



Extent, Associated factors and Effect of delayed antibiotic initiation in adult inpatients receiving antibiotic treatment at Kisenyi Health Center IV and Kiruddu National Referral Hospital, Kampala, Uganda

By

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DECLARATION

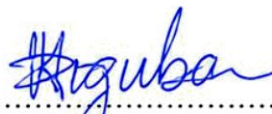
I hereby declare to the best of my knowledge and belief, this research study is original and has never been published and/or submitted for any other degree award to any other university for any other academic award.

Signature..........

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This dissertation has been submitted for examination with approval of the following supervisors

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Date.....6th August 2023.....

Dr. Ibanda Hood

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LIST OF ACRONYMS

LOS: Length of stay

MakCHS: Makerere University College of Health Sciences

SOMREC: School of Medicine Research and Ethics Committee

UBOS: Uganda Bureau of Statistics

UNCTS: Uganda National Council for Science and Technology

WHO: World Health Organization

MOH: Ministry of Health

KCCA: Kampala City Council Authority

NRH: National Referral Hospital

HCIV: Health Center IV

DAAT: Delayed Appropriate Antibiotic Therapy

TAAT: Timely Appropriate Antibiotic Therapy

IAs: Intra-abdominal Infections

UTIs: Urinary Tract Infections

CABM: Community-acquired bacterial meningitis

YLL: Years of life lost

LRTI: Lower Respiratory Tract Infections

ICU: Intensive Care Unit

OPERATIONAL DEFINITIONS

Delayed antibiotic initiation: The use of or advice to use antibiotics more than 48 hours after the initial antibiotic consultation by either admitting or referring health facility.

Antibiotics: Are compounds that kill or prevent bacterial growth and, thus, are intended to treat and prevent bacterial infections.

Adult inpatient: A person 18 years of age or older who has been admitted for bed occupancy for the purposes of receiving inpatient hospital services.

Length of stay: Is the period from hospital admission to discharge.

Duration of antibiotic treatment: Is the period from when antibiotic treatment started to when it stopped.

Healthcare facility: Healthcare facilities are places that provide healthcare. In this context they refer Kiruddu NRH and Kisenyi HCIV.

ABSTRACT

Background: Delayed appropriate antibiotic initiation increases morbidity and mortality particularly amongst critically ill adult inpatients; therefore, timely antibiotic initiation is highly recommended. Adult inpatients are usually affected by bacterial infections which require in-hospital treatment. Delays in antibiotic treatment are associated with many factors including delayed system referrals, poor patient education, misdiagnosis, delayed diagnosis and resource scarcity, among others. There is limited data on this in our setting necessitating this study.

Main objective:

We determined the extent, associated factors, effects of delayed antibiotic initiation in adult inpatients receiving treatment in Kisenyi Health Center IV and Kiruddu National Referral Hospital (KNRH), Kampala Uganda.

Methods: A prospective cohort study was conducted among adult inpatients at Kisenyi HCIV and Kiruddu NRH, Kampala, Uganda, between 17th April and 20th June 2023, 606 consented adult inpatients participated in the study. A pre-tested interviewer-administered questionnaire was used to collect the data. The data were entered into Epi-data and exported to STATA 17 software for cleaning and analysis. Frequency tables and summary statistics were used to analyses categorical and numerical data. Chi-square tests and logistic regression were used to assess associations between the outcome (delayed antibiotic initiation) and exposure variables (age, level of education, household income, patient residence, marital status, time to consultation, health facility accessibility, number health worker,). Responses to the open-ended questions were coded and analyzed.

Results:

The extent of delayed antibiotic initiation was 6 % (36/606), of whom 92% (33/36) were at Kiruddu NRH. Lower household income (adjusted Odds Ratio, aOR= 0.28, p = 0.006 CI =0.12-0.70) and longer patient wait to consultation (aOR= 5.35, p = 0.000 CI =2.10-13.64) were independently associated with delayed antibiotic initiation. Patients who delayed to initiate antibiotics had an average of 81hours (3.38dys) longer in hospital (LOS) than those who received timely antibiotic treatment.

Conclusion and recommendation: The study showed a low extent of delayed antibiotic initiation which was significantly associated with household income and patient wait to consultation. Patients that had delayed antibiotic initiation had longer length of hospital stay. A retrospective mixed methods study at multi-level care should be conducted to explore other effects and associated factors.

Keywords: delayed antibiotic initiation, adult inpatients, extent, length of stay (LOS)

CHAPTER ONE: INTRODUCTION

1.1 Background

Humans are affected by various infection caused by different microorganism such as bacteria, fungi, and virus. Devastating pathogen-borne diseases and plagues, both viral and bacterial in nature, have affected humans since the beginning of human history (Shaw-Taylor, 2020) . The Plague of Athens in 430 BC killed one-quarter of the Athenian, was believed later to be caused by a pathogenic bacterium, *Salmonella enterica* serovar Typhi which causes typhoid fever. From 541 to 750, an outbreak of what was likely a bubonic plague caused by bacterium *Yersinia pestis* eliminated one-quarter to one-half of the human population in the eastern Mediterranean region (Sakai & Morimoto, 2022).

In 2019, bacterial infections were linked to 7.7 million deaths globally, making them the second-leading cause of death worldwide with 230 deaths per 100,000 individuals in sub-Saharan Africa being the region with the highest rate of bacterial infection-related fatalities (Murray et al., 2022).

Uganda specifically, the top 10 causes of death in 2020 included lower respiratory infections, tuberculosis, and diarrheal diseases, which are mostly bacterial in nature (Karamagi et al., 2022). The exact number of deaths from bacterial infections in Uganda is not well documented, but it is likely to be high given the prevalence of these diseases and the challenges of infection prevention and control (R. T. Ssekitoaleko et al., 2020)

Antibiotics are drugs that can treat infections caused by bacteria. They came into broader use in the 1940s, after penicillin (the first antibiotic) was discovered by British scientist Alexander Fleming in 1928. Before that, many people succumbed to common bacterial infections (Hutchings, Truman, & Wilkinson, 2019). The advent of antibiotics led to decreased mortality and morbidity from infections that were previously untreatable (Adedeji, 2016) .Worldwide use of antibiotics, pharmacologically classified as antibacterial agents, increased by 36% in healthcare in the first decade of the new millennium with the current extent of use in Uganda reported at 79% especially among hospitalized patients (Kiguba, Karamagi, & Bird, 2016).

In Uganda, health care seeking and referral starts at low level centers or private clinics where there is limited or no capacity for baseline diagnosis and assessment, therefore antibiotic use is based on

unconfirmed diagnosis (Kiguba, Karamagi, & Bird, 2016). This translates to delayed antibiotic treatment initiation and self-medication (Musoke et al., 2021).

The importance of initiating timely, appropriate, empiric antibiotic therapy has been stressed in guidelines for several types of infection. (Zasowski et al., 2020). Delay in initiating appropriate antibiotic treatment especially in severe bacterial infections has been documented to result in poor treatment outcomes such as increased mortality, longer hospital stay, higher treatment costs, and lower likelihood of being discharged home (Zasowski et al., 2020), (Im, Kang, Ko, Lee, Lim, Park, Na, Chung, Park, & Oh, 2022). A retrospective study of 17,990 patients with severe sepsis and septic shock, indicated that time to first antibiotic treatment was found to be important for survival. Delayed time to effective treatment of Gram-negative infections has also been shown to impact negatively on hospital length of stay and costs (Zasowski et al., 2020).

Delayed antibiotic initiation is associated with several factors which could be system related factors, treatment related and patient related factors. In our setting, delays in the initiation of antibiotics could result from delayed laboratory services, delayed diagnosis, high patient load, financial constraints, resource scarcity and delayed referral systems, among others (Juma, 2018; Sendagire et al., 2010).

Although several recommendations by different stakeholders have been made to ensure timely antibiotic use especially in treatment of severe bacterial infection for hospitalized adult in-patients, little is known about the extent of delay in initiating antibiotic treatment. It is not known to which extent adult in-patients delay in receiving their first medications after initial consultation and which factors are associated with this. This evidence is needed to help physicians identify the likelihood of negative outcomes and guide treatment decisions to optimise timely appropriate antibiotic therapy for patients most at risk.

This study therefore investigated the extent, factors associated with delayed antibiotic initiation and whether delayed antibiotic initiation leads to prolonged hospitalization in adult inpatients receiving antibiotic treatment at Kisenyi Health Center IV and Kiruddu National Referral Hospital.

1.2 Problem Statement

Severe bacterial infections are a common cause of hospital admission (Liyanarachi et al., 2022). Patients hospitalized for other conditions also suffer from hospital-acquired bacterial infections leading to poor treatment outcomes including prolonged hospital stay (LOS), when treatment is delayed (Ankunda et al., 2010).

Delays in antibiotic initiation are associated with expensive tests for determining the appropriate and effective antibiotics leaving many patients unable to afford the basic diagnostics; long laboratory waits for culture and sensitivity tests; and poor access with the need to travel long distances for the tests to be done (Oga-Omenka et al., 2020). System challenges such as late referrals, resource unavailability, and inadequate/unqualified clinicians have also been associated with delayed antibiotic initiation (Oga-Omenka et al., 2020). In Uganda, decisions to prescribe systemic antibiotics to inpatients are often based on unconfirmed diagnosis (Kiguba, Karamagi, & Bird, 2016).

Seventy-nine percent of hospitalized Ugandan patients receive at least one antibiotic during their hospital stay (Kiguba, Karamagi, & Bird, 2016), however, the extent of delayed antibiotic treatment and its associated factors among adult inpatients is not well studied. In addition, the extent to which all these factors contribute to delayed antibiotic initiation is not well known. Effects of delayed antibiotic initiation are in most cases negative treatment consequences like prolonged hospitalization, among others, little has been documented about these in adult inpatient at Kisenyi Health Center IV and Kiruddu NRH.

1.3 Justification of the study

Bacterial infections are among the main causes of morbidity and mortality in adult inpatients in Uganda. Delayed antibiotic treatment leads to poor treatment outcomes which include longer LOS and higher in-hospital costs, and an increase in the risk of in-hospital mortality (N. G. Bonine et al., 2019). This study provides evidence to help physicians identify the likelihood of negative outcomes and guide treatment decisions to optimize prompt appropriate antibiotic therapy for patients most at risk. The aim is to promote timely appropriate use of antibiotics to improve patient outcomes, reduce prolonged hospitalization and mortality due to delayed antibiotic initiation in

adult in-patient receiving antibiotic treatment at Kisenyi HCIV and Kiruddu NRH. This will also contribute to the understanding and importance of quick antibiotic initiation.

1.4 Research Questions

1. What is the extent of delayed antibiotic initiation in adult in-patient receiving antibiotic treatment at Kisenyi Health Center IV and Kiruddu National Referral Hospital?
2. What are the factors associated with delayed antibiotic initiation in adult in-patient receiving antibiotic treatment at Kisenyi Health Center IV and Kiruddu National Referral Hospital?
3. Does delayed antibiotic initiation result in prolonged hospitalization among adult inpatients receiving antibiotic treatment at Kisenyi Health Center IV and Kiruddu NRH?

1.5 Objectives

1.51 General Objective

To determine the extent, associated factors and effect of delayed antibiotic initiation in adult in-patients receiving antibiotic treatment at Kisenyi Health Center IV and Kiruddu NRH.

1.52 Specific Objectives

Primary objectives

1. To determine the extent of delayed antibiotic initiation in adult in-patients receiving antibiotic treatment at Kisenyi Health Center IV and Kiruddu NRH.
2. To determine factors associated with delayed antibiotic initiation in adult in-patients receiving antibiotic treatment at Kisenyi Health Center IV and Kiruddu NRH.

Secondary objective

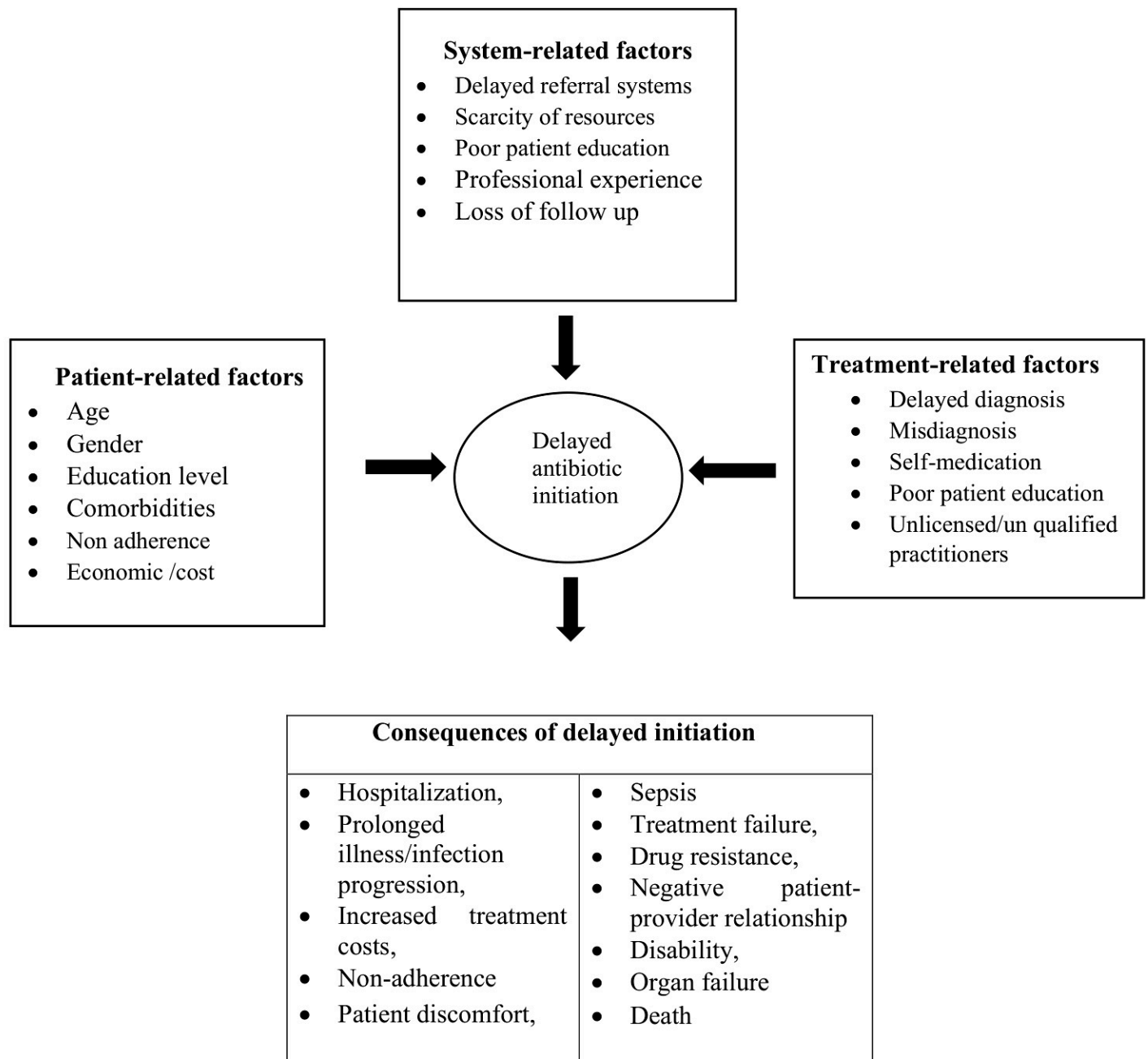
3. To determine if there is a relationship between delayed antibiotic initiation and prolonged hospitalization in adult in-patients receiving antibiotic treatment at Kisenyi Health Center IV and Kiruddu NRH.

1.6 Conceptual Framework

Scope of the study

Various factors are associated with delayed antibiotic initiation among adult in-patients in Uganda. These include patient-related factors, system-related factors and treatment-related factors. Delayed antibiotic treatment results in poor treatment outcomes including prolonged hospital stay, morbidity, mortality, among others. The scope of this study is on the extent, associated factors of delayed antibiotic initiation (age, gender, income status, patient knowledge on disease, number of health workers, medication availability, time to consultation, health facility accessibility, health facility convenience) and association between delayed antibiotic initiation and hospital length of stay (LOS). See **Figure 1**

Figure 1. A conceptual framework developed from a review of literature showing the factors associated with delayed antibiotic initiation.



CHAPTER TWO: LITERATURE REVIEW

2.1 Burden of bacterial Infections

The burden of infectious diseases is high globally, more so in low- and lower-middle income countries. Approximately 7 million people died of infectious diseases in 2019, accounting for nearly 12% of all deaths globally associated with 33 common bacterial infections, with five bacteria (*Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*) alone connected to more than half of all death. It also makes bacterial infections the second largest cause of death globally (Murray et al., 2022).

In sub-Saharan Africa, mortality rate was highest, with 230 deaths per 100,000 population, and lowest in high-income countries at 52 deaths per 100,000 population. The substantial years of life lost (YLL) associated with these bacteria in sub-Saharan Africa magnifies the burden of infections in the region compared with other areas (Murray et al., 2022).

Uganda's burden of disease is dominated by communicable diseases, which account for over 50% of morbidity and mortality (Organization, 2018). The exact number of deaths from bacterial infections in Uganda is not well documented, but it is likely to be high given the prevalence of these diseases and the challenges of infection prevention and control (R. T. Ssekitoleko et al., 2020)

The most frequent bacterial infections in adult inpatients include but are not limited to spontaneous bacterial peritonitis, gastroenteritis, urinary tract infection, pneumonia, community infections and nosocomial infection (Caly & Strauss, 1993). Three types of infections; lower respiratory infections such as pneumonia, bloodstream infections, peritoneal and intra-abdominal infections are responsible for more than 75% of the deaths (Murray et al., 2022).

Salvarsan was the first antibiotic deployed in 1910 (Hutchings, Truman, & Wilkinson, 2019). The first commercially available antibacterial was Prontosil, a sulfonamide developed by the German biochemist Gerhard Domagk in the 1930s. The first of the "modern day" antibiotics were Sulphur containing compounds, and the first Sulphur containing drug, prontosil rubrum, was used to treat human infection in 1935 (Aminov, 2010). However, antibiotics came into worldwide prominence

with the introduction of penicillin in 1941. Penicillin was discovered in 1928 by Scottish bacteriologist Alexander Fleming, but it was not until 1940 that penicillin was purified and used as an antibiotic. The discovery of antibiotics revolutionized the treatment of bacterial infections in humans and other animals, and extended the average human lifespan by 23 years between 1944 and 1972 (Hutchings, Truman, & Wilkinson, 2019).

The use of antibiotics pharmacologically classified as antibacterial agents, increased by 36% worldwide in healthcare in the first decade of the new millennium (Kiguba, Karamagi, & Bird, 2016). Among hospitalized patients the extent antibiotic use varies from 30% to 80% in different countries and settings. In Uganda extent of use is reported at 79% especially among hospitalized patients (Kiguba, Karamagi, & Bird, 2016). The most commonly used antibiotics include ceftriaxone, amikacin, cefoperazone plus sulbactam, ciprofloxacin, and metronidazole (Abubakar, 2020). However, not all of these antibiotics are appropriate for every patient or infection. For severe infections, it is recommended to use antibiotics early and appropriately to prevent complications and mortality (N. G. Bonine et al., 2019).

2.2 Delayed Antibiotic Initiation

2.21. Impact of delayed antibiotic initiation

Early appropriate antibiotic therapy is the administration of adequate antibiotics within a certain time frame after the onset of infection, especially in cases of sepsis or bacteremia. The time frame depends on the severity of the infection and the patient's condition. For non-critically ill patients, it is usually within the first 48 hours (Andersson et al., 2019), while for critically ill patients, it is within one hour (Niederman et al., 2021). Early appropriate antibiotic therapy can improve clinical outcomes and reduce mortality (Gauer, 2013). Timely antibiotic therapy is associated with lower mortality and shorter hospital stay in patients with sepsis, pneumonia, meningitis, and skin and soft tissue infections. the optimal time window for antibiotic administration may vary depending on the type and severity of infection (Nauc  r et al., 2021)

Sepsis treatment guidelines and quality measures indicate that early antibiotic administration as cornerstone for management. Several studies have shown that delay in the

initiation of appropriate antibiotic therapy is a risk factor for mortality (Im, Kang, Ko, Lee, Lim, Park, Na, Chung, Park, & Oh, 2022). The current guideline recommends starting antibiotics within one hour of sepsis recognition (Dugar, Choudhary, & Duggal, 2020), for patients with septic shock, antibiotic therapy within 1 hour of sepsis recognition is associated with lower in-hospital mortality than delayed antibiotic therapy mortality (Im, Kang, Ko, Lee, Lim, Park, Na, Chung, Park, & Oh, 2022)..

It also recommended to start antibiotic therapy as soon as possible after obtaining blood cultures and before or at the same time as performing a lumbar puncture in management of bacterial meningitis. A study that analysed data of 352 patients with community-acquired bacterial meningitis (CABM) in Germany and found that delayed antibiotic therapy (more than 3 hours after hospital admission) was associated with higher mortality and worse neurological outcome than early antibiotic therapy (Bodilsen et al., 2016).

Guidelines for the management of adult lower respiratory tract infections indicate that antibiotic treatment should be considered in patients with lower respiratory tract infections (LRTI) in situations such as suspected or definite pneumonia or selected exacerbations of COPD (Woodhead et al., 2011). One study found that early antibiotic therapy (within 48 hours of symptom onset) was associated with reduced hospitalization and mortality in patients with asthma and acute LRTI. However, this study was observational and did not establish causality (Denholm, van der Werf, & Hay, 2020). most retrospective studies suggest that a delay in antibiotic administration, in particular >4-8 h, is associated with worse outcomes, but prospective studies have failed to corroborate these findings. Studies show divergent results on differential effects relative to disease severity.

For Intra-abdominal infections (IAIs) early and adequate empiric antimicrobial therapy is important because it can reduce morbidity, mortality and bacterial resistance (Blot, De Waele, & Vogelaers, 2012). A consensus statement published in World Journal of Emergency Surgery presented the global clinical pathways for patients with IAIs and emphasized that appropriate antimicrobial therapy is essential to achieve optimal outcomes. It also recommended to start empiric antimicrobial therapy as soon as possible after diagnosis, to tailor it according to the

microbiological results and the patient's clinical response, and to de-escalate or stop it when appropriate (Sartelli et al., 2021)

There were no studies comparing early to delayed antibiotic therapy for febrile urinary tract infections (UTIs) (without sepsis), studies suggest that the severity of illness at presentation and co-morbidities are more significant risk factors for mortality than time to initiation of antibiotics. Three studies evaluating inappropriate empirical therapy (often implicating a delay in effective treatment of >24 h) showed no association with clinical outcome.

Generally, early (e.g. <1-3 h) broad-spectrum therapy is justified in the most severely ill patients with septic shock or bacterial meningitis to reduce mortality. In patients with mild to moderate disease, a delay of therapy (e.g. by 4-8 h) not been shown to be associated with worse clinical outcome.

2.22. Definition of delayed antibiotic initiation

The definition of delayed antibiotic therapy may vary depending on the context, setting, and study. However, a common way to define it is the receipt of appropriate antibiotic(s) that cover the identified causative pathogens after a certain time period from the initial presentation or diagnosis of infection (Balada-Llasat et al., 2022; Rowe & Linder, 2020).

For example, in a systematic review of 37 studies done after 2007 in hospitalized patients who had severe bacterial illnesses, the definition of “delayed” ranged from >1 hour to >5 days (Zasowski et al., 2020).

Arnold and colleagues adopted an operational definition for delayed antibiotic treatment of > 24h after initially meeting diagnostic criteria (Arnold & Hollenberg, 2012). This was a planned secondary analysis of a cluster-randomized controlled trial of 2,796 patients with sepsis from 18 hospitals in Germany.

Bonine et al. (2019a) conducted a retrospective study using the Premier Hospital Database, which contains data from more than 700 US hospitals. They compared the clinical and economic outcomes of patients with serious gram-negative bacterial infections who received delayed appropriate antibiotic therapy (DAAT) or timely appropriate antibiotic therapy (TAAT), stratified

by antibiotic resistance status. They found that DAAT was associated with worse outcomes, such as longer length of stay, higher total costs, and higher mortality, regardless of resistance status, they defined DAAT as “no receipt of antibiotic(s) with relevant microbiological activity on or within 2 days of index date” (N. G. Bonine et al., 2019).

Spurling and colleagues on delayed antibiotic prescriptions for respiratory infections, delayed antibiotic use was defined as the use of or advice to use antibiotics more than 48 hours after the initial consultation. The study found that delayed prescribing reduced antibiotic use and did not affect patient satisfaction or clinical outcomes (Spurling et al., 2004)

There is high heterogeneity in time to appropriate therapy between studies, this may be partly explained by the varying disease severity, infecting organisms and associated drug resistance profiles; however, reduced delay times are generally associated with improved outcomes.

2.2 Factors Associated with Delayed Antibiotic Initiation

Various factors are associated with delayed antibiotic initiation among adult in-patients which could be categorized as patient-related factors such as age; gender, comorbidities, severity of illness, and source of infection, system-related factors; such as availability of antibiotics, laboratory tests, and blood cultures, staffing levels, workload, communication, and protocols and treatment-related factors; such as choice of antibiotics, route of administration, dosage, frequency, and duration (Zasowski et al., 2020).

Public health facilities in Africa face several challenges in providing effective antibiotic treatment, such as; distance to the health facility, many people live in remote areas where access to health care is limited or costly. This may delay seeking care or result in self-medication with substandard or counterfeit drugs. Inadequate drug stocks; many health facilities experience frequent stock-outs of essential antibiotics due to poor supply chain management, lack of funding, or corruption. This may force patients to buy drugs from unregulated sources or use incomplete or inappropriate regimens. Lack of money to pay for services; many people cannot afford to pay for health services or drugs, especially in the absence of health insurance or social protection schemes. This may prevent them from accessing care or adhering to prescribed treatment (Musoke et al., 2014; Oleribe et al., 2019).

Mulla and colleagues, used process mapping to observe the steps involved in the diagnosis and treatment of two pneumonia patients at a referral hospital in Malawi. They identified several factors that influenced the timely administration of initial antibiotic dose, such as; the availability and accessibility of antibiotics, syringes, needles, and infusion sets; the availability and competency of staff to prescribe, dispense, and administer antibiotics; the communication and coordination among different departments and units, The adherence to clinical guidelines and protocols, the patient's condition and compliance (Mula et al., 2018).

Mashao and colleagues in 2021 also reported that a patient's treatment may be delayed because of insufficient staffing that causes a lengthy wait or a shortage of equipment that causes a delay in treatment (Mashao, Heyns, & White, 2021).

Many hospitals in low- and middle-income countries do not have access to a diagnostic microbiology service, and even when they do, the threshold of clinical suspicion for taking a blood culture is often higher than in high-income settings. Both of these factors can lead to longer delays to concordant antibiotic treatment (Lim et al., 2021).

Other factors that delay a patient's antibiotic treatment include delayed diagnosis, delayed referral systems, financial constraints, lack of knowledge, culture and religion, scarcity of resources, lower triage level and lower disease severity on arrival (Leuangerun & Leelarasamee, 2012).

2.3 Effects of Delayed Antibiotic Initiation

The effects and negative consequences of delayed appropriate therapy are widely reported and accepted. In a retrospective analysis of 17,990 patients with severe sepsis and septic shock, time to first antimicrobial treatment was found to be important for survival. The study found that delay in first antibiotic administration was associated with increased in-hospital mortality with a linear increase in the risk of mortality for each hour delay in antibiotic administration. The study concluded that early and appropriate antibiotic therapy is crucial for improving the survival of patients with sepsis and septic shock (Kumar et al., 2006; Schmidt et al., 2018).

The study about the impact of delayed antibiotic treatment and surgical source control on mortality in patients with sepsis which was secondary analysis of a cluster-randomized controlled trial of

2,796 patients with sepsis from 18 hospitals in Germany, found that delayed antibiotic treatment (> 24 hours after meeting diagnostic criteria) was associated with higher mortality (OR 2.3, $P < 0.001$) compared to timely antibiotic treatment (< 1 hour after meeting diagnostic criteria). The study also found that delayed surgical source control (> 12 hours after meeting diagnostic criteria) was associated with higher mortality (OR 1.6, $P = 0.02$) compared to timely surgical source control (< 6 hours after meeting diagnostic criteria). The study concluded that delayed antibiotic treatment and surgical source control are important modifiable factors for improving the survival of patients with sepsis (Rüddel et al., 2022).

Another study was a systematic review of the effect of delayed appropriate antibiotic therapy on patient outcomes for different types of infections. The authors found that delayed therapy was associated with increased mortality, longer hospital stay, and higher costs for patients with bloodstream infections, pneumonia, intra-abdominal infections, and skin and soft tissue infections. They also found that the duration of delay mattered, as every hour or day of delay increased the risk of poor outcomes and that timely initiation of appropriate antibiotic therapy is crucial for improving patient outcomes and reducing the burden of antibiotic resistance (Zasowski et al., 2020).

Delayed time to effective treatment of gram-negative infections has also been shown to impact negatively on hospital length of stay and costs. A retrospective cohort study of 1,000 patients with serious infections due to Enterobacteriaceae from 10 US hospitals, found that among patients with infections due to susceptible pathogens, delayed appropriate therapy was associated with significantly longer duration of antibiotic therapy (+4.9 days), longer length of stay (+5.5 days) and higher in-hospital costs (+\$9,507) compared to those who received timely appropriate therapy (all, $P < 0.01$). The study also found that among patients with infections due to resistant pathogens, delayed appropriate therapy was associated with higher mortality (OR 2.3, $P = 0.03$) compared to those who received timely appropriate therapy. The study concluded that delayed appropriate therapy has a negative impact on patient outcomes regardless of pathogen susceptibility and that carbapenems may be an effective empiric option for serious infections due to Enterobacteriaceae (Lodise et al., 2019).

Lodise Jr et al. (2007) in a retrospective cohort study of 1,264 patients with gram-negative bloodstream infections from 16 US hospitals reported that delayed appropriate therapy was associated with a 35% decrease in the likelihood of being discharged to home and a 24% increase in the risk of in-hospital mortality or being discharged to hospice. The study also found that delayed appropriate therapy was more common in patients with infections due to resistant organisms than those with susceptible organisms and that delayed appropriate therapy has a negative impact on patient outcomes and that antimicrobial resistance may contribute to the delay (Lodise et al., 2018)

The study that investigated the impact of time-to-antibiotics on clinical outcomes in patients with sepsis and septic shock in the intensive care unit (ICU). They found that delayed antibiotic initiation was associated with increased mortality, organ dysfunction, and ICU length of stay (Im, Kang, Ko, Lee, Lim, Park, Na, Chung, Park, et al., 2022). Other studies have also reported similar findings. For example, another study found that delays in any of the steps involved in antibiotic delivery (such as ordering, dispensing, or administering) increased the risk of hospital death for patients with suspected sepsis in the emergency department (Taylor et al., 2021). Another study by Regoes et al. 2008 showed that early initiation of antibiotic therapy and combination therapy with two antibiotics prevented the emergence of resistant bacteria, whereas shorter courses of therapy and sequential administration of antibiotics promoted the emergence of resistant strains (Taylor et al., 2021). A study by Zhang et al. (2021) found that patients with COVID-19 who received antibiotics had longer hospital stay and higher antibiotic consumption than those who did not (Siewierska et al., 2023).

These studies suggest that timely and appropriate antibiotic therapy is crucial for improving the outcomes of patients and preventing the spread of antibiotic resistance.

CHAPTER THREE: METHODS

3.1 Study Design

The study design was a prospective cohort design. This was conducted to determine the extent, associated factors, effects of delayed antibiotic initiation among adult inpatient receiving antibiotic treatment at Kiruddu National Referral Hospital and Kisenyi Health Center IV. The study design looks forward in time, to examine the relationship between the exposure and the outcome and is best design to measure longitudinal associations.

3.2 Study Setting

The study was conducted at two sites Kisenyi Health Center IV and Kiruddu National Referral Hospital. Kisenyi Health Center IV is one of the eight KCCA managed health facilities in Kampala, located on Mwanga II Road. The health facility is barely two kilometers east of Lubiri Mengo and one kilometer west of old Kampala Mosque. Opened in 2014, Kisenyi health center IV serves a population consisting of traders within the central business district and slum occupants from the nearby areas including Mengo, Kisenyi, Nankulabye, Katwe. It is intended to serve about 100,000 people within the health sub-district with about 1,200 on daily basis (Nuwagaba et al., 2021). The health facility provides a wide range of inpatient, outpatient, and emergency care services. They also provide maternal and child health services including emergency cesarean sections and also offers a dental clinic, HIV and a TB unit. The facility has a capacity of 50 beds, with an average of 20-30 patients being admitted on a daily basis (R. Ssekitoleko et al., 2020).

Kiruddu National Referral Hospital is one of the largest hospitals in Uganda, previously operating under Mulago Hospital Complex. It currently offers services in internal medicine, burns, plastic surgery, radiology and palliative care, and also doubles as the teaching hospital for the Department of Medicine, Makerere University College of Health Sciences. The hospital is located in Makindye Division, Kampala, approximately 13 kilometers (8.1 miles) by road, south-east of the Mulago National Referral Hospital. It has a capacity of 200 beds for inpatient treatment and 14 outpatient clinics, which serve approximately 300-500 patients daily (Nabaweesi et al. 2021). On average 100- 150 patients are admitted on a daily basis despite the lower bed capacity. Among other

facilities, the hospital has the largest infectious disease ward in the country, as well as the only ward specializing in the treatment of patients with burns (Kiruddu Hospital, 2022).

At both facilities, patients arrive directly or by referral, at the reception they are registered in the book. Vitals are taken and sent to a doctor for further examination and diagnosis. The doctor takes history, examines, conducts investigations and decides the treatment plan.

Some patients that may not need admission are directed to the pharmacy to pick drugs that may have been prescribed for them. Patients who require admission receive immediate care at the emergency ward until they stabilize and are taken to the respective wards to receive specialized treatment and care. This setting will enable us to screen the patients, make appropriate recordings and follow up for efficient data collection.

3.3 Study Participants

3.31 Target population

The target population was adult in-patients receiving antibiotic treatment in Uganda.

3.32 Accessible population

The accessible population was adult in-patients who received antibiotic treatment, from 17th April 2023 to 20th June 2023 at Kiruddu NRH and Kisenyi HCIV.

3.33 Study Population

The study population was adult in-patients who received antibiotic treatment, from 17th April 2023 to 20th June 2023 at Kiruddu NRH and Kisenyi HCIV during the study period and who gave informed consent to participate in the study.

3.34. Eligibility criteria

3.341. Inclusion criteria

All inpatients aged 18 years and older were eligible for the study after informed consent.

3.342. Exclusion criteria

Critically ill patients whose attendants did not know their medical and social history.

3.4 Sample Size

Sample size calculation

Specific objective 1: Sample size was determined using the Kish Leslie formula as 340, to estimate the extent of delayed antibiotic initiation.

$$N = Z_{\alpha/2}^2 P (1-P) / \delta^2 \quad \text{Where by:}$$

N = Sample size estimate for inpatients that had delayed initiation of antibiotic

P = percentage of inpatients that had delayed initiation (79.2%) according to a similar study (Bonnie et al. 2019).

(1-P) = probability of inpatients that received early antibiotic treatment, so 1-P = 20.8%

Z_{α} = Standard normal deviation at 95% confidence corresponding to 1.96

δ = Absolute error to be taken is 5%. Therefore, the sample size required was;

$$N = 1.96^2 \times 0.28(0.792) / (0.05)^2 \quad N = 340 \text{ patients}$$

10% of this was added to cater for the non-response making the final sample size for the study 362

Specific objective 2: The sample size to be used in determining the factors associated with delayed antibiotic initiation was also calculated using the formula for comparative studies.

$$N = \frac{[z_{\alpha/2} \sqrt{P(1-P)(1/q_1 + 1/q_2)} + z_{\beta} \sqrt{P_1(1-P_1)(1/q_1) + P_2(1-P_2)(1/q_2)}]^2}{(P_1 - P_2)^2}$$

$Z_{\alpha/2}$ is the standard normal value corresponding to the level of significance (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96),

Z_{β} is the standard normal value corresponding to the power of the study (e.g. for a power of 90%, β is 0.2150 and the critical value is 1.64)

Where P_1 is the proportion of participants expected to have delayed antibiotic initiation in one group. P_2 is the proportion of participants expected to have delayed antibiotic initiation in the 2nd group, q_1 is proportion of participants in the first group, q_2 is proportion of participants in the 2nd group who will not delay antibiotic initiation, $P = q_1P_1 + q_2P_2$ and N being total number of participants. Assuming a difference in delayed antibiotic initiation of 7% (N. G. Bonine et al., 2019) between groups. Hence, P_1 of 53%, and $p_2=49\%$. Taking equal numbers in the two groups, hence $q_1 = q_2 = 0.5$, therefore $N= 570$.

Since 570 was greater than 340, the sample size for two proportions (570) was considered for this study. 10% was added to the estimated sample size to cater for non-response making the final sample size for the study of 606.

3.5 Sampling

Proportionate sampling

Proportionate sampling was used to get the proportion of patients in each health facility. The total population of eligible adult in-patients each month is 600 in Kisenyi HCIV and 3000 in Kiruddu NRH admitted each month in these facilities respectively.

The proportions were calculated as follows;

Estimated number eligible at site X required sample size = required sample

Total population $600 + 3000 = 3600$

Proportions per facility

Kisenyi HCIV $(600/3600) \times 606 = 101$

Kiruddu National Referral Hospital $(3000/3600) \times 606 = 505$

Systematic sampling

Systematic sampling was used to recruit the eligible participants. The sampling interval was calculated as follows;

Sampling interval = Estimated number of eligible patients at site/number to be selected from site:

Kiruddu National Referral Hospital $3000/ 505 = 6$

Kisenyi HCV $600/101 = 6$

Every 6th eligible participant was recruited. The first participant at each site was selected from the first 6 patients using simple random sampling by picking a random number from 1 to 6. Number 3 was selected at Kiruddu NRH and number 5 at Kisenyi HCIV; these were the first participants at each site. Thereafter, every 6th eligible participant was selected. In case the 6th participant was not eligible; the next eligible participant was taken. Study participants were accessed in inpatient wards. Both proportionate and systematic sampling methods are probability sampling methods which means that the eligible participants have equal chances of being part of this study.

3.6 Variables

3.6.1 Dependent variables

The dependent variable is delayed antibiotic initiation; extent of delayed antibiotic initiation was determined as the proportion of in-patients with delayed antibiotic initiation in relation to the total number of in-patients in the study.

3.6.2 Independent variable

Independent variables will include factors associated with delayed antibiotic initiation which are categorized into system related factors (delayed referrals, scarcity of resources, poor patient education, professional experience), patient related factors (age, gender, education level, comorbidities, non-adherence, economic /cost and treatment related factors (delayed diagnosis, misdiagnosis, self-medication, poor patient education, unlicensed/un qualified practitioners).

3.7 Data Collection

3.7.1 Data collection tools

A researcher-administered pre-formulated questionnaire (Appendix 1) was completed by the participants (inpatients), to find out (extent, associated factors and effects) delayed antibiotic initiation. It was adopted and modified from the questionnaire used in a study in Uganda (Kiguba, Karamagi, & Bird, 2016). The tool included both closed and open-ended questions to explore participant demographics, associated factors, effects of delayed antibiotic initiation. Prior administration of the tool to 10 inpatients at Kisenyi HCIV for validation purposes was done. These were excluded from the study. No changes were made to the tool after pretesting. The questionnaire was divided into three sections. Section A explored participant demographics.

Section B captured all associated factors (patient related, system related, treatment related). Section C captured consequences of delayed antibiotic initiation including length of stay.

3.7.2 Data collection Procedure.

Four research assistants were employed to carry out the data collection. (3 Kiruddu NRH and 1 in Kisenyi HCIV) from 17 April 2023 to 20 June 2023. They were trained on how to use the data collection tool and how to carry out data collection. Participants were consented and recruited into the study at the time of admission to their respective specialist wards. Administration of the tool took approximately 15 minutes per participant. At the end of each day, each research assistant returned the paper questionnaire to the lockable safety cabinet where they were picked later for follow up at the time of discharge or death. Patient files and records were also used to complete the questionnaire. Completed paper questionnaires were picked weekly by the PI for data entry.

3.8. Data Management

Questionnaires were checked for completeness and accuracy every two days by the principal investigator. Data were entered into Epi data version 4.4.2.1, cleaned and later exported to Stata version 17 for analysis. All data were backed up at all stages of data entry and analysis on an external hard disk. All data were treated with utmost confidentiality and no patient identifiers were collected.

3.9. Data Analysis

Data analysis was done using Stata (version 17). This analysis was done at various levels including univariate, bivariate and multivariable analysis levels.

3.91 Descriptive analysis

Univariate analysis was done to describe the characteristics of the study participants. Continuous variables following a normal distribution were summarized as means and standard deviations and non-normally distributed data as medians and interquartile ranges. Categorical variables were summarized as percentages and proportions with their 95% confidence interval. These results were reported in tables, cross-tabulations and text.

3.92 Analysis for objective one - extent of delayed antibiotic initiation in adult inpatients.

The Extent of delayed antibiotic initiation was determined by dividing the number of adult inpatients that experienced delayed antibiotic initiation by the total number of study participants. Delayed antibiotic use was defined as the use of or advice to use antibiotics more than 48 hours after the initial consultation (Arnold and Hollenberg 2012).

3.93 Analysis for objective two- factors associated with delayed antibiotic initiation in adult inpatient.

For the bi-variate analysis, associations between independent variables and the outcome variable (delayed antibiotic initiation) were assessed. Continuous independent variables were categorized and their association with the outcome variable established using Chi-square tests. The measure of association for categorical variables was odds ratios (OR) with their 95% confidence intervals and P-values less than 0.05 were considered significant. Since the outcome variable was at two level, we used binary logistic regression to assess relationships between predictors and the outcome. Variables with p-value less than 0.2 were considered for further multivariable analysis.

Multivariable analysis, was done using multiple logistic regression models for all the variables that had p-value less than 0.2. We tested for interaction and confounding to develop the final model in order to determine the significant associated factors with delayed antibiotic initiation at the level of significance of 0.05. In order to test for interaction, we ran a stepwise model to obtain significant variables at the level of 0.05. Thereafter, we formed interaction terms among the significant variables and then ran a stepwise model to determine if there were any significant interaction terms at the level of 0.05.

The confounding effect was assessed for as follows; any variables dropped from the model (that has p-value greater than 0.05) by putting them back in the model one by one and calculating the percentage difference in the coefficients in the crude models and adjusted models (variables that caused a greater than 10% difference in the coefficients were considered confounders) was calculated. There were no confounding variables.

3.94 Analysis for objective 3 -effect of delayed antibiotic initiation among adult in-patients

To determine the effects of delayed antibiotic initiation, files of the patients were reviewed during treatment, discharge or death, and the length of stay in hospital (LOS) was calculated from time of admission to discharge time or death. Using Chi-square tests, we compared the LOS between patients who had antibiotics given on time versus LOS among patients in whom use of antibiotics was delayed.

3.10 Quality Control

The tools were translated to Luganda and back translated to English to ensure that the translation process did not distort any information. The questionnaire was pretested in 10 study participants at Kisenyi HCIV. The research assistants were trained for 1 week prior to data collection. The study teams were supervised daily and all questionnaires were checked for completeness every two days by the principal investigator. Where necessary, the participants were contacted to correct any errors, otherwise data with errors were treated as missing data during analysis.

3.11 Ethical Considerations

Ethical approval was obtained from the School of Biomedical Sciences Research Ethics Committee Makerere University (IRB-SBS) to conduct this research. The protocol was presented before the Journal club at department of Pharmacology and Therapeutics Makerere University. Permission to conduct the study was obtained from KCCA directorate of public health, Kiruddu NRH. Participants were absolutely free to decline or withdraw their participation in the study. The risks of taking part in the study were minimal and ranged from minor discomfort during the consent and some information concerning participant identity being known by the study team. It was a minimal risk study without any anticipated problems. Written informed consent was obtained from all the study participants and all information concerning their identities was kept anonymous, with the questionnaires and consent forms kept under lock and key with access only to the study team.

3.12 Dissemination of Results

A report of the findings of this study will be shared with Makerere University Sir Albert Cook Medical library, Directorate of Research and Graduate Training Makerere University, the Department Pharmacology and Therapeutics Makerere University, Kiruddu NRH and Kisenyi HCIV. A presentation of the findings of this study may be made at scientific conferences, and the findings will be published in a scientific journal.

CHAPTER FOUR: RESULTS

4.1 Description of Study Participants

A total of 606 participants were recruited into the study from Kiruddu NRH (505) and Kisenyi HCIV (101). The participants were aged between 18 to 99 years with a median age (1st, 3rd quartile) of 34 (25-52) years and the majority were female (66%, 400/606). Most of the participants were married (61%, 370/606) and had attained primary-secondary level of education (73.8%, 447/606). Two thirds, 65.8% (398/606) of the participants reported that they had a household income less than they need with majority 49.3% (299/606) residing in the suburban. See **Table 1**.

Table 1. Socio-demographic characteristics of 606 adult in-patients at Kiruddu NRH and Kisenyi HCIV

Characteristics	Frequency, n (%) N=606
Gender, n=606	
Male	206 (34.0)
Female	400 (66.0)
Age in years, median (IQR)	34 (25-52)
SD (Range)	18.8 (18-99)
Age (years) groups, n=606	
18-24	137 (22.6)
25-34	177 (29.2)
35-44	94 (15.5)
45+	198 (32.7)
Patient's residence, n=606	
Urban	123 (20.3)
Suburban	299 (49.3)
Rural	182 (30.0)
Homeless	2 (0.3)
Marital status, n=606	
Single	103 (17.0)
Married	370 (61.0)
Divorced/separated	40 (6.6)
Widowed	58 (9.6)
Cohabiting	35 (5.8)
Level of education, n=606	
Advanced/colleague	53 (8.7)
Primary-secondary	447 (73.8)
No formal education	106 (17.5)
Household income, n=605	
More money than you need	11 (1.8)
Just enough money	196 (32.4)
Less money than you need	398 (65.8)

4.2 Extent of Delayed Antibiotic Initiation

The extent of delayed antibiotic initiation was 6 % (36/606), 6.5 % (33/505), 95% CI (4.5-9.1) were in Kiruddu NRH and 3 % (3/101), 95% CI (0.1-8.4) from Kisenyi HCIV see **Table 2**

Table 2: Extent of delayed antibiotic initiation per study site

	Total	Not delayed initiation	Delayed initiation	(95% CI)
Kiruddu NRH	505	472 (93.5)	33 (6.5)	4.5-9.1
Kisenyi HCIV	101	98 (97.0)	3 (3.0)	0.1-8.4
Total	606	570 (94.1)	36 (5.9)	4.2-8.1

4.21 Comparison of patients' characteristics those that had delayed antibiotic initiation and those that didn't have antibiotic initiation

The proportion of delayed antibiotic initiation was described across patients' characteristics using frequency and percentage and compared using Pearson Chi square test. There was a significant difference between the patients that had delayed antibiotic initiation and those that did not have delayed antibiotic initiation for the following variables; household income, reason for choice of facility, time to consultation, number of health workers, not ware of disease severity, Not having a previous satisfactory experience as illustrated in **Table 3**

Table 3: Comparison of characteristics between the patients that had delayed antibiotic initiation and those that didn't have delayed antibiotic initiation, Uganda ,2023

	Overall N=606	Time from consultation to antibiotic initiation		Chi-square p-value
Patient Knowledge		0-48 hours N=570 (row%)	49&Above N=36 (row%)	
Household income, n=605				
More money than you need	11	9 (81.8)	2 (18.2)	
Just enough money	196	180 (91.8)	16 (8.2)	0.047
Less money than you need	398	380 (95.5)	18 (4.5)	
Why choice of facility n= 596				
Close	107	103 (96.3)	4 (3.3)	
Been here before	260	241 (92.7)	19 (7.3)	0.002
Friend/family recommend	78	73 (93.6)	5 (6.4)	
Referred/ Know provider	151	144 (95.7)	7 (4.3)	
How long from when you saw doctor to treatment (time to consultation)				
Half day	532	508 (95.5)	24 (4.5)	
One day	61	57 (93.4)	4 (6.6)	0.000
1-2 days	13	5 (38.5)	8 (61.5)	
Enough health workers n= 568				
Yes	273	263 (96.3)	10 (3.7)	0.041
No	330	305 (92.4)	25 (7.6)	
Patient knowledge on disease severity	330/603(54.7%)	305/330 (92.4)	25/330 (7.6)	0.041
Patient previous satisfactory experience	15/605 (24.7%)	11/15 (73.3)	4/15 (26.7)	0.001

4.3. Factors Associated with Delayed Antibiotic Initiation

4.3.1 Bivariate Analysis

At bivariate level, the following variables had p-values less than 0.2 and were therefore considered for multivariable analysis; Age, marital status, household income, health facility accessibility, convenient health facility hours, enough health workers, time to consultation. See **Table 4** below.

Table 4: Bivariate analysis of factors associated with delayed antibiotic initiation among adult in-patients, Uganda 2023.

	Overall N=606	Time from consultation to antibiotic initiation			
Patients' Characteristics		0-48 hours N=570 (row%)	49&Above N=36 (row%)	Crude OR (95%CI)	p- value
Gender, n=606					
Male	206	192 (93.2)	14 (6.8)	1	
Female	400	378 (94.5)	22 (5.5)	0.80(0.40-1.59)	0.523
Age in years, median (IQR)	34 (25-52)	33 (25-51)	41 (26-55)		
Age (years) groups n=606					
18-24	137	131 (95.6)	6 (4.4)	1	
25-34	177	169 (95.5)	8 (4.5)	1.03(0.35-3.05)	0.952
35-44	94	88 (93.6)	6 (6.4)	1.49(0.47-4.76)	0.503
45+	198	182 (91.9)	16 (8.1)	1.92(0.73-5.04)	0.185
Patient's residence					
Urban/Suburban	422	399 (94.6)	23 (5.5)	1	
Rural	184	171 (92.9)	13 (7.1)	1.32 (0.65-2.66)	0.441
Marital status, n=606					
Single/cohabiting	138	133 (96.4)	5 (3.6)	1	
Married	370	343 (92.7)	27 (7.3)	2.09(0.80-5.55)	0.137
Divorced/separated/widowed	98	94 (95.9)	4 (4.1)	1.13(0.30-4.33)	0.856
Level of education					
Formal education	500	469 (93.8)	31 (6.2)	1	
No formal education	106	101 (95.1)	5 (4.7)	0.75 (0.28-1.97)	0.559
Household income, n=605					
Just enough money	207	189 (91.3)	18 (8.7)	1	
Less money than you need	398	380 (95.5)	18 (4.5)	0.50(0.25-0.98)	0.043

	Overall N=	Time from consultation to antibiotic initiation			
		0-48 hours N=570 (row%)	49&Above N=36 (row%)	Crude OR (95%CI)	p- value
How long from when you saw doctor to treatment n=606					
Half day	532	508 (95.5)	24 (4.5)	1	
More than half a day	74	62 (83.8)	12 (16.2)	4.10 (1.95-8.60)	0.000
Enough health workers n=568					
Yes	273	263 (96.3)	10 (3.7)	1	
No	330	305 (92.4)	25 (7.6)	2.16 (1.02-4.57)	0.045
Bought medication outside n= 594					
Yes	353	333 (93.0)	25 (7.0)	1	
No	236	225 (95.3)	11 (4.7)	0.65 (0.31-1.35)	0.249
Easy access to health Centre n= 533					
Yes	366	341 (93.2)	25 (6.8)	1	
No	167	161 (96.4)	6 (3.6)	0.51 (0.20-1.26)	0.145
Heath Centre has convenient hours n=536					
Yes	429	401 (93.5)	28 (6.5)	1	
No	107	104 (97.2)	3 (2.8)	0.41 (0.12-1.39)	0.152

4.32 Multivariable Analysis

In the adjusted model, factors independently associated with delayed antibiotic initiation were household income and time wait to consultation. These are shown in **Table 5** below. There was no significant interaction or confounding with any of the variables of interest.

Table 5. Multivariable analysis of factors associated with delayed antibiotic initiation

Characteristics	N	Prevalence n (%)	Crude OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Age (years) groups						
19-24	137	6(4.4)	1		1	
25-34	177	8(4.5)	1.03(0.35-3.05)	0.952	0.76(0.23-2.54)	0.660
35-44	94	6(6.4)	1.49(0.47-4.76)	0.503	0.94(0.24-3.75)	0.939
45+	198	16(8.1)	1.92(0.73-5.04)	0.185	2.33(0.68-7.93)	0.176
Marital status						
Single/cohabiting	138	5(3.6)	1			
Married	370	27(7.3)	2.09 (0.80-5.55)	0.137	1.23(0.41-3.70)	0.717
Divorced/separated/widowed	98	4(4.1)	1.13 (0.30-4.33)	0.856	0.26(0.39-1.83)	0.179
Household income						
Just enough money	207	18 (8.7)	1			
Less money than you need	398	18 (4.5)	0.50 (0.25-0.98)	0.043	0.29(0.121-0.70)	0.006
health facility accessibility						
Yes	366	25 (6.8)	1			
No	167	6 (3.6)	0.51 (0.20-1.26)	0.145	0.57(0.20-1.62)	0.291
Health facility convenient hours						
Yes	429	28 (6.5)	1			
No	107	3 (2.8)	0.41 (0.12-1.39)	0.152	0.43(0.11-1.67)	0.212
Enough health workers						
Yes	273	10 (3.7)	1			
No	330	25 (7.6)	2.16 (1.02-4.57)	0.045	2.37(0.91-5.37)	0.080
time waits to consultation						
Half day	532	24 (4.5)	1			
More than half a day	74	12 (16.2)	4.10 (1.95-8.60)	0.000	5.35(2.10-13.64)	0.000
Bought medication outside						
Yes	353	25 (7.0)	1			
No	236	11 (4.7)	0.65 (0.31-1.35)	0.249	0.54(0.21-1.34)	0.182

Patients with lower household income were 71% less likely to have their initial antibiotic treatment delayed than those who had more income (aOR= 0.29, p = 0.006 CI =0.12-0.70). This was the only patient related factor that had significant relationship with delayed antibiotic initiation.

Time waits to consultation, a health system-related factor, was also a risk factor for delayed antibiotic initiation. Patients that took more than half a day to consultation were five times more likely to delay antibiotic treatment initiation than those whose consultation was within half a day after arrival at the facility (aOR= 5.35, p = 0.000 CI =2.10-13.64).

4.4 Relationship between delayed Antibiotic Initiation and Length of Hospital Stay (LOS)

In this study, patients whose antibiotic treatment was delayed had longer length of hospital stay than those who received antibiotic treatment on time. The average length of stay for the 36 in-patients that received delayed antibiotics was 190 (IQR) hours while the average LOS for the 570 in-patients who received antibiotics on time was 109.4 (IQR) hrs. The average LOS was significantly different (i.e. p = 0.0000) for both groups. Delayed antibiotic initiation was positively associated with prolonged length of hospital stay as showed in **Table 6**.

Table 6 showing relationship between length of hospital stay and delayed antibiotic initiation

Time from consultation to treatment start	N	Mean	Median (IQR)	(min-max)
0-48	570	109.3667	79.5 (41-124)	(0-917)
49&Above	36	190	170 (118-249)	(28-534)
Total	606	114.1568	83 (45-137)	(0-917)

CHAPTER FIVE: DISCUSSION

5.1 Extent of Delayed Antibiotic Initiation

The extent of delayed antibiotic initiation among adult inpatients at Kiruddu NRH and Kisenyi HCIV was 6%, 36 out of the 606 participants had delayed antibiotic initiation. This study showed a low extent of delayed antibiotic initiation. This study is an indication that most patients receive their first antibiotic dose(s) on time. This could be explained by the fact that the two study sites are government hospitals located in an urban setting which provides free-of-charge services. Patients here, easily and readily access basic antibiotic medication to initiate treatment. A higher extent of delayed antibiotic initiation (46.2% and 33.0%) was reported by Bonnie and colleagues in a retrospective study of 50,302 patients that compared delayed appropriate therapy among patients with resistant and susceptible infections (N. G. Bonine et al., 2019). Several factors may have contributed to the difference in findings including; different study designs, different delayed antibiotic initiation definitions, different data collection methods and number of patients involved in the studies.

5.2. Factors Associated with Delayed Antibiotic Initiation

Although we theorized that delayed antibiotic initiation was associated with a number of factors (patient residence, marital status, level of education, delayed referral systems, financial constraints, scarcity of resources, lower triage level, lower disease severity on arrival, number of health workers, delayed diagnose), none of the suspected factors were found to be associated with the occurrence of delayed antibiotic initiation in this study. However, household income, patient waits before consultation were associated with delayed antibiotic initiation.

Household income was associated with delayed antibiotic initiation in this study. The lower the household income the less likely treatment was delayed. This is contrary with a study by Huang and Bach (2016), where he demonstrated that lack of money to pay for services is the most commonly reported reason for delayed use or failure to use antibiotics (Huang & Bach, 2016). Zhuang et al, also indicated that financial distress is highly associated with annual household income and that patients who experience higher financial distress are more likely to delay their treatment (Zhuang et al., 2021). The study sites were a National Referral and a Health Center IV where most services are free though patients usually make some financial contributions to their

treatment and care when deemed necessary. The low household income status suggests why majority of study participants preferred seeking free services at these sites than going to private hospitals. The difference between these studies could still be explained by the differences in study sites, study populations, healthcare policies and financing.

The study also found out that the longer the patient waited for consultation the more likely their initiation of antibiotic treatment was delayed. Patient wait time may be inevitable but their reduction is important as they determine when treatment maybe started and thus treatment outcomes. Longer waits are associated with negative patient satisfaction, decreased confidence in care provider and quality of care (Bleustein et al., 2014). In a study (Lai et al., 2021) consistent with this indicates that delay in doctor consultation can increase morbidity and mortality risk associated with various health conditions, and reduce the effectiveness of treatments.

5.3. Relationship Between Length of Hospital Stay (LOS) and Delayed Antibiotic Initiation

The length of hospital stay (LOS) is a relevant outcome measure because it reflects the recovery time of patients and defines hospital costs. LOS in this study was assessed overall from admission to discharge or death. Delayed antibiotic initiation was associated with significantly longer LOS compared with those that were not delayed. The average length of stay was significantly different (i.e. $p = 0.0000$) for both patients with on time and delayed initiation.

The LOS in this study was consistent with a large retrospective cohort study by Bonnie where he found longer LOS (117.6 hours, +4.9 days) for the patients that received delayed antibiotic therapy compared to those that received timely antibiotic therapy (Nicole Gidaya Bonine et al., 2019). The study supports the hypothesis that delayed antibiotic initiation is a risk factor for prolonged hospitalization.

5.4 Limitations of the study

- The study only used quantitative methods, mixed methods with multistage sampling would provide extra information regarding reasons and effects of delayed antibiotic initiation.
- This study was conducted at public facilities where some baseline assessments such as antibiotic resistance, culture and sensitivity are not routinely done because they are not available.
- The study was done in national referral and teaching hospital located in the urban area, however Kiruddu being a national referral hospital also receives patients from rural area.
- As for referrals, limited data was available on previous hospitalization and antibiotic usage, patient treatment referral information was incomplete.
- The study did not take in consideration other patient populations, it was limited to only adult in-patients.
- Although delayed antibiotic initiation is associated with many negative treatments outcomes, we only assessed length of stay (LOS) in this study as a surrogate measure for disease progression among different patients.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusions

- The study result showed an extent of 6 % delayed antibiotic initiation which is a low proportion compared to similar studies. In this study the majority of patients received their antibiotic treatment on time.
- Delayed antibiotic initiation was mainly associated with household income and patient wait to consultation.
- Patients with lower household income were less likely to have delayed antibiotic treatment initiation.
- The longer the patient waited before consultation the more likely their initiation of antibiotic treatment was delayed, this deserves to be explored further.
- The study further corroborates the observation that length of stay (LOS) is associated with delayed antibiotic treatment. Delayed antibiotic initiation prolongs hospitalization and treatment.

6.2 Recommendations

- A retrospective cohort study and qualitative methods should be used in further studies to provide extra information on the extent and associated factors of delayed antibiotic initiation.
- Patient education on importance and benefits of timely antibiotic initiation is highly recommended.
- Further research in different patient populations and at different level of care setting is needed to examine the extent and associated factors.
- Further research to access the effects and complications of delayed antibiotic initiation should be conducted.

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APPENDICES

Appendix 1: Copy of the English consent form

MAKERERE UNIVERSITY COLLEGE OF HEALTH SCIENCES

SCHOOL OF BIOMEDICAL SCIENCES RESEARCH AND ETHICS COMMITTEE

(SBSHD-REC)

INFORMED CONSENT TEMPLATE FOR INTENDING RESEARCHERS

Title of the proposed study;

Extent, associated factors, and effects of delayed antibiotic initiation in adult inpatients receiving treatment at Kisenyi health center IV and Kiruddu National Referral Hospital.

Investigator:

Student

Nsereko Mansoor Kalimunda Tel: +256758535258

Department of pharmacology and therapeutics

Makerere University College of biomedical sciences

Background and rationale for the study:

Adult inpatients are usually affected by either community acquired bacterial infections or nosocomial infection. Delayed appropriate antibiotic therapy leads to treatment complications including prolonged hospitalization and death. This study aims at exploring the extent, associated factors, and effects of delayed antibiotic initiation in adult inpatients receiving treatment at Kisenyi health center IV and Kiruddu National RH.

A description of sponsors of the research project and the organizational affiliation of the researchers:

Purpose:

This study aims to find the extent, associated factors, and effects of delayed antibiotic initiation. We are just asking questions and the answers that we get shall be used to answer our research questions, no experiments are involved in this study

The estimated duration the research participant will take to in the research project:

Procedures:

A researcher administered questionnaire (CRF) will be used to collect data on patient demographics, previous health status and medication history, current diagnosis and time of antibiotic treatment initiation and treatment outcomes. We shall also get information by reading medical records.

Who will participate in the study:

The study will include all adult inpatients receiving treatment in the inpatient department at Kisenyi health center IV and Kiruddu National Referral Hospital. Participation in this study is voluntary. If you decide to join this study, you be in this study from time you are in hospital until you are discharged by attending doctor. 630 patients will be required to participate in the study.

Risks/Discomforts:

We don't expect any harm to happen to study participants because study will involve asking and answering questions, reading medical records which are harmless activities

Benefits:

You will not directly benefit from participating in the study. Information from study will benefit others including policy makers.

Confidentiality:

The results of this study will be kept strictly confidential, and used only for research purposes. My identity will be concealed in as far as the law allows. My name will not appear anywhere on the coded forms with the information. Paper and computer records will be kept under lock and key and with password protection respectively. local Research Ethics Committee (REC) and Uganda National Council for Science and Technology (UNCST) as entities which may have access to private information that identifies the research participants by name.

Alternatives:

Since participation here is not a must, non-participants here will still receive all the necessary treatments everyone can get in the hospital.

Cost:

Since we expect to ask participants questions, we don't expect them spend any money for their participation

Compensation for participation in the study:

There is no direct benefit to participants but we hope the findings will help other people including policy makers.

We don't expect any harm to any participant in the study but in case of any physical injury we will provide medical treatment at this centre, incase during the study you develop other unrelated health conditions for which treatment is needed we cannot assume financial responsibility for treatment; however, we will refer you to your regular healthcare provider /facility for specific evaluation treatment and follow up.

Reimbursement:

You will not receive any payment in form of travel costs, you will not be given food or drink while participating in the study.

Questions about participants rights:

As a participant in this research, you have rights which shall not be violated. any questions about participant rights, they will be addressed by to research student and his supervisors. Lastly, they could be addressed to head of school of biomedical science, research and ethics committee Dr. Erisa Mwaka (0752575050).

Statement of voluntariness:

Participation in this study is completely a choice, if you chose not or if you decide later to stop taking part you will continue receiving all services that would be normally got hospital

Dissemination of results:

The knowledge that we get from this research will be presented to Makerere University and then shared with kiruddu NRH and kisenyi HCIV before it is made widely available to the public. Each participant can view these results at the hospital. We will publish the results of this study and also present them at scientific conferences so that other interested people may learn from the results of this study.

Ethical approval

Permission will be got form Makerere university pharmacology and therpeutic department , kiruddu hospital , kisenyi Health center IV. Ethical approval will be obtained from the School Of biomedical science Research and Ethics Committee at Makerere University.

Consent:

The interviewer has discussed this information with me and offered to answer my questions.

STATEMENT OF CONSENT/ASSENT

..... has described to me what is going to be done, the risks, the benefits involved and my rights regarding this study. I understand that my decision to participate in this study will not alter my usual medical care. In the use of this information, my identity will be concealed. I am aware that I may withdraw at any time. I understand that by signing this form, I do not waive any of my legal rights but merely indicate that I have been informed about the research study in which I am voluntarily agreeing to participate. A copy of this form will be provided to me.

NameSignature/thumb print of participantDate

Name Signature of interviewer/Person obtaining informed consent
.....Date

Appendix 2: Copy of the Luganda consent form

MAKERERE UNIVERSITY COLLEGE OF HEALTH SCIENCES

SCHOOL OF BIOMEDICAL SCIENCES RESEARCH & ETHICS COMMITTEE (SBS-
REC)

INFORMED CONSENT TEMPLATE FOR INTENDING RESEARCHERS

Title of the proposed study:

Extent, associated factors, and effects of delayed antibiotic initiation in adult inpatients receiving treatment at Kisenyi health center IV and Kiruddu National Referral Hospital.

Investigators:

Student

Nsereko Mansoor Kalimunda Tel: +256758535258

Department of pharmacology and therapeutics

Makerere University College of health sciences

Ensibuko n'ensonga lwaki okunoonyereza kuno:

Abalwadde abakulu abajjanjabirwa mu ddwaaliro batera okukosebwa oba yinfekisoni za bakitiriya ezifunibwa mu kitundu oba obulwadde obuwa mu malwaliro. Okulwawo obujjanjabi obutuufu obw'eddagala eritta obuwuka kivaako ebizibu by'obujjanjabi omuli okumala ebbanga eddene mu ddwaaliro n'okufa. Okunoonyereza kuno kugenderera okunoonyereza ku bunene, ensonga ezikwatagana nabyo, n'ebiva mu kulwawo okutandika eddagala eritta obuwuka mu balwadde abakulu abajjanjabirwa mu ddwaaliro lya Kisenyi health centre IV ne Kiruddu National RH.

Omugaso:

Okunoonyereza kuno kugenderera okuzuula ekigero ,ensonga ezikwatagana, n'ebiva mu kulwawo okutandika eddagala eritta obuwuka. Tuli mu kubuuzo bibuuzo byokka era eby'okuddamu bye tufuna bijja kukozezebwa okuddamu ebibuuzo byaffe eby'okunoonyereza, tewali kugezesa kukwatibwako mu kunoonyereza kuno.

Enkola:

Ekibuuzo ekiweebwa omunoonyereza (CRF) kijja kukozezebwa okukung'aanya ebikwata ku bungi bw'abalwadde, embeera y'obulamu obw'emabega n'ebyafaayo by'eddagala, okuzuula obulwadde mu kiseera kino n'obudde obujjanjabi obutta obuwuka bwe butandikibwawo n'obujjanjabi bwe bufuluma. Era tujja kufuna obubaka nga tusoma ebiwandiiko by'abasawo.

Ani agenda okwetaba mu kusoma?

Okunoonyereza kuno kugenda kuzingiramu abalwadde bonna abakulu abajjanjabirwa mu ddwaaliro mu kitongole ky'abalwadde abajjanjabirwa mu ddwaaliro e Kisenyi health centre IV ne Kiruddu National Referral Hospital. Okwetaba mu kunoonyereza kuno kwa kyeyagalire. Bw'osalawo okwegatta ku kunoonyereza kuno, obeera mu kunoonyereza kuno okuva lw'oli mu ddwaaliro okutuusa lw'osiibulwa omusawo akujjanjaba. Abalwadde 393 be bagenda okwetaagibwa okwetaba mu kunoonyereza kuno.

Obulabe/Obutabeera bulungi:

Tetusuubira nti kabi konna kajja kutuuka ku beetabye mu kunoonyereza kubanga okunoonyereza kujja kuzingiramu okubuuza n'okuddamu ebibuuzo, okusoma ebiwandiiko by'abasawo nga bino bikolwa ebitali bya bulabe

Emigaso:

Tojja kuganyulwa butereevu mu kwetaba mu kusoma. Amawulire agava mu kusoma gajja kuganyula abalala omuli n'abakola enkola.

Enkola endala:

Okuva okwetaba wano bwe kitali kikulu, abatali beetabye wano bakyafuna obujjanjabi bwonna obwetaagisa buli muntu bw'asobola okufuna mu ddwaaliro.

Omuwendo

Okuva bwe tusuubira okubuuza abeetabye mu kutendekebwa ebibuuzo, tetusuubira nti basaasaanya ssente yonna olw'okwetabamu

Okuliyirira olw'okwetaba mu kunoonyereza kuno:

Tewali mugaso gwa butereevu eri abeetabye mu kutendekebwa naye tusuubira nti ebizuuliddwa bijja kuyamba abantu abalala omuli n'abakola enkola.

Tetusuubira bulabe bwonna eri omuntu yenna eyeetabye mu kunoonyereza naye singa wabaawo obuvune bwonna ku mubiri tujja kuwa obujjanjabi mu kifo kino, incase during the study you develop other unrelated health conditions for which treatment is needed we cannot assume financial responsibility for obujjanjabi; wabula, tujja kukusindika eri omusawo wo owa bulijjo /ekifo kyo okufuna obujjanjabi obw'enjawulo obw'okwekenneenya n'okugoberera.

Okuddizibwa ssente:

Tojja kufuna kusalulwa kwonna mu ngeri ya ssente z'entambula, tojja kuweebwa mmere oba kunywa nga weetaba mu kunoonyereza.

Ebibuuzo

Ekibuuzo kyonna ekikwata ku kunoonyereza kuno kijja kuweebwa Nsereko Mansoor Kalimunda, 0758535258

Ebibuuzo ebikwata ku ddembe ly'abeetabye mu kutendekebwa:

Ng'omuntu eyeetabye mu kunoonyereza kuno, olina eddembe eritajja kutyoboolwa. ebibuuzo byonna ebikwata ku ddembe ly'abeetabye mu kugezesebwa, bijja kukolebwako okunoonyereza ku muyizi n'abalabirira be. Ekiembayo, bayinza okutuusibwa eri akulira essomero lya ssaayansi w'ebyobulamu, okunoonyereza n'okukwasisa empisa P.O BOX 6062 Makerere university college of health science, Kampala

Ekiwandiiko ky'obwannakyewa:

Okwetaba mu kunoonyereza kuno kwe kulonda ddala, bw'oba wasalawo obutasalawo oba bw'osalawo oluvannyuma okulekera awo okwetaba mu kunoonyereza kuno ojja kusigala ng'ofuna obuweereza bwonna obwandifunye mu ddwaaliro mu budde obwa bulijjo

Okukuuma ebyama:

Ebinaava mu kunoonyereza kuno bijja kukuumibwa nga bya kyama nnyo, era bikozeeddwa mu kunoonyereza kwokka. Endagamuntu yange ejja kukwekebwa mu kifo amateeka we gakkiriza. Erinnya lyange terijja kulabika wonna ku foomu eziriko enkoodi n'amawulire ago. Ebiwandiiko by'empapula ne kompyuta bijja kukuumibwa wansi wa kkufulu n'ekisumuluzo era nga bikuumibwa ebiganbo by'okuyingira.

Omuntu eyabuuzo ebibuuzo ayogeddeko nange ku mawulire gano era n'awaayo okuddamu ebibuuzo byange. Ku bibuuzo ebirala byonna, nnyinza okutuukirira Essimu :(+256) Oba Ssentebe, School of BIOMEDICAL Sciences Institutional Review Board (MakSBS-IRB) oba Uganda National Council of Sciences and Technology. Essimu: (+256) 772-404970 oba (+256)-41-250431

OKUKIRIZA

.....
 annyonnyodde ekigenda okukolebwa, akabi, emigaso egizingirwa n'eddembe lyange erikwata ku kunoonyereza kuno. Ntegedde nti okusalawo kwange okwetaba mu kunoonyereza kuno tekijja kukyusa bujjanjabi bwange obwa bulijjo. Mu kukozeza amawulire gano, endagamuntu yange ejja kukwekebwa. Nkimanyi nti nnyinza okuvaamu essaawa yonna. Ntegedde nti bwe nssa omukono ku ffoomu eno, sivaako ddembe lyange lyonna ery'amateeka wabula ntegeeza kyokka nti ntegeezeddwa ku kunoonyereza kw'okunoonyereza kwe nkiriza okwetabamu kyeyagalire. Kopi ya foomu eno ejja kunweebwa.

Erinnya:..... Omukono gw'omwetabamu

Olunaku olw'omweezi

Erinnya..... Omukono gw'Omubuuzi

Olunaku olw'omweezi.....

Appendix 3: Copy of questionnaire in English

INTRODUCTION AND CONSENT

Hello. My name is _____ and I am working _____ (Name of Project). We are conducting a survey to improve health services for antibiotic use. We would like to ask you a few questions about the care you've received and the information you've been given. Your opinions are very important to us. Your answers will be kept confidential and your name will not be written on the survey so there will be no possibility to identify you. Your participation in this study is voluntary and you can withdraw from the interview at any moment without any negative consequences for you. The survey will take about 30 minutes of your time.

Do you have any questions?

Do you agree to participate in this survey? ____ Yes ____ No

Signature of interviewer: _____ or Verbal consent provided _____

Initials of Interviewer: _____

Patient Number: _____ Investigator initials _____ Date of interview: ____ / ____ / ____

Patient related factors

Demographics

Age in completed years.....	Gender [1] Male [2] Female
Body weight in Kgs (if known)	Height in cms (if known)
place of patient's residence:	1. Urban 2. Suburban 3. Rural 4. Homeless 5. Other
Marital status	1. Single 2. Married 3. Divorced/ separated 4. Widowed 5. cohabiting
Level of education	1. Advanced/colleague 2. Primary-secondary 3. No formal education
In general, would you say that you/your household has:	1. More money than you need 2. Just enough money 3. Less money than you need

Patient knowledge			
What in your own opinion causes this disease?	1. Punishment	2. Unavoidable	3. Don't know 4. Others.....
Do you think this disease is serious	1. Yes 2. No		
Do you know the symptoms of this disease	1. Yes 2. No		
Do you know what causes this disease	1. Yes 2. No		
Where did you first seek treatment when you became ill?	1. Self-treated 2. Traditional healer 3. Public clinic/ Hospital/Health Center 4. Private practitioner 5. Pharmacist/vendor Other.....		
Why?	1. Was cheaper 2. Was closer 3. More convenient schedule 4. Better care received 5. Better attitude form health workers 6. Trusted more 7. Others		
Did you seek treatment from somewhere else?	1. Yes 2. No		
From whom			
Patient Satisfaction/ Feedback			
Are the health care providers supportive and respectful	1. Yes 2. No		
If not, in your opinion, why not?			
Before coming for diagnosis/ treatment, did you expect that the providers would be supportive and respectful	1. Yes 2. No		
Are you happy with the service you are getting from this facility?	1. Yes 2. No		
Is the level of service you are getting from this facility	1. Better than you expected 2. About what you expected 3. Not as good as you expected		
Have health care workers answered all of your questions	1. Yes 2. No		
Are you satisfied with treatment received from other health workers?	1. Yes 2. No		
Are you satisfied with cost of consultation?	1. Yes 2. No		
How much			
Are you satisfied with cost of treatment?	1. Yes 2. No		
How much			
system related factors			
Date and time of referral (if this was a referral)			

Date and time of first consultation before referral	
Date and time when treatment started before referral	
Clinical diagnosis/condition	
Laboratory diagnosis	
Access to diagnosis /treatment	
How far is your home from this health facility? (Distance or time)	_____ hours or _____ Km
Is there other health facility closer to your home?	1. Yes 2. No
Is the health center easy to get to (accessibility/ convenience of transport)	1. Yes 2. No
Do you have to pay for transportation to get to the health center?	1. Yes 2. No
How much?	
Do you have to pay to see a health provider?	1. Yes 2. No
How much?	
Do you have to pay to see have the lab test done?	1. Yes 2. No
How Much?	1. Yes 2. No
Does the health center have convenient hours?	1. Yes 2. No
Treatment related factors	
Date and time of consultation	
Date and time of admission	
Reason for admission	
Date and time of diagnosis	
Confirmed diagnosis	
Date and time when treatment started	
Date and time when treatment stopped	
Duration of treatment	
Date and time of discharge	
Length of stay (LOS)	
Estimation of delays and reasons for delays	

How long were you sick before you first sought treatment?	1. _____ Days 2. _____ Weeks 3. _____ Months
What were the first symptoms you had to seek treatment?	a) Fever b) Cough c) Shortness of breath d) Sweating e) Shaking chills f) Headache g) Muscle pain h) Fatigue i) Chest pain with breathing Other
Mention any other condition /diseases that you have (comorbidities)	a) Kidney disease, b) Allergies, c) Diabetes, d) Pregnancy e) Hypertension Other
Did you take any treatment before you were diagnosed	1. Yes 2. No
Which treatment?	
After you were given the treatment, Did your symptoms	1. Improved 2. Worsened 3. Same
If laboratory test were requested, how long did it take to receive results	1. _____ Days 2. _____ Weeks 3. _____ Months
What was your condition when you arrived at this facility	1) Very sick, unconscious 2) Couldn't move 3) Couldn't talk 4) Could support myself 5) Just slight pain
Why did you choose to come to this health facility?	1. Close 2. Been Here Before 3. Friend/ family recommend 4. Referred 5. Know provider 6. Other
If referral, how long did it take you to be referred to this facility	Half day one day 1-2 days More than 2days

How long did it take from when you saw the doctor and had to begin treatment?	Half day one day 1-2 days More than 2days.....
Did you ever miss any treatment because health worker didn't come or was so busy attending to other patients	Yes No
Do you think there are enough health workers in this facility	Yes No
Did you have to buy any medication/sundries because hospital didn't have	Yes No
What factors may have made you delay seeking treatment?	1. Not aware of the severity of my symptoms 2. Fear of rejection/ losing my job 3. Expensive 4. Lack of time 5. Difficult access to health center/transportation issues 6. Not having a previous satisfactory experience with the health system 7. wrong diagnosis 8. Misdiagnosis 9. Delayed diagnosis 10. Inadequate stocking 11. Insufficient staffing 12. Others
Who do you think can better reduce the delay in the diagnosis and treatment	1. The patient 2. The family 3. The health system 4. The government 5. Others
Treatment outcomes/ effects of delayed initiation (To be extracted from patient files)	
• prolonged illness, • prolonged treatment duration • disability, • Organ failure • increased health expenditure, • non-adherence to medication Other	• sepsis • patient discomfort, • treatment failure, • drug resistance, • negative patient-provider relationship • Death

Appendix 4: IRB approval



29/03/2023

To: mansoor nsereko

makerere university
+256758535258

Type: Initial Review

Re: SBS-2023-296: Extent, associated factors, and effects of delayed antibiotic initiation in adult inpatients receiving antibiotic treatment at Kisenyi Health center IV and Kiruddu NRH Kampala Uganda , 1, 2023-01-28

I am pleased to inform you that at the 126 convened meeting on 23/02/2023, the MAK School of Biomedical Sciences REC (SBSREC), committee meeting, etc voted to approve the above referenced application. Approval of the research is for the period of 29/03/2023 to 29/03/2024.

As Principal Investigator of the research, you are responsible for fulfilling the following requirements of approval:

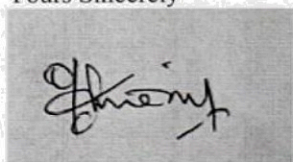
1. All co-investigators must be kept informed of the status of the research.
2. Changes, amendments, and addenda to the protocol or the consent form must be submitted to the REC for re-review and approval **prior** to the activation of the changes.
3. Reports of unanticipated problems involving risks to participants or any new information which could change the risk benefit: ratio must be submitted to the REC.
4. Only approved consent forms are to be used in the enrollment of participants. All consent forms signed by participants and/or witnesses should be retained on file. The REC may conduct audits of all study records, and consent documentation may be part of such audits.
5. Continuing review application must be submitted to the REC **eight weeks** prior to the expiration date of 29/03/2024 in order to continue the study beyond the approved period. Failure to submit a continuing review application in a timely fashion may result in suspension or termination of the study.
6. The REC application number assigned to the research should be cited in any correspondence with the REC of record.
7. You are required to register the research protocol with the Uganda National Council for Science and Technology (UNCST) for final clearance to undertake the study in Uganda.

The following is the list of all documents approved in this application by MAK School of Biomedical Sciences REC (SBSREC):



No.	Document Title	Language	Version Number	Version Date
1	corrected informed consent	english	2	2023-03-22
2	Informed Consent forms	luganda	2	2023-03-22
3	Protocol	English	1	2023-01-28
4	Data collection tools	ENGLISH	1	2023-01-28

Yours Sincerely

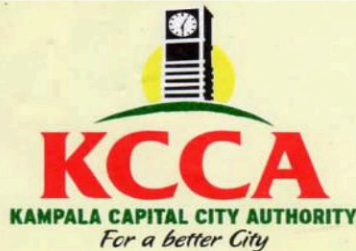


Dr. Moses Ocan

For: MAK School of Biomedical Sciences REC (SBSREC)



Appendix 5: Permission to conduct study at Kisenyi Health center IV



DIRECTORATE OF PUBLIC HEALTH AND ENVIRONMENT

REF: DPHE/KCCA/1301

12th April, 2023

Mr. Mansoor Nsereko

0774345231

Kampala, Uganda

RE: PERMISSION TO CARRY OUT RESEARCH

Reference is made to your letter dated 11th April 2023 on the above subject matter.

This is to inform you that permission has been granted to carry out a study titled "**Extent, associated factors, and effects of delayed antibiotic initiation in adult inpatients receiving at Kisenyi HC.**" has been extended to you for a period of three months from 14th April 2023.

The permission is granted to you on the following conditions:

1. Participation in your study is voluntary and the informed consent process should be observed at all times.
2. You will provide a report to the office of the Director Public Health and Environment of your findings.
3. You will access information from Kisenyi Health Center

By copy of this letter, the In-Charges of the above Health Center is requested to render you all the necessary support.



13 APR 2023

Dr. Sarah Zalwango
AG. DEPUTY DIRECTOR, MEDICAL SERVICES

P.O. BOX 7010 Kampala - Uganda
Plot 1-3, Apollo Kaggwa Road
Tel: 0204 66 00 00 SMS code: 7010
Toll free line: 0800 99 00 00

WhatsApp: 0794274444, Email: info@kcca.go.ug
@KCCAUG
WWW.KCCA.GO.UG

Appendix 6: Permission to carry out a study at Kiruddu National Referral Hospital

TELEPHONE: 0414-672315
: 0414-672308
: 0414-672309
Email : kiruddurh@gmail.com
Website : www.kiruddu.hosp.go.ug
Ref: KRD/ADM/3/101/1



THE REPUBLIC OF UGANDA

Kiruddu National Referral Hospital

Salaama Road Munyonyo.
P.O BOX 6588, Kampala, Uganda

April 5, 2023

Nsereko Mansoor Kalimunda
Principal Investigator

Re: Permission to conduct Research at Kiruddu National Referral Hospital

Reference is made to your letter dated April 04, 2023 in which you requested for permission to conduct your study at Kiruddu National Referral Hospital. This study got approval from the Makerere University School of Biomedical Sciences Research and Ethics Committee with effect from March 29, 2023 through March 29, 2024.

Please be informed that your proposal titled *"Extent, Associated Factors, and Effects of Delayed Antibiotic Initiation in Adult In-patients Receiving Treatment at Kisenyi Health Center IV and Kiruddu NRH Kampala, Uganda"* was reviewed and you were granted permission to conduct your research at this facility. Please take note of the following:

- i. Your research team will be governed by the rules that govern the facility.
- ii. You are expected to obtain final approval of your study from the National Council for Science and Technology (UNCST).
- iii. You are expected to abide by the UNCST regulations for conducting research involving human participants.
- iv. You should alert the hospital administration when you start your study.
- v. Upon completion of your study, you are expected to provide the hospital with a summary report your findings and to acknowledge the hospital on your publication(s).

By copy of this letter, the Head, Pharmacy is informed about your study and is encouraged to co-operate with your team.

Sincerely,

Dr. Seremba Emmanuel
Head, Research

C.c Head, Pharmacy

Dr. Kabugo Charles
Hospital Director



"Leading with innovation and serving with compassion in health care delivery"