>
<td>673</td>
<td>12</td>
<td>1.79 (0.8-2.8)</td>
<td>3321</td>
<td>60</td>
<td>1.81 (1.4-2.3)</td>
<td>2020</td>
<td>34</td>
<td>1.68 (1.1-2.2)</td>
</tr>
<tr>
<td>Total</td>
<td>1526</td>
<td>27</td>
<td>1.77 (1.1-2.4)</td>
<td>9874</td>
<td>191</td>
<td>1.93 (1.7-2.2)</td>
<td>6688</td>
<td>135</td>
<td>2.02 (1.7-2.4)</td>
</tr>
</tbody>
</table>

* Number examined

When analyzed by sex and age females aged 11-15 years had the lowest prevalence of 1.68%, male subjects in the 11-15 years age group had the highest prevalence of 2.16% (Table 3b).
Table 4: Yaws Prevalence by Educational Background, Religion and Ethnicity: Awutu Senya, Ga South and West Akim Districts of Ghana. May 2011-December 2012

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Children screened</th>
<th>No. with confirmed Yaws</th>
<th>Prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In School</td>
<td>14,652</td>
<td>285</td>
<td>1.94 (1.7 to 2.2)</td>
</tr>
<tr>
<td>Out of School</td>
<td>3436</td>
<td>68</td>
<td>1.76 (1.3 to 2.2)</td>
</tr>
<tr>
<td><strong>Religion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Christian</td>
<td>13,602</td>
<td>263</td>
<td>1.93 (1.7 to 2.2)</td>
</tr>
<tr>
<td>Moslem</td>
<td>1212</td>
<td>23</td>
<td>1.90 (1.2 to 2.7)</td>
</tr>
<tr>
<td>Traditionalist</td>
<td>3183</td>
<td>65</td>
<td>2.04 (1.6 to 2.5)</td>
</tr>
<tr>
<td>Others</td>
<td>91</td>
<td>2</td>
<td>2.20 (-0.8 to 5.2)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akan</td>
<td>4269</td>
<td>76</td>
<td>1.78 (1.3 to 2.2)</td>
</tr>
<tr>
<td>Ga</td>
<td>2966</td>
<td>59</td>
<td>1.99 (1.5 to 2.5)</td>
</tr>
<tr>
<td>Ewe</td>
<td>6547</td>
<td>133</td>
<td>2.03 (1.7 to 2.6)</td>
</tr>
<tr>
<td>Northerners</td>
<td>579</td>
<td>12</td>
<td>2.07 (1.0 to 3.2)</td>
</tr>
<tr>
<td>Breku</td>
<td>3364</td>
<td>67</td>
<td>1.99 (1.52 to .5)</td>
</tr>
<tr>
<td>Other</td>
<td>362</td>
<td>6</td>
<td>1.66 (0.4 to 3.0)</td>
</tr>
</tbody>
</table>

Prevalence of yaws cases by education, religion and ethnicity is shown in Table 4; prevalence of yaws was higher among subjects attending school (1.94%) compared to subjects not attending school (1.76%). Among the various ethnic groups prevalence of yaws ranged from 1.66% among subjects classified as other tribes to a high of 2.07% among northerners.
Table 5: Yaws Prevalence by Class Groups: Awutu Senya, Ga South and West Akim Districts of Ghana. May 2011-December 2012

<table>
<thead>
<tr>
<th>Class Group</th>
<th>No. of Children Examined</th>
<th>No. with yaws</th>
<th>Prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-School (Nursery &amp; Kindergarten)</td>
<td>3188</td>
<td>62</td>
<td>1.94 (1.5-2.4)</td>
</tr>
<tr>
<td>Lower Primary (Class 1-3)</td>
<td>7746</td>
<td>154</td>
<td>1.99 (1.7-2.3)</td>
</tr>
<tr>
<td>Upper Primary (Class4-6)</td>
<td>3497</td>
<td>66</td>
<td>1.89 (1.4-2.3)</td>
</tr>
<tr>
<td>Junior High School (JHS1-3)</td>
<td>221</td>
<td>3</td>
<td>1.36 (-0.14-2.9)</td>
</tr>
<tr>
<td>Total</td>
<td>14625</td>
<td>285</td>
<td>1.94 (1.7-2.2)</td>
</tr>
</tbody>
</table>

Out of 285 in-school children with yaws, 54% were in the lower primary classes, 23.2% were in the upper primary classes, 21.8% were preschoolers and 1.05% was in Junior High school. Analysis of prevalence among the various class groups showed that the class group with the lowest prevalence of 1.36% was children in Junior High school and the highest prevalence of 1.99% were children in the lower primary classes. Yaws prevalence was 1.94% among children in nursery or kindergarten and 1.89% among children in the upper primary classes (Table 5).

4.1.2 Prevalence of Yaws by District and Sub Districts

The overall prevalence of yaws in the study area was 1.95%, with a range of 0.96% in the West Akim district and 2.77% in the Awutu Senya district (Table 6). Sub district prevalence is shown in Table 6b, prevalence ranged from a low of 0.35% in the Osenase sub district to a high of 3.70% in the Awutu sub district.
Table 6: District Level and Overall Yaws Prevalence: Awutu Senya, Ga South and West Akim Districts of Ghana. May 2011-December 2012

<table>
<thead>
<tr>
<th>District</th>
<th>No. of children examined</th>
<th>No. with yaws</th>
<th>Prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awutu Senya</td>
<td>4809</td>
<td>133</td>
<td>2.77(2.3 to 3.2)</td>
</tr>
<tr>
<td>Ga South</td>
<td>5474</td>
<td>145</td>
<td>2.65(2.2 to 3.1)</td>
</tr>
<tr>
<td>West Akim</td>
<td>7805</td>
<td>75</td>
<td>0.96( 0.6 to1.0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>18088</strong></td>
<td><strong>353</strong></td>
<td><strong>1.95(1.8 to 2.2)</strong></td>
</tr>
</tbody>
</table>

Table 6b: Sub district Prevalence of Yaws: Awutu Senya, Ga South and West Akim Districts of Ghana. May 2011-December 2012

<table>
<thead>
<tr>
<th>District</th>
<th>Sub District</th>
<th>No. Examined</th>
<th>No. with Yaws</th>
<th>Prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>West Akim</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abankrom</td>
<td>827</td>
<td>4</td>
<td>0.48(0.01-1.0)</td>
</tr>
<tr>
<td></td>
<td>Adeiso</td>
<td>901</td>
<td>20</td>
<td>2.2(1.2-3.2)</td>
</tr>
<tr>
<td></td>
<td>Brekumanso</td>
<td>1563</td>
<td>18</td>
<td>1.1(0.6-11.6)</td>
</tr>
<tr>
<td></td>
<td>Asamankese</td>
<td>2675</td>
<td>21</td>
<td>0.78(0.5-1.1)</td>
</tr>
<tr>
<td></td>
<td>Osenase</td>
<td>569</td>
<td>2</td>
<td>0.35(-0.1-0.8)</td>
</tr>
<tr>
<td></td>
<td>Mepom</td>
<td>1270</td>
<td>9</td>
<td>0.71(0.3-1.1)</td>
</tr>
<tr>
<td><strong>Ga South</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obom</td>
<td>5474</td>
<td>146</td>
<td>2.67(2.2-3.1)</td>
</tr>
<tr>
<td><strong>Awutu Senya</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Awutu</td>
<td>972</td>
<td>36</td>
<td>3.7(2.5-4.9)</td>
</tr>
<tr>
<td></td>
<td>Bawjiwase</td>
<td>3837</td>
<td>97</td>
<td>2.5(2.0-3.0)</td>
</tr>
</tbody>
</table>
4.1.3 Proportion of Communities with Yaws

Distribution of communities with yaws by districts is shown in Table 7. Out of a total of 912 communities in the study area yaws was found in a total of 62 (6.8%) communities; of these the Awutu Senya district had the lowest proportion of 4.3 % compared to 9.2% in West Akim district.

Table 7: Proportion of Communities with Yaws: Awutu Senya, Ga South and West Akim Districts of Ghana. May 2011-December 2012

<table>
<thead>
<tr>
<th>Name of District</th>
<th>No. of Communities in district</th>
<th>No. of Communities with Yaws</th>
<th>% of Communities with Yaws</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awutu Senya</td>
<td>300</td>
<td>13</td>
<td>4.33</td>
</tr>
<tr>
<td>Ga South</td>
<td>362</td>
<td>26</td>
<td>7.18</td>
</tr>
<tr>
<td>West Akim</td>
<td>250</td>
<td>23</td>
<td>9.2</td>
</tr>
<tr>
<td>Total</td>
<td>912</td>
<td>62</td>
<td>6.80</td>
</tr>
</tbody>
</table>

4.1.4 Clinical Presentation of Yaws Lesions

Table 8 shows the clinical presentation of yaws among subjects. The highest numbers of clinical yaws lesions presented by subjects in this study were ulcers (47.3%).

Table 8: Clinical Presentations of Yaws Lesions: Awutu Senya, Ga South and West Akim Districts of Ghana. May 2011-December 2012

<table>
<thead>
<tr>
<th>Lesion</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macule</td>
<td>35(9.92)</td>
</tr>
<tr>
<td>Papule</td>
<td>16(4.53)</td>
</tr>
<tr>
<td>Papilloma</td>
<td>101(28.6)</td>
</tr>
<tr>
<td>Ulcer</td>
<td>167(47.3)</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>25(7.08)</td>
</tr>
<tr>
<td>Maculopapulos</td>
<td>9(2.55)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>353(100)</strong></td>
</tr>
</tbody>
</table>
4.1.4.1. Location of Yaws Lesions

Figure 20: Location of Yaws Lesions: Awutu Senya, Ga South and West Akim Districts of Ghana. May 2011-December 2012

Figure 20 shows location of yaws lesions among subjects. Majority of the lesions (71%) were located on the lower limbs, 11% were located on the upper limbs, 8% were located on the head or face, 6% were located on the trunk and 4% had more than one location.

4.2. Risk Factors Associated with Yaws

4.2.1. Socio-Demographic Characteristics of Cases and Controls

The median age was 10 years among cases and 9 years among controls. The modal age-group was 5-10 years, (51.1%) in cases and (61.1%) in controls. Subjects aged 11-15 years were 41.1% among cases and 27.8% among controls. Subjects below 5 years were 7.8% among cases and 8.9% among controls. There was no significant difference in age-group distribution between cases and controls (p=0.190). (Table 9).
Table 9: Socio-Demographic Characteristics of Cases and Controls: Awutu Senya, Ga South and West Akim Districts of Ghana. May 2011-December 2012

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n, %)</th>
<th>Controls (n, %)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>90</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>26 (28.9)</td>
<td>76 (42.2)</td>
<td>0.033</td>
</tr>
<tr>
<td>Male</td>
<td>64 (71.1)</td>
<td>104 (57.8)</td>
<td></td>
</tr>
<tr>
<td>Age:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>10 (1-15)</td>
<td>9 (1-15)</td>
<td></td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td>7 (7.8)</td>
<td>16 (8.9)</td>
<td></td>
</tr>
<tr>
<td>5-10 years</td>
<td>46 (51.1)</td>
<td>110 (61.1)</td>
<td>0.190</td>
</tr>
<tr>
<td>11-15 years</td>
<td>37 (41.1)</td>
<td>54 (30)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-school</td>
<td>72 (80)</td>
<td>151 (84.4)</td>
<td>0.436</td>
</tr>
<tr>
<td>Out of school</td>
<td>18 (20)</td>
<td>29 (16.1)</td>
<td></td>
</tr>
<tr>
<td>Religion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Christian</td>
<td>67 (74.4)</td>
<td>147 (81.7)</td>
<td></td>
</tr>
<tr>
<td>Moslem</td>
<td>4 (4.4)</td>
<td>11 (6.1)</td>
<td>0.074</td>
</tr>
<tr>
<td>Traditional</td>
<td>19 (21.2)</td>
<td>19 (10.6)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0 (0)</td>
<td>3 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akan</td>
<td>22 (24.5)</td>
<td>56 (31.1)</td>
<td></td>
</tr>
<tr>
<td>Ga</td>
<td>8 (8.9)</td>
<td>30 (16.7)</td>
<td>0.199</td>
</tr>
<tr>
<td>Ewe</td>
<td>32 (35.5)</td>
<td>46 (25.6)</td>
<td></td>
</tr>
<tr>
<td>Northner</td>
<td>4 (4.4)</td>
<td>10 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Breku</td>
<td>22 (24.4)</td>
<td>32 (17.8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.2)</td>
<td>6 (3.3)</td>
<td></td>
</tr>
</tbody>
</table>

Sex distribution among cases and controls is shown in Table 9. There were 64(71.1%) males among cases compared to 26 (28.9%) females; ratio of males to females among cases was 2.5:1. In the
controls there were 104 (57.8%) males and 76 (42.2%) females, giving a male to female ratio of 1.4:1 among the controls. The results showed a statistically significant difference (p-value = 0.033) in sex distribution between cases and controls. In-school subjects formed 80% of cases compared to 83.9% among the controls. Majority of both cases and controls were Christians 67 (74.4%) and 147 (81.7%) respectively. Ewes formed the majority ethnic group in both cases and controls. There was no statistically significant difference in educational, religious and ethnic background of cases and controls (Table 9).

4.2.2. Analysis of Factors Associated with Yaws

Factors analyzed in this study were divided into socio demographic factors, behavioral and environmental factors, results of the univariate analysis of various factors are shown in Table 10.

4.2.2.1 Socio-Demographic factors

The association between yaws and certain socio-demographic factors namely; age group, sex, education, religion and ethnicity was assessed by the estimation of the odds ratios and its corresponding 95% CI in a univariate analysis. The results showed that a male was 1.8 times more likely to have yaws compared to females (OR: 1.8, CI: 1.0-3.2, p-value=0.032). Age group, Religion, education and ethnicity did not show any statistically significant association with yaws (Table 10).
Table 10. Univariate Analysis of Various Risk Factors Assessed for Yaws: Awutu Senya, Ga South And West Akim Districts of Ghana. May 2011-December 2010

<table>
<thead>
<tr>
<th>Factors</th>
<th>No. (%) of Cases</th>
<th>No. (%) Control</th>
<th>OR</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=90)</td>
<td>(n=180)</td>
<td>(95%, CI)</td>
<td></td>
</tr>
<tr>
<td><strong>Socio Demographic:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group(1-10 years)</td>
<td>57(63.3)</td>
<td>123(68.3)</td>
<td>0.6 (0.4-1.2)</td>
<td>0.125</td>
</tr>
<tr>
<td>Sex(male)</td>
<td>64(71.1)</td>
<td>104(57.8)</td>
<td>1.8(1.0-3.2)</td>
<td>0.032*</td>
</tr>
<tr>
<td>Religion(Christian)</td>
<td>67(74.4)</td>
<td>147(81.7)</td>
<td>0.7(0.3-1.3)</td>
<td>0.167</td>
</tr>
<tr>
<td>Ethnicity(Akan)</td>
<td>22(24.4)</td>
<td>56(31.1)</td>
<td>0.7(0.4-1.3)</td>
<td>0.254</td>
</tr>
<tr>
<td>Education(Out-of-school)</td>
<td>18(20)</td>
<td>29(16.1)</td>
<td>1.3(0.6-2.6)</td>
<td>0.426</td>
</tr>
<tr>
<td><strong>Behavioral:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source of Drinking Water</td>
<td>38(42.2)</td>
<td>68(37.8)</td>
<td>1.2(0.7-2.1)</td>
<td>0.480</td>
</tr>
<tr>
<td>Water (river/stream)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source of Bathing Water</td>
<td>40(44.4)</td>
<td>77(42.8)</td>
<td>1.1(0.6-1.8)</td>
<td>0.7945</td>
</tr>
<tr>
<td>Water (river/stream)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bath daily (no)</td>
<td>46(51.1)</td>
<td>46(25.5)</td>
<td>3.04(1.0-5.4)</td>
<td>0.000*</td>
</tr>
<tr>
<td>Always Bath with soap (no)</td>
<td>52(57.8)</td>
<td>66(36.7)</td>
<td>2.4(1.4-4.1)</td>
<td>0.001*</td>
</tr>
<tr>
<td><strong>Environmental:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of house (compound)</td>
<td>70(77.7)</td>
<td>119(66.1)</td>
<td>1.8(1.0-3.4)</td>
<td>0.048*</td>
</tr>
<tr>
<td>Building material of house</td>
<td>72(80.0)</td>
<td>125(69.4)</td>
<td>1.8(0.9-3.4)</td>
<td>0.065*</td>
</tr>
<tr>
<td>(mud)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of occupants of house</td>
<td>26(28.9)</td>
<td>32(17.8)</td>
<td>1.9(1.0-3.5)</td>
<td>0.036*</td>
</tr>
<tr>
<td>(&gt;10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of occupants in bedroom</td>
<td>10(11.1)</td>
<td>5(2.8)</td>
<td>4.4(1.3-16.8)</td>
<td>0.004*</td>
</tr>
<tr>
<td>(&gt;7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Based on case control analysis all variables with P-value of 0.1 or below were entered in a logistic regression model to determine the risk factors that are significantly associated with yaws
4.2.2.2 Behavioral Factors

Behavioral risk factors assessed in the study included source of subjects drinking and bathing water, subject not bathing daily and not always bathing with soap. The results showed an association between yaws and not bathing daily, persons who do not bath daily were 3 times more likely to have yaws compared to those who bathed daily, (OR=3.0, CI: 1.0-5.4, p-value=0.000), there was also a significant association between not always bathing with soap and yaws, persons who do not always bath with soap were 2.4 times more likely to get yaws than those who always bathed with soap (OR= 2.4, CI: 1.4-4.1, p-value=0.001). However results showed no association between sources of drinking and bathing water and yaws (Table 10).

4.2.2.3 Environmental Factors

Several environmental factors were assessed to determine their association with yaws. These included the type of house in which participant lived (single household or compound house), the type of material used to build participants’ house, the number of occupants of participants house, and the number of people sleeping in the same bedroom with participant.

The results showed an association between several environmental factors and yaws namely: compound house (OR= 1.8, CI: 1.0-3.4, p-value =0.048), house with more than 10 occupants (OR=1.9, CI: 1.0-3.5, p-value=0.036), and sleeping in a bedroom with more than 7 occupants (OR= 4.4, CI: 1.4-16.8, p-value =0.004).

Summary of the unadjusted analysis showed that sex, not bathing daily, not always bathing with soap, living in a compound house, living in a house with more than 10 occupants and sleeping in a room with more than 7 occupants were risk factors found to be associated with yaws (Table 10).
4.2.2.4. Multivariate Analysis

In order to control for confounding variables a multiple logistic regression analysis was carried out (Table 11). In the multivariate analysis the risk factors with significant association with yaws were living in a compound house (OR= 2.0, CI 1.0 – 3.8, p-value=0.047) and not bathing daily (OR= 2.4, CI: 1.3-4.4, p value=0.005).

Table 11: Multiple Logistic Regression of Factors Associated with Yaws

<table>
<thead>
<tr>
<th>Factors</th>
<th>Adjusted OR</th>
<th>95% CI Lower bound</th>
<th>95% CI Upper bound</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>1.4</td>
<td>0.7</td>
<td>2.5</td>
<td>0.321</td>
</tr>
<tr>
<td>Material Used to build House (mud)</td>
<td>0.5</td>
<td>0.3</td>
<td>1.1</td>
<td>0.075</td>
</tr>
<tr>
<td>Type of House (compound)</td>
<td>2</td>
<td>1.0</td>
<td>3.8</td>
<td>0.047*</td>
</tr>
<tr>
<td>No. of people sleeping in bedroom (&gt;7)</td>
<td>2.6</td>
<td>0.8</td>
<td>8.5</td>
<td>0.122</td>
</tr>
<tr>
<td>No. of people living in house (&gt;10)</td>
<td>1.5</td>
<td>0.8</td>
<td>3.1</td>
<td>0.233</td>
</tr>
<tr>
<td>Bath daily (No)</td>
<td>2.4</td>
<td>1.0</td>
<td>4.4</td>
<td>0.005*</td>
</tr>
<tr>
<td>Always Bath with Soap (No)</td>
<td>1.6</td>
<td>0.9</td>
<td>2.9</td>
<td>0.099</td>
</tr>
</tbody>
</table>

*Statistically significant
4.3. Results of Randomized Non-Inferiority Trial

To assess validity of reporting and conclusions of the randomized clinical trial the results are reported according to the Consolidated Standards of Reporting (CONSORT) checklist.

4.3.1. Trial Participants

The per-protocol population was selected for primary analysis with supporting analysis in the intention-to-treat population.

**Figure 21: Trial Profile**

- **Enrolment**
  - Assessed for eligibility (n=403)
  - Not meeting inclusion criteria (n=39)
  - Randomized (n=353)

- **Allocation**
  - Allocated to Benzathine Penicillin (n=177), Received Benzathine Penicillin (n=177)
  - Allocated to Azithromycin (n=176), Received azithromycin (n=176)

- **Follow-Up**
  - Lost to follow-up due to relocation (n=15), Refused to continue (n=2), Died (n=1)
  - Lost to follow-up due to relocation (n=6), Refused to continue (n=1)

- **Analysis**
  - Completed study (n=159)
  - Analyzed (n=159)
  - Completed study (n=169)
  - Analyzed (n=169)
The trial profile is shown in Figure 21, from May 2011 to December 2012, four hundred and three subjects with clinically diagnosed yaws lesions were assessed for eligibility; 50 were found to be ineligible (39 were seronegative, 11 declined to participate). Therefore 353 eligible participants were randomly assigned to receive either a single-dose oral azithromycin or a single intramuscular injection of long-acting penicillin. Of the 353 subjects randomised, 25 participants (7.0%) were lost to follow up. Six participants in the azithromycin group relocated and 1 refused to continue participation in the study. In the penicillin group, 15 participants relocated, 2 refused to continue participation and 1 died of an unrelated cause. The remaining 328 participants (169 in the azithromycin group and 159 in the penicillin group) completed the study and were analysed in the per protocol analysis.

4.3.2. Baseline Demographic and Clinical Characteristics of Trial Participants

Demographic and clinical characteristics did not vary between the two treatments groups (Table 12). The mean age of study participants across both groups was 9.5 years (SD: 3.1, range: 1 to 15 years); 274 (70%) were male. Primary yaws was present in 187 cases (53%), 13 participants (3.7%) had fever at presentation, 17 (4.8%) had arthralgia, and 33 (9.4%) had one or more other skin lesions in addition to those of yaws. One hundred and fifty five (43.9%) participants had a baseline RPR titre between 1:4 and 1:16, and 198 (56.1%) had titres between 1:32 and 1:128. One hundred and seventy one participants (48.6%) lived in houses with at least one other individual who had been diagnosed with active yaws within the past one month.

The most frequent clinical lesions were ulcers (167, 47.3%) followed by papillomas (101, 28.6%), hyperkeratosis of the palms and soles (25, 7.1%), while the rest were macules, papules and maculopapular lesions. Three individuals had ulcers with sabre tibia.
Table 12: Baseline Demographic and Clinical Characteristics trial Participants. West Akim, Ga South and Awutu Senya. May 2011-December 2012

<table>
<thead>
<tr>
<th>No. enrolled (n, %)</th>
<th>Penicillin (n, %)</th>
<th>Azithromycin (n, %)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>353</td>
<td>177</td>
<td>176</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>247(70)</td>
<td>124(70)</td>
<td>123(70)</td>
</tr>
<tr>
<td>Females</td>
<td>106(30)</td>
<td>53(30)</td>
<td>53(30)</td>
</tr>
<tr>
<td>Age:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>9.5 (SD:3.1)</td>
<td>9.7 (SD:3.1)</td>
<td>9.3(SD:3.1)</td>
</tr>
<tr>
<td>Clinical Characteristics:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary yaws</td>
<td>187 (53)</td>
<td>94 (53)</td>
<td>93(52.8)</td>
</tr>
<tr>
<td>Secondary Yaws</td>
<td>166(47)</td>
<td>83(47)</td>
<td>83(47.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17(4.8)</td>
<td>6 (3.4)</td>
<td>11(6.3)</td>
</tr>
<tr>
<td>Fever</td>
<td>13(3.7)</td>
<td>4(2.3)</td>
<td>9(5.1)</td>
</tr>
<tr>
<td>Other skin lesions</td>
<td>33(9.4)</td>
<td>15(8.5)</td>
<td>18(10.2)</td>
</tr>
</tbody>
</table>

Table 13: Baseline Clinical Manifestation of Yaws Lesions. West Akim, Ga South and Awutu Senya. May 2011-December 2012

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>No. Enrolled (n, %)</th>
<th>Penicillin (n, %)</th>
<th>Azithromycin (n, %)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macule</td>
<td>35(9.9)</td>
<td>18(10.2)</td>
<td>17(9.6)</td>
<td></td>
</tr>
<tr>
<td>Papule</td>
<td>16(4.5)</td>
<td>10(5.7)</td>
<td>6(3.1)</td>
<td></td>
</tr>
<tr>
<td>Papiloma</td>
<td>101(28.6)</td>
<td>41(23.1)</td>
<td>60(34.1)</td>
<td>0.092</td>
</tr>
<tr>
<td>Ulcer</td>
<td>167(47.3)</td>
<td>92(51.5)</td>
<td>75(42.6)</td>
<td></td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>25(7.1)</td>
<td>14(7.9)</td>
<td>11(6.3)</td>
<td></td>
</tr>
<tr>
<td>Maculopapulos</td>
<td>9(2.6)</td>
<td>2(1.1)</td>
<td>7(4.0)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>353</td>
<td>177</td>
<td>176</td>
<td></td>
</tr>
</tbody>
</table>
4.3.3. Clinical and Serological Cure Rates between Treatment Groups

The primary outcome in this trial was clinical cure defined as total or partial resolution of yaws skin lesions 3 weeks after treatment. Secondary outcomes were serologically defined cure at 3 and 6 months. Cure rates were similar in the 2 treatment groups (Table 14). For the primary outcome of clinical cure, 166 out of 169 participants (98.2%) in the azithromycin group and 155 out of 159 participants (96.9%) in the penicillin group showed complete or partial resolution of yaws lesions 3 weeks after treatment (risk difference: -1.3%, (-4.7 to 2.0)).

Table 14: Per Protocol and Intention-to-Treat Analysis of Endpoints

<table>
<thead>
<tr>
<th>PP Population Analysis</th>
<th>Penicillin (95% CI)</th>
<th>Azithromycin (95% CI)</th>
<th>Risk difference % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=328</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Outcome:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical cure at 3 weeks</td>
<td>96.9% (94.1-99.6)</td>
<td>98.2% (96.2 - 100)</td>
<td>-1.3% (-4.7 to 2.0)</td>
</tr>
<tr>
<td>Secondary Outcome:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serological cure at 3 months</td>
<td>42.8% (35.2-50.7)</td>
<td>36.7% (29.7-44.3)</td>
<td>6.1% (-4.5 to 16.7)</td>
</tr>
<tr>
<td>Serological cure at 6 months</td>
<td>49.1% (41.2-56.9)</td>
<td>57.4% (49.9-64.9)</td>
<td>-8.3% (-19.1 to 2.4)</td>
</tr>
<tr>
<td>ITT Population Analysis N=328</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Outcome:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical cure at 3 weeks</td>
<td>96.6% (92.6-98.5)</td>
<td>98.3% (94.8-99.5)</td>
<td>-1.7% (-5.0 to 1.6)</td>
</tr>
<tr>
<td>Secondary Outcome:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serological cure at 3 months</td>
<td>39.0(32.0 -46.4)</td>
<td>35.2(28.5-42.6)</td>
<td>3.8 (-6.3 to 13.8)</td>
</tr>
<tr>
<td>Serological cure at 6 months</td>
<td>44.6%(34.4-52.1)</td>
<td>55.7%(48.2-62.9)</td>
<td>-11.0 (-21.4 to 0.7)</td>
</tr>
</tbody>
</table>
For the secondary outcome of serological cure 97 out of 169 (57.4%) participants in the azithromycin group showed a 4-fold or greater decline in baseline RPR titres by 6 months after treatment compared to 78 out of 159 participants (49.1%) in the penicillin group. (risk difference: -8.3(-19.1-to 2.4). Azithromycin therefore met the criteria for non-inferiority in both the primary and secondary outcomes. Sub group analysis was in the per protocol population, in all the sub groups azithromycin met the criteria for non-inferiority. For the primary outcome among subjects with primary stage yaws cure rate was 98.9% in the azithromycin group and 98.7% in the penicillin group. For subgroup analysis according to sex, age group, baseline RPR titre and household exposure results were similar (Table 15).

**Table 15: Sub Group Analysis based on Age, Sex, Stage, RPR and Exposure**

<table>
<thead>
<tr>
<th>Age:</th>
<th>Penicillin (95% CI)</th>
<th>Azithromycin (95% CI)</th>
<th>Risk difference % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5years</td>
<td>100%</td>
<td>100%</td>
<td>0</td>
</tr>
<tr>
<td>5-10years</td>
<td>97.6% (90.5-99.4)</td>
<td>97.0% (90.9-99)</td>
<td>0.8 (4.2 to 5.3)</td>
</tr>
<tr>
<td>11-15years</td>
<td>95.4% (86.3-98.5)</td>
<td>100%</td>
<td>-4.6 (-9.7 to 0.5)</td>
</tr>
<tr>
<td><strong>Sex:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>98.2% (93.1-99.6)</td>
<td>97.5% (92.4-99.2)</td>
<td>0.8 (-3.0 to 4.5)</td>
</tr>
<tr>
<td>Female</td>
<td>93.5% (80.9-98.0)</td>
<td>100%</td>
<td>-6.5 (-13.7 to 0.6)</td>
</tr>
<tr>
<td><strong>Clinical Stage of Yaws:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>98.7% (96.2-100)</td>
<td>98.9% (96.7-100)</td>
<td>-0.2(-3.4 to 3.1)</td>
</tr>
<tr>
<td>Secondary</td>
<td>95.0% (90.1-99.9)</td>
<td>97.5% (93.9-100)</td>
<td>-2.5 (-8.4 to 3.4)</td>
</tr>
<tr>
<td><strong>Baseline RPR titre:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:4 -1:16</td>
<td>93.7% (87.5-99.7)</td>
<td>98.6% (96.0-100)</td>
<td>-5.1 (-11.6 to 1.6)</td>
</tr>
<tr>
<td>1:32-1:128</td>
<td>99.0% (96.7-100)</td>
<td>97.9% (95.0-100)</td>
<td>1.1 (-12.5 to 4.6)</td>
</tr>
<tr>
<td><strong>Household Exposure:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>98.7% (96.1-100)</td>
<td>92.6% (94.2-100)</td>
<td>1.1(-3.4 to 5.3)</td>
</tr>
<tr>
<td>Not exposed</td>
<td>95.1% (90.2-99.9)</td>
<td>8.8% (96.5-100)</td>
<td>3.8(-9.0 to 1.5)</td>
</tr>
</tbody>
</table>

* Data are for Per-Protocol analysis.
4.3.4 Treatment Failure

Three (1.8%) participants in the azithromycin group and 4 (2.5%) in the penicillin group with ulcerative yaws lesions did not resolve 3 weeks after treatment and were classified clinically as “treatment failure”. All participants considered “treatment failure” were re-treated with intramuscular benzathine benzylpenicillin, ulcers resolved in 2 weeks. Four participants with ulcerative lesions which had healed at 3 weeks and had achieved serological cure were found to have recurred during the 3 months follow up. Of these 2 (1.2%) occurred in the azithromycin group and 2 (1.3%) in the penicillin group. Subjects were treated with benzathine benzylpenicillin and lesions resolved.

4.3.5 Adverse Events

No incidence of serious adverse events related to the treatment drugs were reported in this trial. Minor adverse events were reported by 4 participants (2.4%) in the azithromycin group, most commonly gastrointestinal upset, and 8 participants (5%) in the penicillin group, most commonly pain at the injection site.
Figure 22: Before and After Treatment with Azithromycin
Figure 23.: Before and after Treatment with Injection Benzathine benzylpenicillin
CHAPTER FIVE

5.0 DISCUSSIONS

Resurgence of yaws in countries in which the disease was almost eradicated fifty years ago has become a public health issue that needs to be addressed both globally and locally. Although yaws has been targeted for eradication by 2020, epidemiological information to guide control programmes is spars. For the goal of eradication to be achieved, identification and treatment of cases must be accompanied by actions that will mitigate the effects of factors that favor transmission (146).

5.1. Epidemiological Characteristics of Yaws

5.1.1. Prevalence of Yaws in Awutu Senya, Ga South and West Akim districts

The results of this study confirm that yaws is endemic in the Awutu Senya, Ga South and West Akim districts of Ghana. Yaws was found focalized in 62 out of a total of 912 communities in the study area. The overall prevalence of yaws among children aged 1-15 years in the study area was 1.95%, however when analyzed by districts prevalence ranged from 0.96% in the West Akim district to a high of 2.77% in the Awutu Senya district. Sub district prevalence ranged from 0.35% to a high of 3.7%. These district and sub district prevalence may hide localized high burden of the disease in certain communities, resulting in high rates of infectivity in these communities. The findings are similar to results of a yaws treatment survey in 2008 in three purposively selected districts in the Eastern Region of Ghana and bordering the districts of this study, which found a prevalence of 1.92% suspected yaws cases among children in basic schools (18). Studies conducted in other countries sharing boundaries with Ghana have also shown similar results. In a treatment survey in Cameroon among 6000 children in 2 districts by Coldiron and others the prevalence
of serologically confirmed yaws was 2.9%. Studies by Toure in 3 districts in Togo found a clinical prevalence rate of 1.0% -3.9% (118), another study by Toure and others in the Ivory Coast reported notified yaws at an incident rate of 0.5%, a follow up cross sectional survey showed a clinical prevalence rate of 5% (147). Yaws prevalence studies in Vanuatu and the Solomon Islands showed similar findings (148). Although the true extent of the current yaws problem is not yet fully determined globally, the results of these isolated studies reaffirms the fact that despite the successes of the WHO/UNICEF yaws eradication campaigns of the 1950s and 1960s, integration of yaws control activities with other national public health activities has led to its resurgence and calls for renewed global and individual efforts in the control of the disease.

Prevalence of yaws within the various age groups ranged from 1.77% among children below 5 years to 2.02% among children aged 11-15 years. In a study which investigated the histories of about 2000 yaws patients in Jamaica the greatest numbers of infection were children in the second five year period in life (15). Studies by Findley in West Africa however put the peak incidence between 2 to 5 years of age with a gradual decline towards puberty(149).

Prevalence of yaws is described as equal between males and females, some studies have however found a slightly higher prevalence among males; similar to findings in this study which found the prevalence among males (2.05%) slightly higher than prevalence among females (1.76%).

This study found a slightly higher prevalence of yaws among children found attending school at the time of the study (1.94%), compared to children who were not in school (1.76 %). However in the study area there was no clear distinction between an in-school child and an out-of-school child. A child found in school at registration may be found as an out-of-
school child during follow-up or vice versa, yaws is a poverty related disease and most children registered in school at the beginning of the year usually leave school in the rainy season to help their parents on their farms, a child may also drop out of school due to lack of school uniforms. During meetings with parents and guardians on yaws, investigators used the opportunity to convince them on the need to keep their children in school throughout the year. Where possible children who were out of school due to lack of school uniforms were provided with uniforms through the help of local NGOs.

Studies by De Silva concluded that there was no racial immunity to yaws, and given the same circumstances such as poverty, unhygienic and insanitary surroundings any racial type will be affected in an endemic area (150). This was consistent with findings in this study, which showed infection in all ethnic groups and religions in the study area with no significant difference in prevalence between these groups.

Seventy one percent of yaws lesions in this study were located on the lower limbs, similar to findings in a study by Turner which found that 75.5% of initial yaws lesions were located on the legs and feet (151). Yaws lesions have preponderance for the lower limbs due to the fact that children are the most affected and in warm tropical areas where yaws occurs their clothing may not cover their legs and arms, they also tend to sustain injuries to their limbs during play. Two subjects with ulcerative yaws lesions had advanced sabre tibia which had rendered one of them invalid and unable to attend school.

In this study we observed that although most community members knew that yaws could advance and cause deformities, the disease was accepted as part of growing up and parents did not see the need to send their children to hospital when they have yaws. This is significant in yaws detection and management; most yaws cases will not report to health facilities although there is available treatment and will often end up with the tertiary forms of the
disease which involves scaring and deformities. This calls for effective strategies to detect and manage cases and contacts that focus on community involvement. Regular screening of children and treatment of cases and contacts through sustained community campaigns and the setting up of sensitive surveillance systems that ensures that all new and recurrent cases are detected and treated are the options available to enable the achievement of eradication. This could be achieved through collaboration between the health sector, education sector and community opinion leaders.

The high school enrollment offers an opportunity to incorporate yaws control activities in school activities, this offers the opportunity for effective and efficient yaws control activities through the school health program which is an integral part of child health services rendered by the health sector in all schools. Teachers could be trained to identify early yaws for notification to the health sector to ensure prompt treatment of both cases and contacts.

5.2 Risk Factors Associated with Yaws

A case control study with a community based control was performed to test the hypothesis that there is no difference in the characteristics of people who have yaws and those who do not. The study investigated the effect of several socio-demographic characteristics including sex, age, religion, education, and ethnicity as risk factors for yaws, and also looked at the association between several behavioral and environmental factors and yaws.

The association between sex and yaws was assessed in the univariate analysis, and showed that a male child was 1.8 times more likely to have yaws compared to a female (OR=1.8, CI: 1.1-3.2). The higher risk among males may be due to several reasons: firstly males are more susceptible to trauma due to the fact that they are more active as children and prone to injuries, secondly at school going age girls are better clothed than boys and clothing protects skin from trauma therefore reducing the incidence of yaws among females and thirdly males
are more likely to sleep in more crowded rooms compared to females thereby increasing their chance of infection with yaws (12, 100).

Seventy five percent of persons affected by yaws are children aged below 15 years, with a peak incidence in the 6-10 age groups. This study assessed the association between age group as a socio-demographic factor and yaws infection, and found no significant association between yaws and age groups. The risk of yaws among subjects aged 1-10 years was not significantly different than the risk in those above 10 years.

When the association between ethnicity, religion and educational backgrounds as social factors and yaws was assessed, the univariate analysis found no association between yaws and ethnicity, religion and education. This is consistent with findings in other studies which showed that given the same circumstances such as poverty, unhygienic and insanitary surroundings any person could be affected in an endemic area (150).

In assessing behavioral factors associated with yaws, it was observed that subjects who did not have their baths daily were 3 times more likely to get yaws compared to those who bathed daily (OR=3.0, CI:1.0-5.4). Always bathing with soap was protective against yaws, the univariate analysis showed that subjects who did not always bath with soap were 2.4 more likely to have yaws compared to those who always bathed with soap (OR=2.4, CI:1.4-4.1). The results are consistent with other studies which describes yaws as a disease that attacks persons with poor socio-economic circumstances with low standard of hygiene (101). The study did not however show an association between the sources of drinking and bathing water and yaws.

Overcrowding has been described as a non-specific factor in yaws infection, several studies have shown a high risk of yaws in crowded environments with poor hygienic conditions (12). This study showed that persons living in a compound house was 1.8 times more likely to
have yaws compared to those who do not (OR=1.8, CI: 1.0-3.4). Compound houses have multiple households living in them and are often more crowded therefore posing a higher risk for yaws compared to single households which are less crowded.

Yaws is transmitted through direct skin to skin contact, therefore living in a house or sleeping in a room with many occupants was more likely to increase the risk of transmission of yaws, in this study we found that a person sleeping in a room with more than 7 occupants was 4.4 times more likely to have yaws compared with those who slept in a room with fewer people (OR=4.4, CI: 1.3-16.8), and a person living in a house with more than 10 occupants was 1.9 times more likely to have yaws compared to persons living in a house with fewer occupants (OR=1.9, CI: 1.0-3.5).

However living in a compound house and not bathing daily were the two factors still significant in the multivariate analysis.

5.3 Comparison of Cure Rates between Treatment with Azithromycin and Penicillin

The second hypothesis: ‘Clinical cure rate’, in subjects treated with a single dose of oral azithromycin is inferior to clinical cure rates in subjects treated with a single injection of benzathine benzylpenicillin by more than 10%’ is refuted in this study. In the randomized non-inferiority trial we demonstrated that the cure rate for azithromycin was not inferior to that achieved with injection benzathine penicillin, in fact cure rates among participants treated with azithromycin was higher than cure rates among those treated with penicillin in both primary and secondary outcomes and in subgroup analysis of primary outcome. Clinical cure rate was 98.2% in the azithromycin group and 96.9% in the penicillin group. The 95% confidence interval for the difference in cure rate ranged from -4.7 to 2.0 in favour of azithromycin. For the secondary outcome of serological at 6 months cure rate was 57.4% in the azithromycin group 49.1% in the penicillin group. The 95% confidence interval for the
difference in cure rate ranged from -19.1 to 2.4 in favour of azithromycin. Azithromycin was non-inferior to intramuscular penicillin in all subgroup analysis, confirming the robustness of this conclusion.

The results of this study is similar to a randomized trial that compared the efficacy of a single oral dose azithromycin to a single dose of injection penicillin for the treatment of early syphilis in Tanzania, the cure rates after 6 months in the azithromycin group was 85.5% compared to a cure rate of 81.5% in the penicillin group (23).

Serological cure rate defined by a 4 fold drop in baseline RPR was much lower in this study compared to the results of a multicentre randomized clinical trial involving patients with syphilis in which results showed that serological cure among the azithromycin group was 77.6% compared to 78.5% among the penicillin group (135). In this trial, 42.6% of participants treated with azithromycin and 50.9% of those treated with penicillin did not achieve serological cure. However it is clinically and serologically impossible to distinguish treatment failure from re-infection. As this study was conducted in an endemic community where exposure to antibiotics is uncommon, it is possible that many of these cases probably reflect re-infection rather than treatment failure. Failure to achieve serological cure may also have been due to prolonged antibody excretion after eradication of pathogens.

Azithromycin was well tolerated by participants, with no serious adverse events reported after treatment. Side effects were mild to moderate, most commonly gastrointestinal upset, in keeping with the known side effect profile of the drug.

Results of this study showed that a single oral dose of azithromycin given at a dosage of 30mg/kg was non-inferior to a single dose of intramuscular benzathine benzylpenicillin for
the treatment of yaws, consistent with a previous study conducted in Papua New Guinea (152).

Treatment of yaws with azithromycin calls for caution as azithromycin treatment failure among patients with *T. pallidum* subspecies *pallidum* has been widely reported in high-resource settings where overuse of antibiotics is common. Treatment failure is associated with a single amino acid mutation at position 2058 and 2059 in the 23S rRNA gene (153), which prevents binding with the bacterial 50S ribosomal subunit. Resistance of *T. pallidum* subspecies *pertenue* to azithromycin has not yet been documented. Although populations in yaws endemic areas are typically not exposed to excessive antibiotic use, there is a clear need to strengthen surveillance systems and closely investigate possible treatment failures for evidence of azithromycin resistance.

These findings offer a second opportunity in yaws eradication efforts. A single dose oral drug that is equally effective and avoids the challenges of the standard drug is key to achievement of eradication by 2020. The use of azithromycin for the treatment of yaws is a significant milestone in the health care system strengthening for several reasons: The standard drug for the treatment of yaws injection penicillin faces a lot of financial challenges because of the cost of logistics like syringes, needles, swabs, water for injection needed with injection use. This is avoided by the use of a single dose oral azithromycin and these extra costs could be channelled to health education on yaws and strengthening yaws surveillance.

The use of azithromycin also affords an opportunity for strengthening collaboration between the health sector and other informal health care givers including teachers, health volunteers, opinion leaders and parents/guardians. The standard treatment with injection requires the use of trained health workers who can administer treatment by injection; the health system however does not have adequate numbers of skilled workers especially in rural communities.
Oral azithromycin is easy to administer and side effects are mild, the services of informal healthcare givers within the communities could be solicited for the distribution of azithromycin in mass yaws treatment campaigns.

Community participation in mass treatment has several advantages to both the health system and the community. Firstly there is a higher possibility of uptake of oral intervention in a community-distributed approach to mass drug treatment. Secondly there is cost saving as drug distributors will come from communities and cost of transportation to reach target population will be reduced. Thirdly collaboration between the health sector and the community in yaws treatment will empower the communities and foster good relationship between the health sector and community. Lastly community participation in mass drug treatment with azithromycin offers an opportunity for capacity building of community members through improved knowledge and experience in yaws management and reporting.

There were a number of limitations in the randomised clinical trial; most notable was the inability to mask treatment assignments due to the fact that azithromycin was administered orally whilst benzathine benzylpenicillin was by intramuscular injection. To mitigate these, independent assessors blinded to treatment allocation evaluated trial outcomes. Secondly neither darkfield microscopy, PCR nor cultures of lesion exudates were performed in this study, we could not determine whether lesions that did not heal or recurred were true treatment failures or recurrence or were due to mixed infection with other organisms.

Thirdly the definition of serological cure in research on treatment of treponemal infections usually poses problem. The true rates of cure may be overestimated or underestimated due to the imprecision of the definition of cure (23). To address this in the trial laboratory technicians were blinded to the treatment assignments of participants and therefore the comparison of cure rates between the treatment groups could not be biased. Fourthly
participants in this trial were followed up for only 6 months, after which no serological or clinical data were collected. It is possible that if individuals had been followed up to 12 months that the rate of serologically confirmed cure may have been higher in both groups.

In the course of this study there have been two major breakthroughs that favours accurate diagnosis of yaws. A rapid diagnostic point-of-care test originally developed for syphilis which detects both treponemal and non-treponemal antibodies has shown to be effective for the diagnosis of yaws. The dual POC test offers opportunity for screening and confirmation of the serological status of patients with suspected yaws within 15 minutes, therefore giving a better indication of active disease for early treatment (154).

Although standard PCR- assays cannot distinguish yaws from venereal syphilis, in the course of this study PCR assays developed at the CDC are now able to differentiate yaws from syphilis. Based on this new development data collected in the West Akim district of Ghana in 2013 showed that only 42% of ulcers and papillomas clinically diagnosed as yaws were *T. pertenue* positive, 26% were due to *H. Ducreyi* with the rest PCR negative. The significance of this finding is that yaws can be serologically and PCR confirmed therefore avoiding the wrong diagnosis of the disease. This finding also offers the opportunity to further investigate the aetiologies of various skin lesions that have in the past been classified as yaws in other to apply the appropriate treatment for cure.

This randomized controlled trial has clearly demonstrated that a single oral 30mg/kg dose of azithromycin is non-inferior to a single dose of intramuscular injection of benzathine benzylpenicillin for the treatment of early yaws in Ghana. Oral treatment with azithromycin overcomes the logistical and operational problems of treatment with IM penicillin, especially in resource-poor countries where yaws occurs. These findings support the use of a single dose oral azithromycin as the optimal regimen in yaws eradication programs.
Interpretation

The availability of an orally effective treatment for yaws is key if the goal of eradication of yaws is to be attained. In this trial the efficacy of azithromycin for the treatment of yaws is demonstrated in a second setting, confirming its place in the WHO yaws eradication strategy (11). Effective treatment of yaws involves treatment of whole communities, azithromycin is well suited to administration by community health volunteers, even in poorly resourced rural communities where yaws occurs. A recent study has demonstrated the impact of a single round of mass treatment with azithromycin in reducing transmission of yaws in Lihir Island, Papua New Guinea(155).

The sustained success in the use of penicillin in the treatment of yaws and the report of azithromycin - resistant *T. pallidum* calls for caution. Resistance of syphilis treponemes to azithromycin has been found to be geographically clustered; although azithromycin has been used in the treatment of syphilis in HIV/AIDS patients in Ghana no cases of resistance have been reported. To avoid resistance of yaws treponemes to azithromycin, surveillance systems must be put in place to monitor all treatment failures.
6.0. CONCLUSION AND RECOMMENDATIONS

6.1. Conclusion

This study set out primarily to demonstrate the efficacy of a single oral dose of azithromycin compared to the standard benzathine benzylpenicillin for the treatment of yaws through a randomised controlled non-inferiority trial. The epidemiological characteristics of yaws including the burden within the various socio demographic groups and risk factors associated with the disease among children in the study area are also described.

The study concludes that a single oral dose of azithromycin given at a dosage of 30mg/kg is non-inferior to intramuscular benzathine benzylpenicillin for the treatment of early yaws. This finding is particularly useful in developing countries in removing the requirement for logistics and trained health personnel needed to administer treatment by intramuscular injection during mass campaigns.

6.2. Recommendations

In view of the findings of this study the following recommendations are made:

The Ministry of Health/Ghana Health Service

- Support follow-up studies to determine the efficacy of 20mg/kg versus 30mg/kg azithromycin for the treatment of yaws, since a dosage of 20mg/kg has been used successfully in the treatment of blinding Trachoma in Ghana
• Organise prevalence surveys nationwide to determine true burden of the disease in the country to inform government on resources needed for treatment

• Organise mass treatment campaigns for cases and their contacts using azithromycin tablets for treatment

**District Health Management Teams**

• Integrate active yaws surveillance into school health activities and sensitize teachers on clinical diagnosis and reporting

• Plan health education activities for schools pupils paying particular attention to the male child and personal hygiene

• Regularly sensitize clinicians on yaws diagnosis, treatment and follow-up

• Sensitize communities on yaws disease, its risk factors and treatment

• Strengthen surveillance at all levels through regular training and sensitization of health workers and CBSVs on clinical manifestations of yaws.

• Set up community health teams to relay health education information including yaws treatment and prevention to community members.

**District Assemblies**

• Support DHMTs of endemic districts financially on yaws eradication activities including community sensitization on treatment and prevention
Ghana Education Service

- Intensify education on personal hygiene with special attention to male children
- Collaborate with Ghana Health Service in school based research on yaws
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APPENDICES

APPENDIX A

Consent Form

(To be translated into local languages)

A SINGLE DOSE ORAL AZITHROMYCIN VERSUS INTRAMUSCULAR BENZATHINE BENZYLPENICILLIN FOR THE TREATMENT OF YAWS – A RANDOMISED NON INFERIORITY TRIAL IN GHANA

Name of Child: ____________________________ ID No. ____________________________

Due to the frequent reports from the Ghana Education Service about the high incidence of yaws among school children in your district, a research is being conducted to determine the true burden of yaws amongst school children in your district and to determine if azithromycin a drug whose mode of administration is not painful and has fewer adverse effects can be as effective as the standard drug of treatment injection Benzathine benzylpenicillin. Children between the ages of 1-15 years with yaws lesions will be recruited into the study, and treated with either oral azithromycin or injection penicillin. If oral Azithromycin is found to be as effective as injection Benzathine penicillin, it could replace injection Benzathine penicillin in the treatment yaws cases. The advantages of treatment with azithromycin is that there will not be the need for a trained health worker to administer treatment; Community Based Surveillance Volunteers could distribute medicine to people with yaws and their contacts within the communities.

Your child or ward is being invited to take part in the research study. During this study participants will be randomly assigned to receive treatment with either injection benzathine penicillin or oral azithromycin. Photographs of yaws lesions will be taken before drugs are administered. Blood samples will be taken to the laboratory for test before treatment and at 3 months and 6 months after treatment. Yaws lesions will be reexamined 3 weeks after treatment to determine if the lesion has healed.

The possible discomforts of treatment will be pain at injection site and some gastrointestinal discomfort.
After obtaining information we will be able to determine the true burden and risk factors associated with yaws in your district. The results will also enable us decide whether to replace injection penicillin with oral azithromycin for the treatment of yaws.

You are assured that information collected will be handled with strict confidentiality. Your child will be given a research code and will not be named in any report. With the exception of the principal investigators no other persons will have access to information about your child. All data about this research will be kept in a password secured computer.

Any cost that will be incurred by you during this research due to the adverse effects of drugs administered will be refunded. Participation in this study is voluntary and decision to participate, stay or withdraw from study is at the discretion of participant and parent/guardian without any penalty.

Thank you for your cooperation, information provided will contribute to efforts to eradicate yaws in the near future.

Contacts for Additional Information:

If you have further enquiries or concerns about this research contact the principal investigator:

Dr Cynthia Kwakye-Maclean,
Ga West MHMT,
Ghana Health Service.
Amasaman
Tel:0244121272
I have been given an opportunity to have any questions about the research answered to my satisfaction. I permit my child/ward to participate in study.

_________________________________________  _________________________________________________
Date                                                                             Signature / Right Thumbprint (parent/guardian/pupil)

If parent/guardian cannot read the form themselves, a witness must sign here:

I was present while the benefits, risks and procedures were read to the volunteer. All questions were answered and the parent/guardian has agreed for their child/ward to take part in the research.

_________________________________________  _________________________________________________
Date                                                                             Signature/Right Thumbprint of Witness

I certify that the nature and purpose, the potential benefits, and possible risks associated with participating in this research have been explained to the above individual.

_________________________________________  _________________________________________________
Date                                                                             Name and Signature of person who Obtained Consent
APPENDIX B
A SINGLE DOSE ORAL AZITHROMYCIN VERSUS INTRAMUSCULAR BENZATHINE BENZYPENICILLIN FOR THE TREATMENT OF YAWS – A RANDOMISED NON INFERIORITY TRIAL IN GHANA

Clinical Screening Record Form

<table>
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</tr>
</thead>
<tbody>
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<td>1. Is child in school (tick):</td>
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<td>□ No</td>
</tr>
<tr>
<td>2. Name of School:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Class:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Age:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Sex (tick): Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>6. Skin Problem Present(tick):</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>7. Yaws Lesion Present:</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>8. 5mls of blood taken for TPHA and RPR tests:</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>9. Other Skin Lesions Present:</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>10. Enrolled:</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>11. Referred for Treatment</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
APPENDIX C

A SINGLE DOSE ORAL AZITHROMYCIN VERSUS INTRAMUSCULAR BENZATHINE BENZYL-PENICILLIN FOR THE TREATMENT OF YAWS – A RANDOMISED NON INFERIORITY TRIAL IN GHANA

School/Community Recruitment Form

<table>
<thead>
<tr>
<th>Section A: Demographic Data</th>
<th>Section B: History and Clinical Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Name of Participant (First/Last)</td>
<td>8. Fever: ☐ Yes ☐ No</td>
</tr>
<tr>
<td>2. Age:</td>
<td>Adenopathy: ☐ Yes ☐ No</td>
</tr>
<tr>
<td></td>
<td>Arthralgia: ☐ Yes ☐ No</td>
</tr>
<tr>
<td>3. Is child in school (tick): ☐ Yes ☐ No</td>
<td>Other Medical conditions Specify:</td>
</tr>
<tr>
<td>If yes proceed to question 4</td>
<td>9. Type of Yaws lesion (tick): ☐ Ulcer ☐ Papiloma ☐ Macule</td>
</tr>
<tr>
<td></td>
<td>☐ Papule ☐ Maculopapule ☐ Hyperkeratosis</td>
</tr>
<tr>
<td></td>
<td>Other (Specify):</td>
</tr>
<tr>
<td></td>
<td>10. Location of yaws lesion (Tick): ☐ Upper limb ☐ Lower limb ☐ Head/ Neck/</td>
</tr>
<tr>
<td></td>
<td>☐ Trunk</td>
</tr>
<tr>
<td></td>
<td>11. Stage of yaws (tick): ☐ Primary ☐ Secondary</td>
</tr>
<tr>
<td></td>
<td>12. Photograpg Taken (tick): ☐ Yes ☐ No If yes Photo ID #:</td>
</tr>
</tbody>
</table>

Unique ID: [ ] District: [ ]
### Section C: Results of Serology Test

<table>
<thead>
<tr>
<th>13.</th>
<th>TPHA Test:</th>
<th>Positive</th>
<th>Negative</th>
<th>Baseline RPR Titre:</th>
</tr>
</thead>
</table>

### Section D: Referral (Tick as appropriate)

| 14. | Referred? (tick): | Yes | No |

### Section E: Details of Person Completing Form

<table>
<thead>
<tr>
<th>15.</th>
<th>Name: (First/Last)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Date(dd/mm/yyyy):</td>
</tr>
<tr>
<td></td>
<td>Phone Number:</td>
</tr>
</tbody>
</table>
APPENDIX D

A SINGLE DOSE ORAL AZITHROMYCIN VERSUS INTRAMUSCULAR BENZATHINE BENZYL-PENICILLIN FOR THE TREATMENT OF YAWS – A RANDOMISED NON INFERIORITY TRIAL IN GHANA

Treatment Allocation Form

Treatment Date: dd/mm/yyyy

Randomization number: ________________

<table>
<thead>
<tr>
<th>Section A : Study identifiers and Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Unique ID:</td>
</tr>
<tr>
<td>2. Age:______________ years</td>
</tr>
<tr>
<td>3. Weight:________kg</td>
</tr>
<tr>
<td>4. Height:__________cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section B: Treatment (Randomization of TPHA positive and RPR&gt;1:4 cases only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Group 1: Benzathine Penicillin (0.6 million units if Age &lt;10 years, 1.2 million units if Age ≥10 years)</td>
</tr>
<tr>
<td>6. Group 2: Azithromycin (30mg/kg)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section C: Details of person completing the form</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Name: (First/Last)</td>
</tr>
<tr>
<td>Date (dd/mm/yyyy): __________ / ______ / _______</td>
</tr>
<tr>
<td>Phone Number: ________________________________</td>
</tr>
</tbody>
</table>
APPENDIX E

A SINGLE DOSE ORAL AZITHROMYCIN VERSUS INTRAMUSCULAR BENZATHINE BENZYLПENICILLIN FOR THE TREATMENT OF YAWS – A RANDOMISED NON INFERIORITY TRIAL IN GHANA

Three Week Follow-Up Form

Review Date: dd/mm/yyyy

<table>
<thead>
<tr>
<th>Randomization number:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>School/Community Name:</td>
<td></td>
</tr>
</tbody>
</table>

**Section A: Demographic Data**

1. Name of participants(First/Last):

2. Unique ID:

**Section B: Treatment Outcome**

3. [ ] Completely Healed [ ] Partially Healed [ ] No Improvement

5. Photograph Taken: [ ] Yes [ ] No Photo ID# ______________

**Section C: Treatment and Referral**

6. Treatment of persistent lesion:
   - Benzathine penicillin [ ] 0.6MU or [ ] 1.2MU

7. Referred: [ ] Yes [ ] No

9. Comments:

**Section D: Details of Person Completing Forms**

10. Name: (First/Last) _______________________________________
    Date(dd/mm/yyyy): _____ / _____ / ________
    Phone Number: ____________________________
### Section A: Demographic Data

1. **Name of participants (First/Last):**

2. **Unique ID:**

3. **Available at 3 months follow-up:**
   - [ ] Yes
   - [ ] No
   
   **If No give reasons:**

### Section B: Status of Patient

4. **Lesion Completely Healed**
   - [ ]
   **Lesion Not Healed**
   - [ ]
   **Lesion Recurred**
   - [ ]

5. **Photograph Taken:**
   - [ ] Yes
   - [ ] No
   **Photo ID#:**

### Section C: Serology Test

6. **Blood Taken for RPR test:**
   - [ ]
   **5mls Blood Taken**
   - [ ] Yes
   - [ ] No
   
   **If No give reasons why:**

7. **Referred:**
   - [ ] Yes
   - [ ] No

### Section D: Details of Person Completing Forms

10. **Name (First/Last):**

11. **Date (dd/mm/yyyy):**

12. **Phone Number:**

---

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APPENDIX G
A SINGLE DOSE ORAL AZITHROMYCIN VERSUS INTRAMUSCULAR BENZATHINE BENZYLPPENICILLIN FOR THE TREATMENT OF YAWS – A RANDOMISED NON INFERIORITY TRIAL IN GHANA

Six Months Follow-Up Form

Date: dd/mm/yyyy: ______________

<table>
<thead>
<tr>
<th>School/Community Name:</th>
</tr>
</thead>
</table>

**Section A: Demographic Data**

1. Name of participants (First/Last):

2. Unique ID:

3. Available at 3 months follow-up: ☐ Yes ☐ No
   If No give reasons: ___________________________________________

**Section B: Status of Patient**

4. ☐ Lesion Completely Healed ☐ Lesion Not Healed ☐ Lesion Recurred

5. Photograph Taken: ☐ Yes ☐ No Photo ID# __________

**Section C: Serology Test**

6. Blood Taken for RPR test:
   5mls Blood Taken: ☐ Yes ☐ No
   If No give reasons why: ______________________________________

7. Referred: ☐ Yes ☐ No

9. Comments:

**Section D: Details of Person Completing Forms**

10. Name: (First/Last) ___________________________________________

    Date(dd/mm/yyyy): _____ / _____ / _______

    Phone Number: ___________________________
**APPENDIX H**

A SINGLE DOSE ORAL AZITHROMYCIN VERSUS INTRAMUSCULAR BENZATHINE BENZYL-PENICILLIN FOR THE TREATMENT OF YAWS – A RANDOMISED NON INFERIORITY TRIAL IN GHANA

**Adverse Events Reporting Form**

<table>
<thead>
<tr>
<th>Randomization Number: ______________________</th>
<th>Date:</th>
</tr>
</thead>
</table>

**Section A : Demographic Data**

1. Name:  

2. Age:  
   | Sex: | Male | Female |

3. Address:  

4. Enrolment Site:  

**Section B: Medicine Given:**

5. [ ] Benzathine Penicillin  [ ] Azithromycin  

7. Dose Given:  

8. Date medication Given:  

9. Batch Number:  

**Section C: Adverse Event Details**

10. Date and Time patient Seen:  

11. Person reporting AE:  
   | Patient | Relative | Study Clinician | Other (Specify) |

12. Symptoms:  
   - Abdominal Pain  
   - Nausea  
   - Vomiting  
   - Diarrhea  
   - Fever  
   - Headache  
   - Dizziness  
   - Pain at injection site  
   - Allergic reaction  
   - Anaphylaxis  
   - Other (Specify) .................................................................  

13. Details of Adverse Event:  

**Section D: Action Taken:**
Details of Treatment Given:

Outcome: Hospitalised □  Recovered □  Died □

Section C: Details of person completing the form

Name: (First/Last) ______________________________
Date(dd/mm/yyyy): _____/_____/_______
Phone Number: ____________________
APPENDIX I

A SINGLE DOSE ORAL AZITHROMYCIN VERSUS INTRAMUSCULAR BENZATHINE BENZYPENICILLIN FOR THE TREATMENT OF YAWS – A RANDOMISED NON INFERIORITY TRIAL IN GHANA

Semi Structured Questionnaire for Case Control Study

<table>
<thead>
<tr>
<th>Date:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Community/ School</th>
<th>District:</th>
</tr>
</thead>
</table>

**Section A: Socio-Demographic Data**

1. Name of Participant(First/Last)  
2. Code:

3. Is child in school (tick): [ ] Yes [ ] No  
   If yes go to question 4.

4. Name of School: __________

4b. Class: __________

5. Age: ________  
6. Sex (Tick): [ ] Male [ ] Female

7. Religion(tick): Christian [ ] Moslem [ ]
   Traditional [ ] Other [ ]

8. Ethnicity (tick): Akan [ ] Ga [ ] Ewe [ ] Northners [ ] Breku Other [ ]

9. Community of Residence:

**Section B: Environmental Factors**

10. What type of material is your house built with?(tick):
    Mud [ ] Cement [ ] Block [ ] Wood [ ] Raffia [ ] Others [ ]


12. How many people live in your house?(tick):
    1-3 [ ] 4-7 [ ] 8-10 [ ] More than 10 [ ]

13. How many people sleep in your bedroom?(tick):
    1-3 [ ] 4-7 [ ] More than 7 [ ]

**Section C: Behavioral factors**
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>14.</td>
<td>Do you bath daily? (tick):</td>
<td>Yes [   ] No [   ]</td>
</tr>
<tr>
<td>15.</td>
<td>Do you always bath with soap? (tick):</td>
<td>Yes [   ] No [   ]</td>
</tr>
<tr>
<td>16.</td>
<td>Where do you obtain your drinking water? (tick):</td>
<td>Handdug well [   ] Borehole [   ] Pond [   ] Pipe [   ] River/Stream [   ]</td>
</tr>
<tr>
<td>17.</td>
<td>Where do you obtain your bathing water? (tick):</td>
<td>Handdug well [   ] Borehole [   ] Pond [   ] Pipe [   ] River/Stream [   ]</td>
</tr>
</tbody>
</table>

**Section D: Details of Person Completing Forms**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>15.</td>
<td>Name of Interviewer:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Name: (First/Last)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Date (dd/mm/yyyy):</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phone Number:</td>
<td></td>
</tr>
</tbody>
</table>

**Early Stage Yaws lesions**