PREVALENCE AND ANTIBIOTIC SUSCEPTIBILITY PATTERN OF GROUP A STREPTOCOCCUS IN CHILDREN WITH ACUTE PHARYNGITIS

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DECLARATION

This dissertation is my original work and has not been presented for the award of a degree in any other university

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ABBREVIATIONS

AAP	American Academy of Paediatrics
AOR	Adjusted Odds Ratio
ARF	Acute Rheumatic Fever
CDR	Clinical Decision Rules
CME	Continuous Medical Education
GAS	Group A *Streptococcus*
KNH	Kenyatta National Hospital
KNH ERC	Kenyatta National Hospital Ethics and Research Committee
MCS	Microscopy Culture and Sensitivity
MHC	Major Histocompatibility Complex
PANDAS	Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections
PEU	Pediatric Emergency Unit
RADT	Rapid Antigen Detection Test
RHD	Rheumatic Heart Disease
UON	University of Nairobi
WHO	World Health Organisation

DEFINITIONS

Acute Pharyngitis: symptoms of inflammation of the throat and/or tonsils present less than one week

Exudates: white/yellow material or spots covering the tonsils or the back of the throat

Palatal petechiae: pinpoint erythematous spots on the soft palate

Pharyngitis: inflammation of the throat and/or the tonsils

Scarlatiniform rash: erythematous, fine, popular rash, typically beginning in the groin or the axilla then spreading to the trunk and extremities, followed by desquamation

Tonsillitis: inflammation of the tonsils

ABSTRACT

Background: GAS pharyngitis remains an important infection in children due to its potential to cause Acute Rheumatic Fever and Rheumatic Heart Disease. These are complications that are preventable with the initiation of timely and appropriate antibiotics.

Objectives: The primary objective of this study was to determine the prevalence and antibiotic sensitivity of GAS isolates in children aged 2-15 years who presented to KNH PEU with acute pharyngitis.

Materials and Methods: This was a descriptive cross sectional study conducted at KNH PEU. It assessed 198 children who met the inclusion criteria and whose parents provided informed consent and participants who provided informed, written assent The participants were recruited through consecutive sampling until the required sample size was met. Using a questionnaire, guardians and participants were interviewed to determine sociodemographic and clinical characteristics. Participants underwent a clinical assessment and throat swabs which were subjected to RADT and Throat Cultures for microscopy, culture and sensitivity.

Results: Of 198 children with acute pharyngitis 76 had GAS (38.4%) There was significant association with a scarlatiniform rash (AOR 2.7; 95% CI 1.0-7.0; P value 0.044) and an inflamed pharynx (AOR 1.9; 95% CI 1.1-3.6; P value 0.032) with GAS. The antibiotic susceptibility pattern of GAS isolates revealed resistance to Augmentin (11.8%), amoxicillin (26.3%) and erythromycin (35.5%)

Conclusion: The prevalence of GAS in children aged 2-15 years who present with acute pharyngitis in KNH is 38.4%. 11.8% of GAS isolates are resistant to Augmentin, while 26.3% are resistant to amoxicillin. 35.5% are resistant to erythromycin

Recommendation: We recommend that all negative RADT results should be followed up with a throat culture as well as continuous surveillance of antibiotic resistance patterns to improve the use of antibiotics in hospitals

1. BACKGROUND

Streptococcus pyogenes also known as Group A Streptococcus (GAS) is a facultative, gram positive coccus that occurs in chains or pairs. It is catalase and oxidase negative, non-motile, and non-sporing, responsible for a diverse spectrum of infections, both invasive and non-invasive. It is a ubiquitous organism whose only known reservoir is the skin and mucous membranes of the human host.

Group A Streptococcus (GAS) infections, despite the introduction of effective antibiotics, remain common. There are an estimated 18.1 million people suffering from a serious GAS disease, with another 1.78 million new cases occurring each year with approximately 500,000 deaths.(1) These diseases range from minor infections, to life threatening illness. Complications of GAS infections, both suppurative and non-suppurative are common and cause severe morbidity and mortality.

Most GAS infections begin in the throat or on the skin of a susceptible host and each year, the World Health Organization (WHO) reports conservatively that there are 111 million cases of streptococcal pyoderma and 616 million new cases of GAS pharyngitis every year.(1) Upper respiratory tract infections account for a substantial portion of visits to clinical services and almost 30% of such illnesses feature a sore throat as a primary symptom. While the most common agents causing pharyngitis are viruses, GAS pharyngitis, is the most common cause of bacterial pharyngitis in children aged 5-15 years, responsible for 15-30% of all cases of pharyngitis in this age group. It is rare before 2-3 years of age, has a peaks in early school years, in children aged 5-15 years and declines in adolescence and adulthood. (2)

There is considerable overlap between the clinical features of GAS pharyngitis and viral and other bacterial throat infections that may not require antibiotic treatment. There is no single symptom or sign that will reliably identify GAS as the cause of pharyngitis and the use of clinical algorithms such as the modified Centor Criteria have time and again, proved ineffective in predicting the presence of GAS in children. (3) The modified Centor Criteria is a scoring system that assigns points to signs and symptoms to ultimately identify the likelihood of GAS pharyngitis to guide testing and treatment.

Figure 1: Modified Centor Criteria

Criteria	Points
Absence of Cough	1
Swollen and tender anterior cervical nodes	1
Temperature >38C	1
Age (years)	
3-14	1
15-44	0
45+	-1
Cumulative Score	

Guidelines for Management

-1,0,1 points

No antibiotic, no throat culture

Risk of GAS <10%

2,3 points

Throat culture Antibiotic if Positive

Risk of GAS 2points 15% 3points 32%

4 points

RADT or throat culture, treat if positive

Risk of GAS 56%

Clinicians who rely solely on clinical judgement risk underestimating streptococcal pharyngitis or prescribing antibiotics where they are not necessary. The diagnosis is supported by a positive microbiologic test in patients with symptoms of GAS pharyngitis in the absence of viral signs and symptoms

While positive throat cultures remain the gold standard for identification of GAS, newer and faster Rapid Antigen Detection Tests (RADT) have been introduced into clinical practice. RADTs offer the benefit of diagnosis at point of care within a relatively short time- minutes compared to 48-120 hours for culture. (4) Tests with high specificity (>95%) allow appropriate

initiation of treatment after a positive test,. Various assessments of the impact on antibiotic prescription rates following the introduction of highly specific RADTS into clinical practice have found reductions in the prescription of antibiotics to children where they are not needed of between 30%. (4) and 42.6% (5) The end result is a reduction in antibiotic costs to the patient by as much as 80% as demonstrated by Kose, Sirin et al in 2016. (5) RADTs however, are less sensitive than culture, depending on the commercial kit used. A large multicenter study carried out in resource limited countries reported a wide range from 72.4%- 91.8% (6) The factors associated with this include the expertise and the training of the user as well as the quality of the specimen collected from the throat(4). With this in mind, as per American and European guidelines where these RADTs are routinely used in practice, a confirmatory throat culture is recommended to confirm a negative test if the clinical suspicion of GAS is high to avoid missing children who would test positive following culture and require antibiotics (7)

Although the symptoms of GAS pharyngitis, treated and untreated tend to resolve spontaneously in a few days, its identification and treatment with an appropriate course of antibiotics remains of paramount importance. The early initiation of antibiotics not only hastens clinical recovery by 12-24 hours, it also reduces the period of infectivity as patients are non-contagious as early as 24 hours after the initiation of therapy, reducing transmission to close contacts. Schwartz, Kim et al enrolled 111 children who tested positive for GAS on a RADT for follow up after receiving a single dose of amoxicillin. A second throat swab, performed 12-24 hours later resulted in non-detection of GAS in 91% of these children. (8) Appropriate antibiotic use also prevents the development of suppurative and non-suppurative complications. The persistence of GAS in the upper respiratory tract may elicit an immune response that leads to the development of Acute Rheumatic Fever (ARF) if the host is predisposed genetically and the strain is rheumatogenic. Penicillin, the first line drug of choice world over, in non-allergic patients, has been shown to be effective in preventing primary attacks of ARF even when commenced as late as 9 days after the onset of acute illness (9).

Penicillin or amoxicillin, given over the course of ten days, remains the drug of choice for the treatment of GAS except in patients allergic to it. It is a beta lactam antibiotic that binds to penicillin binding proteins to inhibit the synthesis of peptidoglycans- a major component of the bacterial cell wall, thereby compromising the integrity of the bacterial cell. The concerns over

the long duration of therapy, the cost to the patient, and potential issues over compliance have led to the evaluation of the duration of treatment. In 1981, Schwartz et al demonstrated a significantly greater failure rate (31%) in a group of patients receiving Pen V over seven days compared to patients receiving ten days (18%) supporting the recommendation of a longer duration of therapy (10). Newer studies concluded that three to six days of oral antibiotics had comparable efficacy compared to the standard ten-day treatment. A shorter duration, resulted in better compliance, but more side effects, such as abdominal pain, diarrhea and vomiting. Moreover, the risk of bacteriological recurrence was worse in the short duration treatment. The authors concluded that a short duration was safe and efficacious but only in countries with low rates of ARF and RHD (11)

Penicillin is also relatively affordable, has a narrow spectrum of activity, adverse reactions are infrequent and it is highly effective. To date penicillin resistant GAS strains have not been documented.(9, 12) Macrolides such as erythromycin have long been recommended for patients with penicillin allergies. However, the increased emergence of erythromycin resistant strains has been noted in the United States, Canada and Yemen leading to the development of current guidelines which recommend first generation cephalosporins as an alternative for penicillin-allergic patients. (13, 14). Clindamycin. azithromycin or clarithromycin are also recommended as effective options in penicillin allergic individual

1.1 PATHOGENESIS OF GAS AND ACUTE RHEUMATIC FEVER

Infections are initiated by adherence of the microorganism to human epithelial cells of the nasal and oral cavities as well as the skin. Its capsule, composed of hyaluronic acid resembles host connective tissue allowing the bacterium to go unrecognized as antigenic. This capsule also protects the organism from opsonisation and phagocytosis by neutrophils or macrophages.(1)

The cell wall is a chemically complex structure, with antigenic components that contribute to its success as a pathogen. These include capsular polysaccharide (C Substance), cell wall peptidoglycan and lipoteichoic acid. In addition, it also contains a host of surface proteins including, fibronectin binding proteins, fimbrial proteins, M protein, and cell bound

streptokinase. The M protein which extends from the cell membrane of GAS is its major virulence factor. It facilitates resistance to phagocytosis, by neutrophils. The fimbrial like proteins adhere to and bind human extracellular matrix proteins such as fibronectin, laminin and collagen and once human epithelial tissue is colonized and invaded, the pathogen uses a variety of defense mechanisms to evade natural host immunity and initiate infections.

GAS secretes proteases that degrade Complement C3b and inhibitors of complement C5a. C5a is a known chemotaxin, which recruits neutrophils and it has been demonstrated that in invasive GAS infections, there is no neutrophil migration to the site of infection. Moreover, GAS inhibits Membrane Attack Complex (MAC) polymerization, and thus it escapes from neutrophils and the complement system, the cornerstones of innate immunity.

Having successfully evaded the immune system, the organism survives and grows, spreading hematogenously to various tissues and organs. It carries with it a variety of secretory proteins and products that mediate its invasion and pathogenesis. These include leukocidins such as Streptolysin S, NADase and Streptolysin O. Hyaluronidase facilitates spreading, by digesting host connective tissue. Streptokinases lyse fibrin and its proteases are implicated in tissue necrosis and toxic shock syndrome. Pyrogenic exotoxins (A, B and C) as well as superantigens (9 described so far) bind class II MHC molecules directly resulting in the release of massive amounts of pro-inflammatory cytokines. Activation of the innate immune system leads to GAS antigen presentation to T Cells. B and T cells respond through the production of immunoglobulins (M and G) and activation of CD4+ T Cells.

Following infection with GAS, if left untreated, the infected host is at risk of developing complications. Suppurative complications include tonsillopharyngeal abscess or cellulitis, sinusitis, otitis media, skin and tissue infections, and streptococcal bacteremia. Non suppurative complications include ARF, poststreptococcal reactive arthritis, acute glomerulonephritis, PANDAS syndrome, scarlet fever and streptococcal toxic shock syndrome.

In susceptible hosts, following a latent period (2 weeks) some may develop ARF. The pathogenesis is thought to be through molecular mimicry whereby there is a cross reactive immune response that involves both humoral and cellular components of the adaptive immune

system. This cross reaction is responsible for the clinical features of ARF: transient arthritis through immune complex formation; carditis due to antibody binding and infiltration of T cells; chorea secondary to antibody binding on the basal ganglia.

In less industrialised nations ARF and RHD affects over 33 million people and is the leading cause of cardiovascular death in the first 50 years of life.

In a summary of population based studies on the incidence of ARF worldwide, Tibarzawa, Mayosi et al found that ARF occurs most commonly in children aged 5-15 years with a worldwide incidence of 19 per 100,000 school aged children(15) However, the incidence of ARF in industrialised nations ids much lower at <2 cases per 100,000 school aged children(16). The high incidence in economically disadvantaged countries is largely due to environmental factors such as household overcrowding and poor ventilation which favours increased transmission of GAS. Jaine, Baker et al examined household crowding as a risk factor for the development of ARF and enrolled 1249 patients with ARF between 1996 and 2005. They found that ARF rates were positively and significantly related to household crowding after controlling for age, ethnicity and household income with an incidence ratio of 1.065 (95% confidence interval).(17)

2. LITERATURE REVIEW

2.1 ACUTE PHARYNGITIS

A sore throat is listed as the primary symptom in approximately 30% of all visits to paediatricians, with symptoms of an upper respiratory tract infection, in the United States. (18) Viral agents are the most common causes of pharyngitis, *adenovirus, rhinovirus enterovirus, coronavisus, Respiratory Syncitial Virus, metapneumovirus and Epstein-Barr Virus* and *herpes* are frequently implicated. Other organisms associated with pharyngitis include *Group C Streptococcus, Mycoplasma pneumonia, Neisseria gonnorhoeae, Fusobacterium necrophorum, Arcanobacterium haemolyticum* and *Corynebacterium diptheriae.*

These organisms are spread from person to person through large droplet nuclei. Transmission is facilitated through close contact, subsequently, daycare facilities, schools, dormitories and homes are important environments for spread. These infections tend to increase in colder months and in the temperate regions, they are prevalent in winter, fall and spring. The drivers for the seasonality of GAS infections remain unknown and it has been postulated that an interplay between climate, behavioral patterns (crowding indoors when it's cold outside) and the incidence of predisposing viral infections may explain this. (17)

With regards to clinical features there is considerable overlap between sore throats of viral and bacterial origin. Viral pharyngitis is likely to be of more gradual onset with rhinorrhea, diarrhea, conjunctivitis, coryza, hoarseness and cough featuring more prominently. A sore throat, usually of acute onset, fever, headache, vomiting, abdominal pain and nausea usually in the absence of cough, have been reported in children, who have tested positive for GAS. The pharynx is red and the tonsils are enlarged and classically covered in a yellow, blood tinged exudates. The anterior cervical lymph nodes are enlarged and often tender. There may be petechiae or "doughnut" lesions on the soft palate and posterior pharynx. The uvula may be red, stippled and swollen. The incubation period is 2-5days and as such, a sore throat that lasts more than a week is unlikely to be GAS pharyngitis. Some patients may demonstrate signs of scarlet fever with circumoral pallor, a strawberry tongue and an erythematous popular rash. (2)

These clinical features are not pathognomic for GAS and several attempts have been made to correlate the clinical features with the isolation of GAS, with limited success. The WHO Acute

Respiratory Infection Control Program and the WHO IMCI Adaptation Guidelines suggest a Clinical Decision Rule (CDR): acute streptococcal pharyngitis should be suspected and presumptively treated when pharyngeal exudates plus enlarged cervical lymph nodes are found. The main aim of employing a CDR strategy is to identify a group of children who are at low risk of GAS pharyngitis in order to avoid antibiotic use in these (low risk) patients and to propose a plan of action such as a throat swab or a throat culture in patients identified as high risk by the CDR.(19)

Several studies have been carried out to evaluate the utility of the WHO CDR for streptococcal pharyngitis and the results have been astonishing. In 2005, Ramza et al carried out a large multicenter study to assess the WHO CDR for GAS pharyngitis in three countries, Brazil, Croatia and Cairo. 2225 children aged 2-12 with cough, rhinorrhea, red or sore throat were considered eligible and 1810 children were enrolled. While the number of children presenting with sore throat who were found to have GAS varied widely (ranging from 24.6% in Brazil to 42.0% in Croatia)they found that the CDR was low at all sites , failing to detect up to 96% of children with laboratory confirmed GAS.(19)

Le Marechal, Martinot et al conducted a meta-analysis and analyzed 171 references of CDRs for diagnosing GAS pharyngitis in children. The articles involved 10523 children, with a mean age of 7 and a mean prevalence of 34% of GAS pharyngitis. They concluded, as several other studies have, that no single symptom was sufficient for diagnosis and that symptoms alone are insufficient to rule out this diagnosis. Most CDRs (they examined 4 derived and 12 validated CDRs) had poor specificity. They determined that the CDR should be used to focus rapid diagnostic tests to children with high risk of GAS pharyngitis to reduce antibiotic use. (20)

This underscores the futility of relying on the presentation of the child to distinguish between GAS and viral pharyngitis and makes a strong case for screening and testing for diagnosis of GAS

2.2 GAS PREVALENCE ARF AND RHD

In addition to the acute illness, GAS infections are responsible for a number of post streptococcal sequelae. Suppurative complications include tonsillopharyngeal cellulitis or abscesses, sinusitis

otitis media, and necrotizing fasciitis. Non suppurative complications include scarlet fever, toxic shock syndrome, acute glomerulonephritis, Pediatric Autoimmune Neuropsychiatric Disorders associated with Streptococcal infections (PANDAS). The greatest burden of GAS disease is Acute Rheumatic Fever (ARF) and the subsequent development of Rheumatic Heart Disease (RHD)

ARF and RHD are a significant disease burden, especially in less industrialised nations. There are over 15 million cases of RHD worldwide with 282000 new cases and 233000 deaths per year. An estimated 79% are from less developed nations.(1)

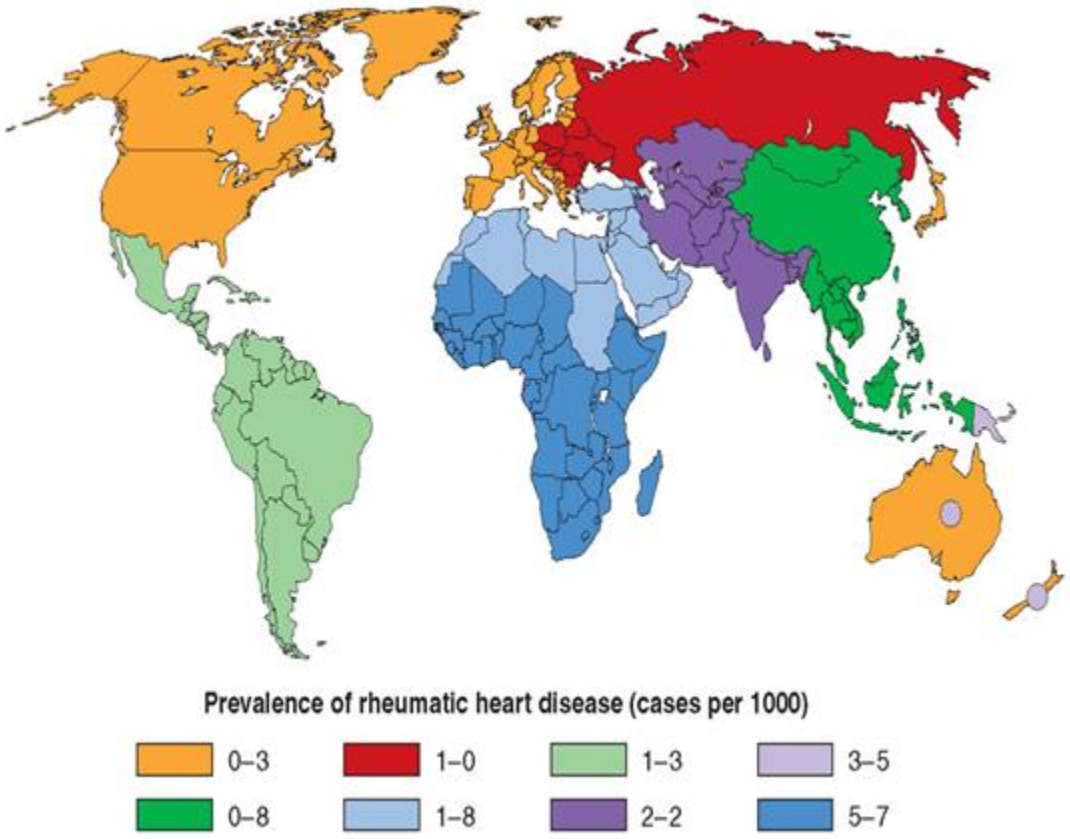


Figure 2: Worldwide Prevalence of RHD

Shaikh et al in a 2010 meta-analysis of 17 studies carried out in industrialized and developing countries calculated a pooled prevalence estimate of 37% among children presenting with a sore throat (21). There was a dearth of data from Africa and only one study, a multicenter study done in Egypt, Croatia and Brazil met the inclusion criteria. In addition, they found that GAS was more prevalent in the winter months and amongst children aged 5-15 years.

Data from India, a lower- middle income country like Kenya with a similar tropical climate, varies widely. Singh, Kumar et al carried out a cross sectional study to determine the prevalence of GAS pharyngitis and enrolled 300 school children from six schools in Uttar Pradesh India, of whom 63 were symptomatic. Only 3 of these children tested positive giving an overall prevalence of 1%. (22) While over a period of 2 years, (2000-2002) the results of a cross sectional survey in which 4249 children participated the prevalence of GAS pharyngitis was found to be 15.2% (23)

From a hospital based study carried out in Jimma, in South West Ethiopia, Tesfaw, Abdissa et al studied 355 children with pharyngitis, over a six-month period from March to December 2013. 40 of 355 children tested positive for GAS resulting in a prevalence of 11.3% with a slight preponderance in females at 57.7% The mean age of children who tested positive was 8.5 years. The antimicrobial drug susceptibility profile revealed that all isolates of GAS were susceptible to penicillin, erythromycin, clindamycin, chloramphenicol, ceftriaxone and amoxicillin. It was noted however, that more than half, 52.5% of GAS isolates were noted to be resistant to tetracycline. The authors observed that the low prevalence may have been attributed to the seasonality of GAS infections further underscoring the importance of continuous surveillance to provide a more complete understanding of the actual burden of disease. From this study, the absence of cough, presence of exudates, tonsillar swelling and a fever >38 were found to be independent predictors of GAS (24)

In an assessment of 146 children in Zambia in 2012, Chisambo found only 22 had positive throat cultures for GAS giving a prevalence of 15.1%. Among the clinical features, cervical lymphadenopathy, tonsillar exudates, fever, scarlatiniform rash and conjunctivitis were associated with GAS pharyngitis. Of note, none of the features were statistically significant,

further underlining the need for testing in children. All GAS isolates were sensitive to penicillin (100%) while only 81% demonstrated sensitivity to erythromycin, which is in keeping with studies from the west which indicate an increasing resistance to erythromycin

2.3 DIAGNOSIS AND TREATMENT

Timely and accurate diagnosis of GAS is essential to reduce the duration and severity of symptoms, prevent disease transmission and prevent suppurative complications as well as acute rheumatic fever

A pharyngeal swab specimen, correctly sampled and plated yields culture results that are 90-95% sensitive. (25) This remains the microbiological gold standard for identification of GAS. However, throat culture and sensitivity testing depends on optimal conditions to promote the growth of beta hemolytic colonies, which may take 48-72 hours. Rapid Antigen Detection Tests, depending on the kit used, have specificity ranging from 90-99%. (26, 27) and sensitivity varies widely from 72-91%(6) Moreover, specimens should be obtained before initiation of antimicrobial therapy since a single dose of antibiotics can result in a negative culture or RADT

American and European guidelines, where these kits are often used in practice, still recommend that all initial negative RADT results are followed up by a throat culture. RADT may miss as many as 30% of GAS pharyngitis which can lead to misdiagnosis, spread of GAS and an increase in complications (2, 27)

Macrolides are recommended as a first line treatment option for patients with penicillin allergies. Of grave concern is the increasing incidence of macrolide resistant strains cropping up in centers across the world. In 2002 Martin, Green et al studied 1794 throat cultures obtained from school age children in Pittsburgh and using the Kirby –Bauer disk diffusion test, screened these isolates for resistance to erythromycin and found that 48% of the isolates were resistant. (13) while in Italy a national surveillance program on antibiotic resistance revealed a 20 fold increase in erythromycin resistant strains of GAS in several centers across the country (28) Furthermore there have been documented cases of macrolide treatment failure that resulted in acute rheumatic fever (29)

The 2016 Kenyan clinical guidelines for the management of common conditions in Level 3-6 hospitals advise a full blood count and a throat swab if possible as investigations for patients who

present with pharyngitis or tonsillitis. By way of management, if conjunctivitis is present, treat symptomatically at home. If the patient presents with tender lymph nodes, yellow spots or a membrane on the tonsils, treat empirically as suspected GAS with amoxicillin. Erythromycin is also recommended as first line therapy for patients allergic to penicillin. The current antibiotic susceptibility pattern of GAS isolates in Kenya is unknown.

3. STUDY JUSTIFICATION

The primary prevention of Acute Rheumatic Fever, the autoimmune inflammatory sequelae that follows GAS infections involves the identification of children at risk, and elimination of GAS with timely and appropriate antibiotics before the immune response is initiated.

There is growing evidence of increasing resistance to erythromycin from studies carried out in the West and current Kenyan guidelines recommend erythromycin as first line therapy in patients allergic to penicillin.

This study will provide hospital based data on the prevalence of GAS pharyngitis and investigate the current antibiotic sensitivity pattern of GAS. This data may then inform policy on the appropriate allocation of resources on diagnosis and treatment of children who present with pharyngitis.

4. STUDY OBJECTIVES

4.1 PRIMARY OBJECTIVE

1. To determine the prevalence of Group A Streptococcus in children aged 2-15 years presenting with pharyngitis at Kenyatta National Hospital outpatient services

4.2 SECONDARY OBJECTIVES

1. To describe the clinical profile of the study participants
2. To determine the antibiotic susceptibility pattern of Group A Streptococcus isolates

5. METHODOLOGY

5.1 STUDY DESIGN

This was a cross sectional descriptive study.

5.2 STUDY POPULATION

The study population was comprised of children aged 2-15 years who presented with pharyngitis to Kenyatta National Hospital pediatric outpatient services; whose caregivers gave informed consent and where applicable those who assented to the administration of a questionnaire, a physical exam and a throat swab.

5.3 STUDY AREA

Participants were recruited in the Pediatric Emergency Unit of Kenyatta National Hospital, Kenya's largest teaching and referral hospital. Approximately 50,000 patients are seen annually at the PFC where triage is done to determine patients who require admission or outpatient management. Children who present with tonsillitis or pharyngitis are usually seen by a specialist pediatric clinical officer and an estimated 700 patients are seen every month with tonsillitis and pharyngitis.

5.4 STUDY PERIOD

The study was carried out during the 1st quarter of 2018. The period was terminated when the sample size was achieved

5.5 SELECTION AND ENROLLMENT OF PARTICIPANTS

5.5.1 INCLUSION CRITERIA

1. The participant aged between 2 and 15 years.
2. The participant presented with pharyngitis.
3. Written informed consent for study participation obtained from their parents or informants and written informed assent where applicable

5.5.2 EXCLUSION CRITERIA

1. Child aged less than 2 years or over 15 years.
2. A child who had not obtained written informed consent from their parent or informant to participate in the study. Children for whom assent was applicable who had not assented to the study.
3. A child who was on antibiotics or who had been treated with antibiotics in the week preceding the study

5.6 SAMPLE SIZE DETERMINATION

The sample size was determined using Fisher's Formula for sample size determination in prevalence studies

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

Where:

Z - standard normal value corresponding to 95% confidence interval for a two sided test = 1.96

P - estimated prevalence of GAS carriage in children aged 2-15 years (15.2%)

From a study carried out in India on prevalence of GAS pharyngitis by Kumar, Vohra et al this was estimated to be 15.2% (18)

Where **N** is the desired sample size, **Z** is the normal standard deviation corresponding to 95% confidence interval for a two sided test (1.96) and **P** is the estimated prevalence (15.2%). **D** is the margin of error = 5%

Substituting into the formula, ***n*** was 198.

5.7 PARTICIPANT RECRUITEMENT PROCEDURE

Approval to carry out the study was sought from the Kenyatta National Hospital –University of Nairobi Ethics Research Committee (KNH-UON ERC).

Once the relevant approval to carry out the study was obtained, the study employed simple random sampling whereby any participant presenting with pharyngitis to the Kenyatta National Hospital Pediatric Outpatient Services who met the eligibility criteria and provided written informed consent and assent where applicable was enrolled into the study.

The principal investigator and/or research assistants made it clear that the study was voluntary and non-participation would have no repercussions. The consent and assent forms contained a brief introduction, information about the study; described its purpose, the study procedure to be followed and the potential benefits and risks of participating in the study. It also contained information on safeguarding the participant's privacy and the sharing of the study's findings. The investigator conducted the consent discussion and confirmed that the informant understood the information provided on the consent and assent form. Any pertinent questions regarding the study from the informant were answered prior to signing the consent form. Consent obtained was voluntary and free from coercion

Data were then collected by means of a structured, pre tested questionnaire and a physical examination. Throat swabs were taken from all participating children.

5.8 DATA COLLECTION MANAGEMENT AND ANALYSIS

5.8.1 DATA COLLECTION

Following participant recruitment, data were collected from enrolled children or their caregivers using a pre-tested questionnaire administered by the interviewer. The interviewer was the principal investigator and two research assistants. The research assistants were qualified Pediatric Clinical Officers who underwent a half day training on data collection and filling the questionnaire prior to the study. They were also trained by the principal investigator on how to examine the participants and take throat swabs as per the study protocol.

The participant was subjected to a physical examination. Two throat swabs were taken. The first was tested using the RADT the second was transported to the laboratory for microscopy, culture and antibiotic susceptibility testing

5.8.2 PARTICIPANT/CAREGIVER INTERVIEW & QUESTIONNAIRE

Enrolled participants and caregivers in cases where the participant was unable to answer questions themselves were interviewed using a structured pre-tested questionnaire, which assessed the following: Biodata and socio-demographic information. Participant's symptoms-spectrum and duration. Odynophagia, headache, fever, nausea, vomiting, abdominal pain, cough, rhinitis, conjunctivitis,

5.8.3 PHYSICAL EXAMINATION

The participant was examined for the following signs: fever, palatal petechiae, uvulitis, cervical lymphadenopathy, tonsillar exudates, scarlatiniform rash, and conjunctivitis.

5.8.4 PARTICIPANT THROAT SWABS

Following Good Laboratory Practices, the investigator carrying out the test wore protective clothing, used disposable gloves, goggles and a mask.

Samples were labelled with the participants allocated study number

Throat swab Method: adapted from WHO guidelines for the collection of specimens from the throat.

- The swab was removed from its packing.
- The participant's head was tilted back and the throat was illuminated.
- The tongue was depressed with a clean tongue depressor.
- The specimen was collected with a sterile swab from the tonsils and the back of the throat avoiding the teeth, gums, tongue and cheek surfaces. Two swabs were taken
- The swabs were placed in its container and closed firmly, then labelled with the study ID issued to the participant.
- The used tongue depressor and gloves were discarded in a yellow dustbin with a yellow bin liner (clinical waste).
- The first swab was subjected to an RADT The second swab was placed in a Ziploc bag labelled biohazard for transportation to the laboratory for processing, within 1hour of collection.
- After processing in the laboratory, the soiled swab was discarded in a yellow dustbin with a yellow bin liner

5.8.4.1 RADT

The RADT used was the Detector *Strep A* Rapid Detection Kit a colored chromatographic immunoassay for the qualitative detection of GAS from throat swabs.

This test kit has a specificity of 97% and a sensitivity of >95%

The RADT Kit used was the Detector Strep A Rapid Test Kit. It is a qualitative chromatographic immunoassay for the detection of Strep A antigen from throat swab specimens. Its sensitivity is 97% and specificity is 95%

Materials

The Test Kit contains: Detector Strep A card tests, 25 dipsticks, 1 vial Reagent A (2M Sodium Nitrite), 1 vial Reagent B (0.15M Acetic Acid), 25 Swabs, 25 Disposable Pipettes, 25 disposable extraction Test Tubes, Instructions for use, 1 vial Positive Control, 1 vial Negative control and instructions for use

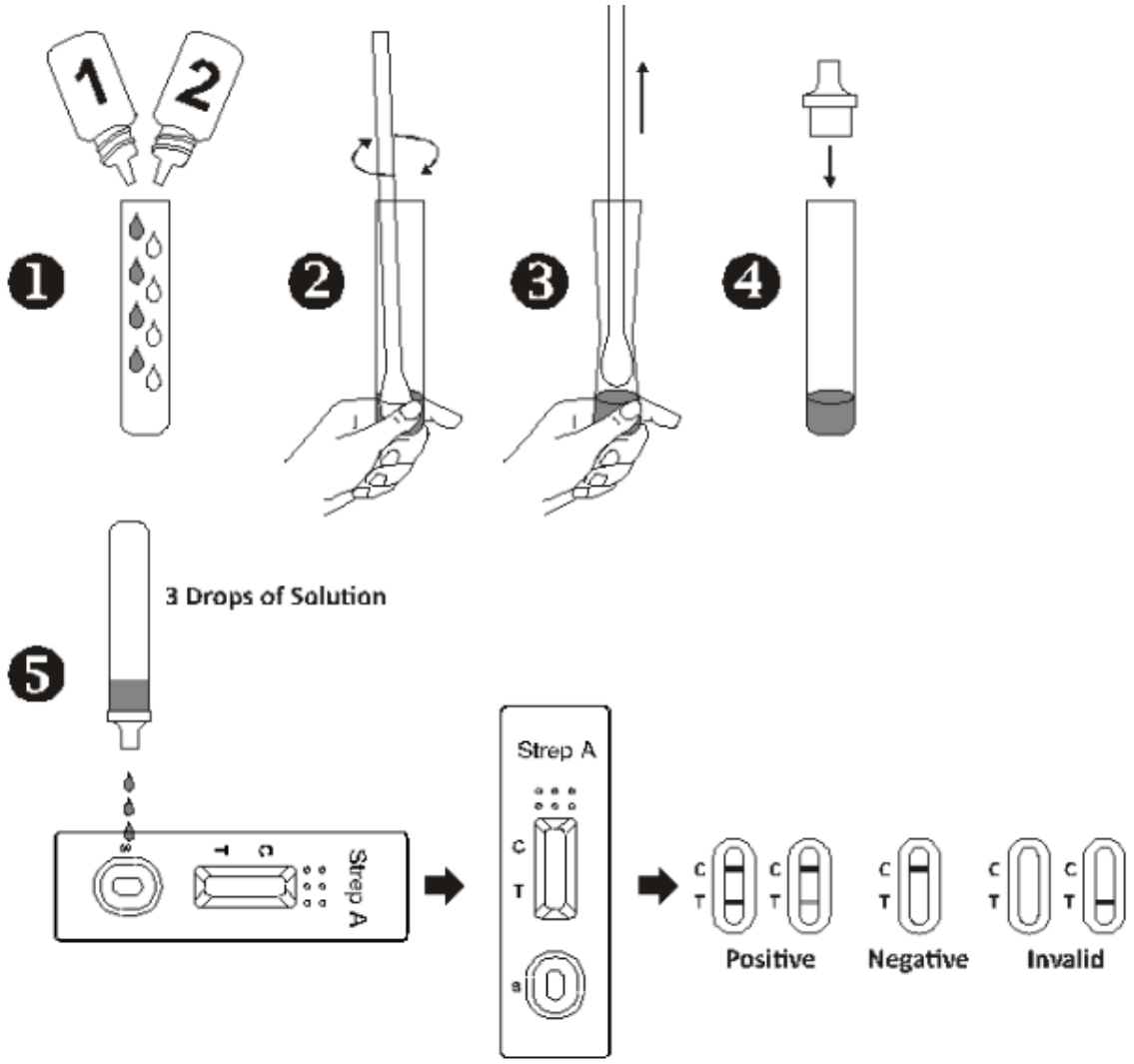
Materials Required (Not provided in the Test Kit)

Specimen Collection container, Disposable Gloves, Masks and Goggles, Torch, Tongue Depressors, Timer, Alcohol based hand sanitizer, Sterile swabs

Test Procedure

Add 4 drops of Reagent A (light Pink) and 4 drops of Reagent B in a test tube. The solution should turn light yellow/colorless. Immediately put the throat swab into the tube

Rotate the swab forcefully against the side of the tube for at least 1 minute.. Extract as much liquid as possible from the swab squeezing or rotating the swab against the side of the tube as the swab is withdrawn. Discard the used swab. Remove Detector Strep A card from its sealed bag just before use. Using a separate pipette, test for each sample or control. Pour exactly 4 drops from the testing tube into the circular window marked with the letter S. Start the timer and read the results at exactly 10 minutes.



Quality Control

Internal procedural control is included in the test kit. When adding Reagent B to Reagent A in the test tube, the color changes from pink to yellow or colorless. This is an internal extraction reagent control. The color change means that you mixed the extraction reagent properly and that the reagents are working properly.

An inoculated sample specimen is provided. A BLUE line appearing in the control line C in the results window is an internal control that confirms sufficient specimen volume and correct

procedure. A RED line appearing in the test line T in the results window confirms sufficient volume and proper technique

5.8.4.2 THROAT SWAB FOR MICROSCOPY CULTURE AND SENSITIVITY

The specimen was taken within 30 minutes of collection to the UON Department of Paediatrics Laboratory. It was cultured on Sheep Blood Agar, incubated in air, for 72 hours at 37^0C

After 72 hours, typical GAS colonies were noted to be dome shaped, smooth and moist surface, white or gray, each around 0.5mm diameter. They demonstrated showing beta hemolysis, a clear zone around the bacterial growth

The colony was then sub cultured, streaked on a fresh Sheep Blood Agar plate with a disk impregnated with 0.04U of bacitracin placed on it. This was incubated at 37^OC in 5% $C0_2$

GAS was identified by the typical morphology, demonstrated beta hemolysis and bacitracin susceptibility

The results were entered into a log book and an electronic data base

6. DATA MANAGEMENT AND ANALYSIS

The dependent variables were:

- Presence of GAS- the RADT and the culture results
- Antibiotic susceptibility

The independent variables were:

- Age
- Sex
- Household size
- Crowding
- Ventilation
- Symptoms Pain on swallowing, Fever >38.0^0 C, Cough, Vomiting, Abdominal pain
- Signs: Rhinitis, conjunctivitis, scarlatiniform rash, exudates (yellow/white matter seen on tonsils or pharynx), Tender or large anterior cervical lymph nodes (Large >1.5cm Tender child statement or facial expression)

Data were coded and entered into a Microsoft Excel 2013 data entry sheet. Data cleaning was performed continuously in the course of data entry. The final dataset was exported to SPSS version 21.0 for analysis.

At the univariate stage, demographic and clinical characteristics of the sample population we summarized into percentages and means/medians for categorical and continuous data respectively. Prevalence of GAS was calculated and presented as a proportion with 95% confidence interval. Antibiotic susceptibility was determined for the isolates and presented as proportion of resistance or sensitivity to antimicrobial agents.

At the bivariate stage, we tested for the presence of relationships between our independent variables and the dependent variable (Presence of GAS) using chi square test of associations and the results were presented in tables and narratives

At the multivariate stage we sought to establish the presence of statistically significant relationships between the independent variables and dependent variable, to assess the strength and direction of the established relationships. This was conducted through binary logistic regression model using the significant variables obtained at bivariate level of analysis The study findings were presented in tables and narratives. All statistical tests were performed at 5% level of significance.

7. ETHICAL CONSIDERATIONS

Ethical approval was sought from the Kenyatta National Hospital- University of Nairobi Ethics and Research Committee and obtained prior to commencing the study

Informed consent was obtained after explanation to the parent or caregiver on procedures to be conducted. The purpose of the study was explained. Parents or caregivers were invited to ask questions. Consent and assent was voluntary

No experimental investigations or procedures were carried out during this study

Strict confidentiality was observed throughout the period of the study by the participating investigators, research assistants and study institution. Participants were given study identification numbers and no personal identifiers were used

8. RESULTS

A total of 198 children were eligible, met the inclusion criteria and were enrolled as participants in the study. Of the 198, 76 tested positive for GAS (culture) and 122 were negative

The prevalence of GAS identified from samples taken from the participants was 38.4%

Table 1: Demographic and Clinical Characteristics

Variable		**Frequency (%) n=198**
Mean age (SD) 6.4 years	2-5 years 6-10 years 11-15 years	84 (42.4) 91 (46.0) 23 (11.6)
Sex	Male Female	104 (52.5) 94 (47.5)
Crowding in the household	<5 people 5-10 people	102 (51.5) 96 (48.5)
Shared bedrooms in the household	<3 rooms 3-5 rooms	155 (78.3) 43 (21.7)
General appearance	Well Ill	155 (78.3) 43 (21.7)
Temperature	$>38^0$ C $<38^0$ C	33 (16.7) 165 (83.3)
Symptoms **Signs**	Painful throat Headache Cough Vomiting Abdominal pain Enlarged tonsils Inflamed tonsils Inflamed pharynx Tonsillopharyngeal exudates Uvulitis Palatal petechiae Running nose Injected conjunctiva Tender cervical lymphadenopathy	132 (66.7) 47 (23.7) 119 (60.1) 49 (24.7) 58 (29.3) 102 (51.5) 102 (51.5) 112 (56.6) 21 (10.6) 25 (12.6) 25 (12.6) 79 (39.9) 41 (20.7) 51 (25.8)

The age group 6-10 years contributed to the largest population representing 46%. The mean age was 6 years with a slight male preponderance at 52.5% From this population, slightly more

children were from households with fewer than 5 members (51.5%) but a greater proportion had fewer bedrooms to share (78.3%) The most common symptom observed in approximately two thirds of the participants was a painful throat (66.7%)and the most common sign was an inflamed throat seen in 56.6% of all participants

Table 2: Prevalence of GAS (CULTURE RESULTS)

Variable	**Frequency (%) n=198**	**95% CI**
GAS		
Yes	76 (38.4)	31.3-45.5
No	122 (61.6)	54.5-68.7

The prevalence of GAS from this study, identified by culture was 38.4%

Table 3: RADT Results

Variable	**Frequency (%)**	**95% CI**
GAS		
Yes	72 (36.4)	28.8-42.4
No	126 (63.6)	57.6-71.2

The RADT registered positive for 72 cases, of which GAS was confirmed by culture in 71. There were 5 false negative results and 1 false positive result (subsequently identified in the laboratory as Streptococcus Pneumoniae)

Table 4: Performance of the RADT

RADT results	GAS		Total
	Present	**Absent**	**Total**
Positive	71	1	72
Negative	5	121	126
Total	**76**	**122**	**198**

The sensitivity of the RADT was 93.4% while the specificity was 99.2% The positive predictive value was 98.6% and the negative predictive value was 96%

Table 5: Associations between the sociodemographic and clinical characteristics of the study population and GAS

	Variable	**GAS Present**	**GAS Absent**	**OR (95% CI)**	**P value**
Sex	Male	43 (56.6)	61 (50.0)	1.3 (0.7-2.3)	0.376
	Female	33 (43.4)	61 (50.0)	1.0	
Household Size	<5	38 (50.0)	64 (52.5)	0.9 (0.5-1.6)	0.736
	>=5	38 (50.0)	58 (47.5)	1.0	
Number of Shared Bedrooms	<3	61 (80.3)	93 (76.9)	1.2 (0.6-2.5)	0.573
	>=3	15 (19.7)	28 (23.1)	1.0	
Painful throat	Yes	54 (71.1)	78 (63.9)	1.4 (0.8-2.6)	0.070
	No	22 (28.9)	44 (36.1)	1.0	
Headache	Yes	17 (22.4)	30 (24.6)	0.9 (0.5-1.7)	0.721
	No	59 (77.6)	92 (75.4)	1.0	
Cough	Yes	49 (64.5)	70 (57.4)	1.4 (0.8-2.4)	0.321
	No	27 (35.5)	52 (42.6)	1.0	
Abdominal pain	Yes	17 (22.4)	32 (26.2)	0.6 (0.3-1.1)	0.091
	No	59 (77.6)	90 (73.8)	1.0	

Vomiting	Yes	17 (22.4)	32 (26.2)	0.8 (0.4-1.6)	0.540
	No	59 (77.6)	90 (73.8)	1.0	
General appearance	Well	62 (81.6)	93 (76.2)	1.4 (0.7-2.8)	0.375
	Ill	14 (18.4)	29 (23.8)	1.0	
Temperature	>38	17 (22.4)	16 (13.1)	1.9 (1.0-4.1)	0.089
	<38	59 (77.6)	106 (86.9)	1.0	
Enlarged tonsils	Yes	41 (53.9)	61 (50.0)	1.2 (0.7-2.1)	0.589
	No	35 (46.1)	61 (50.0)	1.0	
Inflamed tonsils	Yes	42 (56.0)	60 (49.2)	1.3 (0.7-2.3)	0.352
	No	33 (44.0)	62 (50.8)	1.0	
Inflamed pharynx	Yes	50 (65.8)	62 (50.8)	1.9 (1.0-3.4)	0.039
	No	26 (34.2)	60 (49.2)	1.0	
Tonsillopharyngeal exudates	Yes	8 (10.5)	13 (10.7)	1.0 (0.4-2.5)	0.977
	No	68 (89.5)	109 (89.3)	1.0	
Uvulitis	Yes	10 (13.2)	15 (12.4)	1.1 (0.5-2.5)	0.876
	No	66 (86.8)	106 (87.6)	1.0	
Palatal petechiae	Yes	13 (17.1)	12 (9.8)	1.9 (0.8-4.4)	0.134
	No	63 (82.9)	110 (90.2)	1.0	
Runny nose	Yes	33 (43.4)	46 (37.7)	1.3 (0.7-2.3)	0.424
	No	43 (56.6)	76 (62.3)	1.0	
Injected conjunctiva	Yes	21 (27.6)	20 (16.4)	2.0 (1.0-3.9)	0.058
	No	55 (72.4)	102 (83.6)	1.0	
Scarlatiniform rash	Yes	12 (15.8)	8 (6.6)	2.7 (1.0-6.9)	0.036
	No	64 (84.2)	114 (93.4)	1.0	
Tender cervical lymphadenopathy	Yes	25 (32.9)	26 (21.3)	1.8 (1.0-3.5)	0.070
	No	51 (67.1)	96 (78.7)	1.0	

Male sex (OR 1.3) and residing in a house that had fewer than 3 bedrooms (OR 1.2) were associated with the presence of GAS. The clinical features associated with GAS were a painful throat (OR 1.9); cough (OR 1.4); a well appearance (OR 1.4); Fever (OR 1.9); enlarged (OR 1.2) and inflamed tonsils (OR 1.3); palatal petechiae and uvulitis (OR1.9); runny nose (OR 1.3); injected conjunctiva (OR 2.0); tender cervical lymphadenopathy (OR 1.8). The presence of an

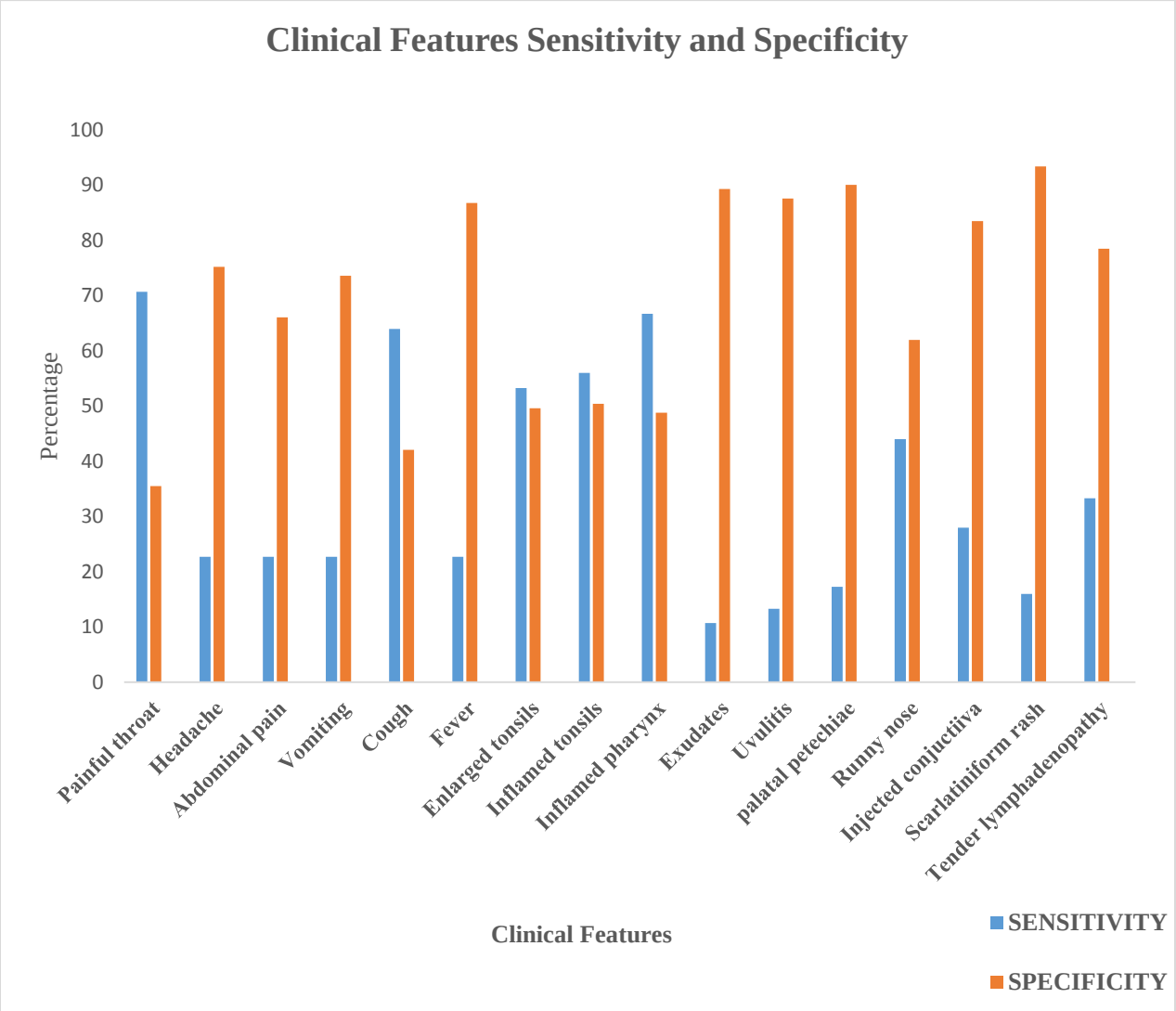
inflamed pharynx (OR 1.9) and a scarlatiniform rash (OR 2.7) were associated with the GAS and had a statistically significant relationship with p values of 0.039 and 0.036 respectively

Table 6: Relationship between the statistically significant variables and GAS using a logistic regression model

Variable	**Adjusted OR (95% CI)**	**P value**
Inflamed pharynx	1.9 (1.1-3.6)	0.032
Scarlatiniform rash	2.7 (1.0-7.0)	0.044

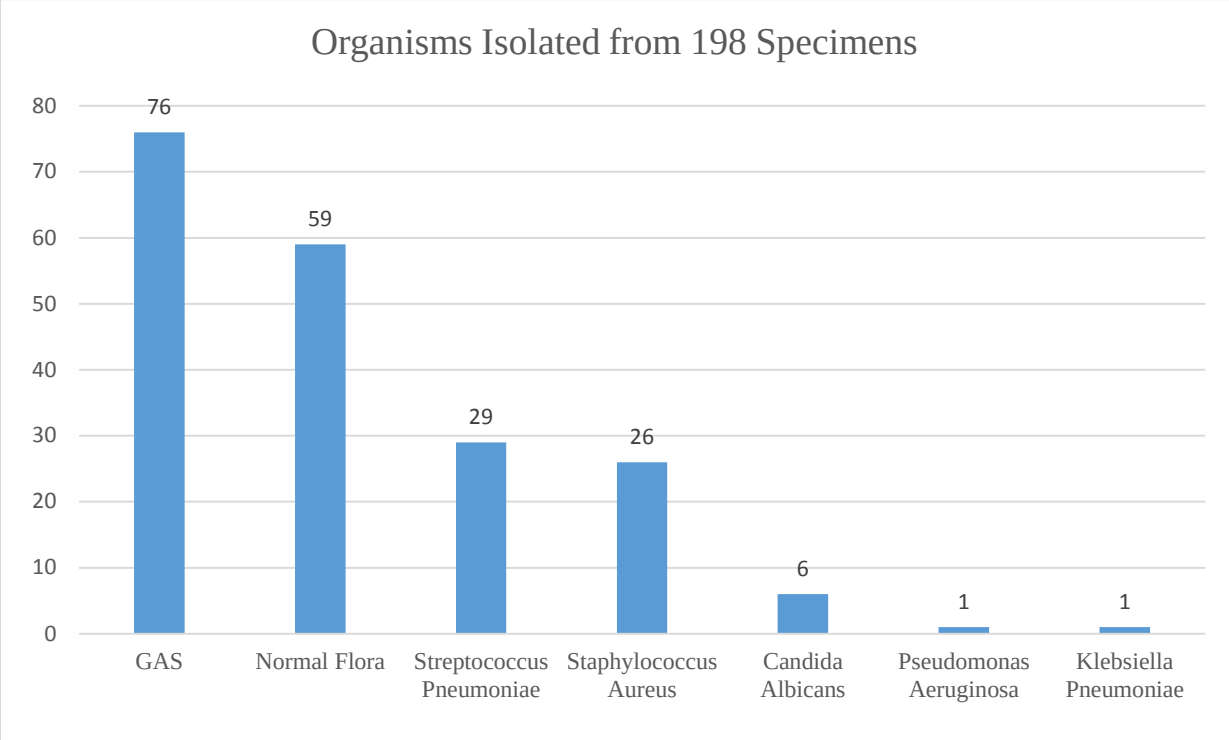
From the logistic analysis we concluded that participants with an inflamed pharynx were 1.9 times more likely to have GAS and those who presented with a scarlatiniform rash were 2.7 times more likely to have GAS after controlling for all the other variables they remained statistically significant with p values of 0.032 and 0.044 respectively

Figure 3: Sensitivity and Specificity of the individual clinical features and the identification of GAS



From our study a scarlatiniform rash was the most specific sign 93.4% and a painful throat was the most sensitive sign at 70.7%

Figure 4: Spectrum of Organisms Isolated



Of 198 specimens cultured, 76 grew GAS for an overall prevalence of 38.4% while normal oral flora accounted for 29.8%

Table 7: Antibiotic Susceptibility Pattern of GAS

ANTIBIOTIC	Sensitive (%)	Resistant (%)
AUGMENTIN	67 (88.16)	9 (11.84)
AMOXICILLIN	56 (73.68)	20 (26.32)
ERYTHROMYCIN	49 (64.47)	27 (35.53)

Of the 76 isolates of GAS, the least resistance was seen with Augmentin (11.8%) and the highest resistance was noted with erythromycin at 35.5%

9. DISCUSSION

This study investigated 198 children aged 2years to 15 years who presented to KNH PEU with acute pharyngitis, with most of the children seeking treatment aged between 6 and ten years. This study showed a slight preponderance in males (OR 1.3), unlike studies from Ethiopia in which females were more likely to test positive for GAS (24) but in both studies these findings were not associated in a statistically significant.

The study revealed that children residing in homes in which there were fewer than three bedrooms to share were 1.2 times more likely to test positive for GAS. This finding was not statistically significant either, in contrast to conclusions drawn by Baker et al that significantly and positively related household crowding to the isolation of GAS and the subsequent development of ARF(17)

The only two signs that remained statistically significant after controlling for all other variables were a scarlatiniform rash (AOR 2.7; P value 0.044) and an inflamed pharynx (AOR 1.9; P value 0.032) A systematic review carried out in 2012, by Shaikh et al aimed to establish whether clinical findings can be used to rule in or rule out GAS pharyngitis in children. They analyzed 38 articles and found that in children with a sore throat, the following individual findings: presence of a scarlatiniform rash, palatal petechiae, exudates, vomiting, and tender cervical nodes were moderately useful in identifying those with GAS, however they concluded that symptoms and signs, either individual or combined into CDRs cannot be used to definitively diagnose or rule out GAS pharyngitis in children or adolescents (30)

The prevalence of GAS was found to be 38.4% considerably higher than reports of 4.6% in Egypt and 3.6% in Croatia (19) but approximating the prevalence reported in Yemen 41% (31)and 30.7% from Karnataka India (22) This is hardly surprising given the high prevalence of RHD in Kenya and underscores the importance of primary prevention of ARF through the early diagnosis and treatment of GAS pharyngitis.

The performance of the RADT was acceptable with a sensitivity of 93.4% and a specificity of 99.2% The 5 false negative results however suggest we should adopt American and European diagnostic guidelines, where theses kits are routinely used in practice, which recommend following up all false negative results with a throat culture (2)

Our study demonstrated most resistance to erythromycin at 35.53% of the isolates. Bingen, Bidet et al studied the antimicrobial susceptibility of 322 GAS isolates from French children and concluded that 22.4% were resistant (32) with much lower rates observed from the United States 6.8% (33) and Greece 18.8% (34) The resistance to Augmentin 11.3% contrasted greatly with findings from Nigeria in which 94% of all isolates were resistant to Augmentin(35) The identification of isolates resistant to amoxicillin (26.3%) was of grave concern as in vitro resistance of GAS to penicillin and amoxicillin has not been documented. What has been emerging and is well documented is penicillin and amoxicillin treatment failure, from the first recorded cases in the 1980s to the current rate of 35% The theories that have been advanced to explain this in vivo resistance include the coexistence of oropharyngeal beta lactamase producing bacteria, interference by aerobic and anaerobic commensals, reinfection and penicillin tolerance. As the production of beta lactamase is a well-known mechanism of the development of in vitro resistance, this may well explain the “discovery” of amoxicillin resistant isolates.

10. LIMITATIONS

1. The identification of GAS either by RADT or culture cannot distinguish between those currently infected, or GAS carriers with an inter-current viral illness.
2. The study was a cross sectional study carried out over a limited period of time and the influence of environmental factors on variations in prevalence could therefore not be established.
3. As this was a hospital based study, this introduced selection bias, and as such the results may have limited applicability to the general population.

11. CONCLUSIONS

1. We conclude that the prevalence of GAS in children aged 2-15 years presenting with acute pharyngitis to KNH PEU is 38.4%
2. There is significant association with a a scarlatiniform rash (AOR 2.7; P value 0.044) and an inflamed pharynx (AOR 1.9; P value 0.032) with GAS
3. 11.8% of GAS isolates are resistant to Augmentin, while 26.3% are resistant to amoxicillin. 35.5% are resistant to erythromycin.

12. RECOMMENDATIONS

1. We recommend that all negative RADT results should be followed up with a throat culture as the prevalence of GAS and ARF is high in our setup
2. We also recommend continuous surveillance of both patients with acute pharyngitis and asymptomatic carriers to establish seasonal patterns if any and the prevalence rate among carriers
3. With evidence of resistance to the commonly used antibiotics, we recommend the implementation of antibiotic stewardship programs and surveillance of antibiotic resistance patterns to improve the use of antibiotics in hospitals
4. We recommend the introduction of throat swabbing for patients who present with acute pharyngitis
5. We also recommend the use of an RADT with high specificity and sensitivity in our pediatric outpatient clinic

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14. APPENDICES

14.1 APPENDIX 1: QUESTIONNAIRE

Demographic data

Date…….

Study ID……

Age (completed years)……..

Sex 1 male…… 2 female……

Number of people living in the home

Number of shared bedrooms in the house

Symptoms

Painful throat	1 yes	2 no
Headache	1 yes	2 no
Abdominal pain	1 yes	2 no
Vomiting	1 yes	2 no
Cough	1 yes	2 no

Physical Examination

General appearance	1 well	2 ill
Temperature	1 >38	2< 38
Enlarged tonsils	1 yes	2 no
Inflamed tonsils	1 yes	2 no
Inflamed pharynx	1 yes	2 no
Tonsillopharyngeal exudates	1 yes	2 no
Uvulitis	1 yes	2 no

Palatal petechiae	1 yes	2 no
Runny nose	1 yes	2 no
Injected conjunctiva	1 yes	2 no
Scarlatiniform rash	1 yes	2 no
Tender cervical lymphadenopathy	1 yes	2 no

RADT Results

POSITIVE	1
NEGATIVE	2
INVALID	3

Throat Culture

Take throat swab for MCS. Label with participant's Study ID

Specimen ID…….

Throat MCS Results……

Signature……..

14.2 APPENDIX 2: CONSENT FORM

Study Title: **THE PREVALENCE AND ANTIBIOTIC SUSCEPTIBILITY OF GROUP A STREPTOCOCCUS IN CHILDREN AGED 2-15 PRESENTING WITH ACUTE PHARYNGITIS IN KENYATTA NATIONAL HOSPITAL**

Study number:

Investigator: **Dr. Brenda Kunga MBChB**
Paediatric Resident, University of Nairobi
Tel Number: - 0721- 225092

Supervisors: **Prof Christine Yuko-Jowi**
Associate professor, Department of Paediatrics and Child Health,
University of Nairobi

Dr. Daniel Njai
Lecturer, Department of Paediatrics and Child Health,
University of Nairobi

Dr. Jasper Muruka
Consultant, Department of Diagnostic Imaging and Radiology Medicine
Kenyatta National Hospital

Introduction

Prevalence of rheumatic heart disease is still high among children. It follows a sore throat caused by bacteria (Group A Streptococcus). In some parts of the world this bacterium has begun to show resistance to antibiotics we commonly use in our country.

Purpose of the Research

Researchers from the University of Nairobi are conducting research on children who present to the hospital with sore throats.

This study aims at learning how many children with sore throats have this bacterium, the factors that may increase the likelihood of this bacterium being present and how it responds to the antibiotics we commonly use. It is being conducted among children aged 2-15 who present with

sore throats at Kenyatta National Hospital. Your participation in the study will help us learn about the response of this bacterium to antibiotics so as to help institute proper policy regarding the rational prescription of antibiotics to children

Participant selection

We invite all children aged 2-15 years who present to KNH with pharyngitis to participate in the study

Voluntary Participation and Right to Refuse

Your participation in this research is entirely voluntary as such no remuneration or compensation will be offered to the participants of the study. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this research project, you will still be offered the treatment that is routinely offered in this clinic/hospital for pharyngitis

Duration

The research takes place over 90 days during that time we will require only 15 minutes of your time to gather information from you.

Procedures

This study will be conducted through use of a pre-tested questionnaire for the care givers of the children. Two throat swabs will be taken from your child. A rapid test will be performed on one and you will receive results within 10 minutes. The other will be taken for culture and antibiotic susceptibility testing

Safeguarding Privacy and Confidentiality

The interviewer will keep all information about you secure. Your name will be removed from all records involved in the study. A number will be assigned to the survey questionnaire instead. Only project staff will have access to the study data. We will not use your name when we report results of the survey.

Risks and Benefits

The throat swabs may cause some discomfort to your child. Your child will benefit from a rapid diagnosis with appropriate and timely prescription of antibiotics. The overall impact for your community may be great because the data on prevalence and antibiotic susceptibility will help

guide better care of children and in the long run reduce the prevalence of rheumatic heart disease.

Problems or questions

If you have any questions about this research or about the use of the results, you can contact the principal investigator, Dr. Brenda Kunga by calling 254-721-225092.

If you have any questions on your rights as a research participant, you can contact Professor Chindia M.L, secretary, KNH/UoN- ERC by calling Tel. 2726300, ext. 44102, Nairobi.

Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I as an informant/parent to: _____consent voluntarily to participate as a participant in this research.

Name of Participant_____ Researchers Name: Dr. Brenda Kunga

Signature of Participant _____ Researchers Signature_____

Date _____ Date _____

Who to Contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following: I understand that if I have questions about this survey or my rights in taking it, I may contact Dr. Brenda Kunga on 0721225092 or Professor Chindia M.L,Secretary, KNH/UoN- ERC, Tel. 2726300,ext. 44102, Nairobi.

14.3 APPENDIX 3: FOMU YA IDHINI

UTAFITI: MAAMBUKIZI NA UCHUNGUZI WA NGUVU YA MADAWA AMBAYO YANATUMIKA KUTIBU UCHUNGU WA KOO UNAOSABABISHWA NA BAKTERIA GAS IKIPATIKANA KWA MTOTO MWENYE UMRI 2-15 KATIKA KENYATTA NATIONAL HOSPITAL

Nambari ya utafiti:

Mtafiti Mkuu **Dr. Brenda Kunga MBChB**
Nambari ya Simu: - 0721- 225092

Wasimamizi: **Prof Christine Yuko-Jowi**
Chuo Kikuu Cha Nairobi

Dr. Daniel Njai
Chuo Kikuu Cha Nairobi

Dr. Jasper Muruka
KNH

Kuanzishwa

Kuenea kwa ugonjwa wa moyo (RHD) bado ni juu kati ya watoto. Inafuata koo kubwa iliyosababishwa na bakteria (GAS). Katika sehemu fulani za dunia hii bakteria hii imeanza kuonyesha upinzani dhidi ya madawa tunayotumia kwa kawaida katika nchi yetu.

Umuhimu wa utafiti huu

Watafiti kutoka Chuo Kikuu cha Nairobi wanafanya utafiti juu ya watoto wanaohudhuria hospitali kwa koo.

Utafiti huu una lengo la kujifunza jinsi watoto wengi walio na koo kubwa wanavyo na bakteria hii, sababu ambazo zinaweza kuongeza uwezekano wa bakteria hii kuwapo na jinsi inavyojibu kwa madawa tunayotumia kawaida. Inafanywa kati ya watoto wenye umri wa miaka 2-15 ambao wanahudhuria kwa koo katika Hospitali ya Taifa ya Kenyatta. Ushiriki wako katika utafiti utatusaidia kujifunza juu ya majibu ya bakteria hii kwa antibiotics ili kusaidia kuanzisha sera sahihi kuhusu dawa nzuri ya antibiotics kwa watoto

Wakati utakaotumika

Kwa ujumla, utafiti huu utachukua siku tisini (90). Kwa wakati huu, tutahitaji dakika kumi na tano tu kujaza fomu na kuchukua maelezo mengine yatakayohitajika

Usiri

Matokeo ya utafiti huu yatawekwa siri wala hayatapatiwa mtu yeyote asiyehusika ma utafiti huu. Zaidi ya hayo badala ya jina la mtoto, numbari zitatumiwa kutambuliwa watoto hawa. Matokeo yatazungumziwa na idara ya afya ya watoto pekee wala sio mtu mwingine

Utaratibu wa utafiti

Utafiti huu utafanyika kwa kutumia dodoso kwa wazazi wa watoto. Tutatumia usufi kutoa sampuli mbili kwa koo ya mtoto wako, halafu kupima sampuli hiyo. Jibu moja litakuwa tayari kwa dakika 10. Sampuli ya pili litapelekwa kwa maabara kuiipima zaidi

Hiari ya kushiriki na siri ya utafiti

Msaidizi ataweka habari zote kuhusu wewe salama. Majina yote yatatolewa kutoka rekodi zote walioshiriki katika utafiti. Nambari itawekwa kwa jitihada utafiti badala yake. Majina hayatatumika katika ripoti za utafiti huu.

Madhara na Manufaa ya utafiti huu

Kutoa sampuli kwa koo inaweza kusababisha usumbufu kwa mtoto wako. Mtoto wako atafaidika kutokana na uchunguzi wa haraka na dawa sahihi. Kwa ujumla jumuiya yako itafaidika kwa sababu majibu ya utafiti huu utaongoza huduma bora kwa watoto na katika muda mrefu kupunguza kiwango cha maambukizi ya ugonjwa wa shida ya moyo.

Matatizo au maswali

Ukiwa na maswali yoyote kuhusu utafiti au matumizi ya matokeo unaweza kuwasiliana na mpelelezi mkuu, Daktari B Kunga kwa kupiga nambari 0721 225092**.** Kama una maswali yoyote

juu ya haki zako kama mshiriki katika utafiti huu, unaweza kuwasiliana na Professor Chindia M.L, katibu, KNH/UoN- ERC,simu. 2726300 ,Ext. 44102, Nairobi

Kukubali kwa muhojiwa

Nimeelezwa vizuri juu ya utafiti huu na nimeelewa. Nimepata fursa ya kuuliza maswali na kujibiwa. Najua kushiriki katika utafiti huu ni kwa hiari yangu na nikikataa sitanyimwa matibabu yoyote ninayopokea. Ninajua kwamba kama nikona swali lolote ninaweza kuuliza Daktari B Kunga nambari ya simu 0721-225092, ama Professor Chindia M.L, katibu, KNH/UoN-ERC,simu. 2726300 ,Ext. 44102, Nairobi

Sehemu ya 2: Shahada ya Idhini

Nambari Maalum:_____

Nimesoma maaelezo yote ya utafiti huu au nimesomewa maaelezo haya na nimekuwa na fursa ya kuuliza maswali ambayo yamejibiwa kadri na matarajio yangu kwa njia ya kuridhisha.
Kwa hio, kama mzazi wa:_____ningependa kupeana idhini yangu na pia kujitolea kushiriki kwa utafiti huu.

Jina la mshiriki: _____ **Sahihi la mshiriki: _____**

Mtafiti mkuu: Dkt Brenda Kunga **Sahihi ya mtafiti mkuu: _____**

Tarehe: _____ **Tarehe: _____**

14.4 APPENDIX 4: ASSENT FORM

Study Title: THE PREVALENCE AND ANTIBIOTIC SUSCEPTIBILITY OF GROUP A STREPTOCOCCUS IN CHILDREN AGED 2-15 PRESENTING WITH ACUTE PHARYNGITIS IN KENYATTA NATIONAL HOSPITAL

Informed Assent Form for _____

This informed assent form is for children above 7 years of age who present to KNH PEU with pharyngitis who we are inviting to participate in research to determine the prevalence and antibiotic susceptibility patterns of GAS

The principal investigator is Dr Brenda Kunga under supervision from Prof Christine Jowi, Dr Jasper Muruka and Dr Daniel Njai

This Informed Assent Form has two parts:

- Information Sheet (gives you information about the study)
- Certificate of Assent (this is where you sign if you agree to participate)

You will be given a copy of the full Informed Assent Form

Part I: Information Sheet

My name is Brenda Kunga and I am a doctor at Kenyatta National Hospital. I am interested in doing research on germs we might find in your throat that may cause heart disease in some children

I am going to give you information and invite you to be part of a research study. You can choose whether or not you want to participate. We have discussed this research with your parent(s)/caregivers and they know that we are also asking you for your agreement. If you are going to participate in the research, your parent(s)/caregiver also have to agree. But if you do not wish to take part in the research, you do not have to, even if your parents have agreed.

You may discuss anything in this form with your parents or friends or anyone else you feel comfortable talking to. You can decide whether to participate or not after you have talked it over. You do not have to decide immediately. There may be some words you don't understand or

things that you want me to explain more about because you are interested or concerned. Please ask me to stop at any time and I will take time to explain.

Purpose: Why are you doing this research?

We want to look for germs that can be found in the throats of some children, that sometimes cause heart disease in some children

Choice of participants: Why are you asking me?

Your throat hurts which sometimes gives us a clue that the germs might be in there

Participation is voluntary: Do I have to do this?

You don't have to be in this research if you don't want to be. It's up to you. If you decide not to be in the research, it's okay and nothing changes. This is still your clinic, everything stays the same as before.

I have checked with the child and they understand that participation is voluntary

_____ (signature)

Procedures: What is going to happen to me?

If you allow us we are going to ask you some questions mostly asking you how well you have been and then we will swipe the back of your throat with a swab of cotton wool on a stick.

I have checked with the child and they understand the procedures _____(signature)

Risks: Is this bad or dangerous for me?

You will not be in any harm when you take part in this research The throat swab may be uncomfortable.

I have checked with the child and they understand the risks and discomforts

_____ (Signature)

Benefits: Is there anything good that happens to me?

Nothing might happen to you, but the information you give us might help us learn more about the germs that may cause heart disease

I have checked with the child and they understand the benefits

_____(Signature)

Reimbursements: Do I get anything for being in the research?

Unfortunately, there will be no gifts if you choose to participate in the study.

Confidentiality: Is everybody going to know about this?

We will not tell other people that you are in this research and we won't share information about you to anyone who does not work in the research study. Information about you that will be collected from the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone.

Sharing the Findings: Will you tell me the results?

When we are finished with the research we will not contact you personally to give you the results but you can come find out about the research at the Department of Paediatrics, University of Nairobi. We will be telling more people, scientists and others, about the research and what we found. We will do this by writing and sharing reports.

Right to Refuse or Withdraw: Can I choose not to be in the research? Can I change my mind?

You do not have to be in this research. No one will be mad or disappointed with you if you say no. It's your choice. You can think about it and tell us later if you want. You can say "yes" now and change your mind later and it will still be okay.

Who to Contact: Who can I talk to or ask questions to?

You can ask me questions now or later. I have written a number and address where you can reach us or, if you are nearby, you can come and see us. If you want to talk to someone else that you know like your teacher or doctor or auntie, that's okay too.

If you choose to be part of this research I will also give you a copy of this paper to keep for yourself. You can ask your parents to look after it if you want.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

PART II: Certificate of Assent

I understand that this research is about finding factors associated with hospitalization of patients with sickle cell disease and I'll be asked a set of questions if I choose to participate in the research.

I have read this information (or had the information read to me) I have had my questions answered and know that I can ask questions later if I have them.

I agree to take part in the research.

OR

I do not wish to take part in the research and I have NOT signed the assent below

_____ (initialled by child/minor)

Only if child assents:

Print name of child _____

Signature of child: _____

Date:_____

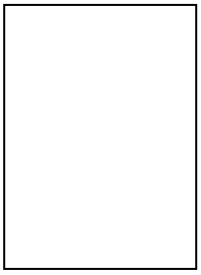
If illiterate:

I have witnessed the accurate reading of the assent form to the child, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness (not a parent) _____ AND Thumb print of participant

Signature of witness _____

Date _____



I have accurately read or witnessed the accurate reading of the assent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given assent freely.

Name of researcher: Dr Brenda Kunga

Signature of researcher_____

Date_____

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the child understands the purpose and procedure of the study. I confirm that the child was given an opportunity to ask questions about the study, and all the questions asked by him/her have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this assent form has been provided to the participant.

Name of Researcher: Dr Brenda Kunga

Signature of Researcher _____

Date _____

Copy provided to the participant _____(initialed by researcher)

Parent/informant has signed an informed consent: Yes_____ No_____

Who to Contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following:

Name: Dr Brenda Kunga (Primary Researcher)

Mobile Number: 0721225092

Email: mukami.kung@gmail.com

Kenyatta National Hospital/University of Nairobi Ethics and Research Committee

College of Health Sciences

P. O. Box 19676 00202 Nairobi

Tel. (254-020) 2726300-9 Ext 44355

E-mail: uonknherc@uonbi.ac.ke

14.5 APPENDIX 5: ASSENT FORM SWAHILI VERSION

Fomu ya kutiwa saini na watoto ya _____

Fomu hii ni ya kutiwa saini na watoto wenye umri wa miaka saba na juu wanaokuja cliniki ya watoto ya Kenyatta na uchungu wa koo

Hi fomu ya kutiwa saini na watoto ina sehemu mbili:

- Sehemu ya Maelezo (kukuelezea zaidi kuhusu utafiti)
- Shahada ya Kutiwa saini na watoto (sahihi ikiwa umekubali kujihusisha na utafiti huu)

Utapewa nakala ya maalezo ya utafiti huu**.**

Sehemu 1: Maelezo

Watafiti kutoka Chuo Kikuu cha Nairobi wanafanya utafiti juu ya watoto wanaohudhuria hospitali kwa koo.

Utafiti huu una lengo la kujifunza jinsi watoto wengi walio na koo kubwa wanavyo na bakteria hii, sababu ambazo zinaweza kuongeza uwezekano wa bakteria hii kuwapo na jinsi inavyojibu kwa madawa tunayotumia kawaida . Inafanywa kati ya watoto wenye umri wa miaka 2-15 ambao wanahudhuria kwa koo katika Hospitali ya Taifa ya Kenyatta. Ushiriki wako katika utafiti utatusaidia kujifunza juu ya majibu ya bakteria hii kwa madawa ili kusaidia kuanzisha sera sahihi kuhusu dawa nzuri ya antibiotics kwa watoto

Hatari

Hakuna hatari yoyote itakayotarajiwa utakaposhiriki utafiti huu.

Nimethibitisha kuwa mtoto ameelewa ya kwamba hakuna hatari yoyote ile itayomkabili _____ (saini)

Faida ya utafiti

Utafiti hii utasaidia kwa ujumla jumuiya yako itafaidika kwa sababu majibu ya utafiti huu utaongoza huduma bora kwa watoto na katika muda mrefu kupunguza kiwango cha maambukizi ya ugonjwa wa shida ya moyo

Nimethibitisha kuwa mtoto ameelewa faida ya utafiti _____ (saini)

Waanaoalikwa kujihusisha na utafiti

Mtafitii anawakaribisha watoto wote wanaoonekana kliniki ya watoto Kenyatta ambao wanakuja na uchungu wa koo

Kushiriki

Kushiriki utafiti huu utakuwa kwa njia ya kujitolea na kwa hivyo hakuna malipo yoyote atakayolipwa mshiriki wa utafiti huu. Iwapo hungependa kushiriki, uamuzi huu hautaathiri kwa njia yoyote matibabu yako au utakavyiohudumiwa.

Nimethibitisha kuwa mtoto ameelewa ya kwamba kujihusisha na hii utafiti ni kwa njia ya kujitolea _____ (saini)

Maelezo kuhusu mchakato

Iwapo utakubali kushiriki utapewa fomu ya kujaza iliyo na seti ya maswali, na sampuli litatolewa kwa koo za wanaokubali kushiriki

Nimethibitisha kuwa mtoto ameelewa maelezo kuhusu mchakato_____ (saini)

Wakati utakaotumika

Kwa ujumla,utafiti huu utachukua siku tisini (90).Kwa wakati huu,tutahitaji dakika kumi na tano tu kujaza fomu na kuchukua maelezo mengine yatakayohitajika

Usiri

Matokeo ya utafiti huu yatawekwa siri wala hayatapatiwa mtu yeyote asiyehusika na utafiti huu. zaidi ya hayo badala ya jina la mtoto, numbari zitatumiwa kutambuliwa watoto hawa.Matokeo yatazungumziwa na idara ya afya ya watoto pekee wala sio mtu mwingine.

Haki ya kutoshiriki

Kushiriki kwa utafiti huu ni kwa kujitolea na iwapo hungependa kushiriki,uoamuzi wako utaheshimiwa na pia hautathiri kwa njia yoyote matibabu yako. Bali utaendelea kupokea matibabu na huduma ya hospitali hii kama hapo awali.

Pendekezo hili limeangaliwa na kuidhinishwa na Idara ya afya ya watoto ya Chuo kikuu cha Nairobi na kamiti ya maadili ya utafiti katika hospitali ya Kenyatta inayohakikisha kuwa haki za wanaoshiriki utafiti wowote inchini,zinazingatiwa .

Iwapo utakuwa na swali lolote kumbuka una uhuru kuuliza.

Sehemu ya 2: Shahada ya Kutiwa Saini na Watoto Nambari Maalum:_____

Nimesoma maaelezo yote ya utafiti huu au nimesomewa maaelezo haya na nimekuwa na fursa ya kuuliza maswali ambayo yamejibiwa kadri na matarajio yangu kwa njia ya kuridhisha.Kwahio ningependa kupeana saini langu na pia kujitolea kushiriki kwa utafiti huu .

Nakubali kujihusisha na utafiti huu.

AMA

Si kubali kujuhusisha na utafiti huu na sijatia saini lolote._____ (alama ya mshiriki)

Mtoto akikubali:

Jina la mtoto: _____

Saini la mtoto: _____

Tarehe:_____

Iwapo mtato awezi akasoma:

Nimeona na ninaweza thibitisha ya kwamba mtoto amesomewa yaliyo kwenye hii fomu ya kutiwa saini na mtoto, na mtoto mwenyewe ameweza kuuliza maswali atakayo. Na thibitisha ya kwamba mtoto amekubali kwa hiari yake kushirikiana na hii utafiti.

Jina la shahidi (isiwe mzazi): _____ NA Alama ya Kidole ya Mshiriki

Saini la shahidi:_____

Tarehe: _____

Nimemsomea ama nimeona na ninaweza thibitisha ya kwamba mtoto amesomewa yaliyo kwenye hii fomu ya kutiwa saini na mtoto, na mtoto mwenyewe ameweza kuuliza maswali atakayo. Na thibitisha ya kwamba mtoto amekubali kwa hiari yake kushirikiana na hii utafiti.

Jina la mpelelezi: Dr Brenda Kunga

Saini ya mpelelezi: _____

Tarahe: _____

Nakala imepewa kwake mshiriki _____(alama ya mpelelezi)

Mzazi/Mgarini amaitia saini Shahada ya Idhini : Ndiyo_____ Hapana_____

Kwa maelezo Zaidi hata baada ya utafiti huu una uhuru wakuwasiliana na watu wafuatao kupitia anwani na numbari za simu silizoandikwa hapa chini.

Jina: Dr Brenda Kunga (mtafiti mkuu)
Nambari ya simu: 0721225092
Barua pepe: mukami.kunga@gmail.com

Kenyatta National Hospital/University of Nairobi Ethics and Research Committee
College of Health Sciences
P. O. Box 19676 00202 Nairobi
Simu. (254-020) 2726300-9 Ext 44355
Barua pepe: uonknh_erc@uonbi.ac.ke