UNIVERSITY of RWANDA

COLLEGE OF MEDICINE & HEALTH SCIENCES

SCHOOL OF MEDICINE & PHARMACY

INTERNAL MEDICINE DEPARTMENT

ASSESSMENT OF DISCREPANCY BETWEEN EMPIRICAL ANTIBIOTICS AND CULTURES RESULTS IN FEBRILE PATIENTS AT CHUK

Submitted for partial fulfillment of the requirements for the award of the Degree of Master of Medicine in Internal Medicine, School of Medicine and Pharmacy, College of Medicine and Health Sciences, University of Rwanda.

Investigator: Olivier Bizimungu, MD Registration number: 219014256

Supervisor: Léopold Bitunguhari, MD, MMed

Co supervisor: Jean Félix Babane, MD, MMed

Kigali, September 2022

DECLARATION

I hereby declare that the work presented in this dissertation entitled "Assessment of discrepancy between empirical antibiotics and cultures results in febrile patients at CHUK" is my original work. I have not copied from any other colleagues' work or any other sources except where due reference or acknowledgment is made explicit in the text, nor has another person written any part of this work on my behalf.

Olivier Bizimungu, MD

Department of Internal Medicine, University of Rwanda.

Signed Kigali September 14th, 2022

Approved for submission by:

Léopold Bitunguhari, MD, MMed

Physician, CHUK

Senior Lecture, University of Rwanda, CMHS, SMP

Signed Kigali September 15th, 2022

Jean Félix Babane, MD, MMed

Physician, CHUK

Signed Kigali September 15th, 2022

DEDICATION

To God the Almighty, who is the provider of everything.

To my late father Vincent Bizimungu and mother Grâce Béatrice Makuza, who couldn’t live long to witness this work.

To my unique wife Luce Geneviève Muhumurize and our lovely daughter Bria Loanne Bizimungu, beloved sister Nadine Bizimungu and brother Pascal Bizimungu thank you for your support and prayers.

To my friends, in you, I learned the meaning of true friends.

ACKNOWLEDGEMENTS

I could not have successfully finished this dissertation for the awarding of masters of Medicine without the cooperative efforts of various persons in terms of moral support, financial, and guidance. I am grateful to all these people.

I would like to express my thanks to Dr. Léopold Bitunguhari and Dr. Jean Félix Babane, my supervisors, for their guidance and consistent support throughout the realization of this work. Their dedication toward the completion of this project was beyond my most optimistic expectations.

I am grateful to the nurses and doctors working in the department of internal medicine and ICU at CHUK, whose work ethics and diligence contributed greatly to this project.

To my co-residents, teaching hospital staff members, the CMHS at the University of Rwanda, and the Ministry of health; I am forever grateful for my Internal Medicine training.

ABSTRACT

Background: Inappropriate use of antibiotic therapy is a global public health concern. This significantly contributes to an increase in antimicrobial resistance, disproportionately higher in low and middle-income countries. In Rwanda, there is a lack of information about the accurate use of empirical antibiotic therapy. It is in this regard we did this study to compare the empirical prescription of antibiotic therapy to the antibiogram results at the university teaching hospital of Kigali (CHUK), Rwanda.

Methods: This is a cross-sectional study among population aged 15 years and above with febrile illnesses and exposed to empirical antibiotics who have either positive cultures, positive genexperts, or positive cryptococcal antigen at the tertiary teaching hospital CHUK. The study evaluated the accurate use of empirical antibiotic therapy and the short-term outcome in hospitalized patients from August 2021 to April 2022. Demographic data, clinical presentation, and laboratory test results were recorded using a questionnaire after a signed consent. Stata version 13 was used to conduct descriptive, univariate, and multivariate analyses to determine the distribution of antibiotic prescriptions and factors associated with mortality.

Results: Over 9 months, we enrolled 150 participants in the study. The mean age was 48 ranging from 15 to 98 years of age, and there was a nearly equal distribution of gender with 52.7% of females and 47.3% of males. 64% of the study population had discordance between empirical antibiotic use and the antibiogram results. Of all cultures and genexperts done, E.coli was the most commonly isolated germ at 28.7% followed by Klebsiella pneumonia, Mycobacterium tuberculosis, and Staphylococcus aureus at 23.3%, 17.3%, and 6.7% respectively. Inappropriate use of empirical antibiotic therapy was associated with high in-hospital mortality (OR=7.73, 95% CI: 1.74-34.31, p=0.007).

Conclusion: There is an inappropriate use of antibiotic therapy in tertiary hospital settings and this may be associated with high in-hospital mortality. The majority of admitted patients received third-generation cephalosporins, which have a high resistance rate, and the most common germs isolated in hospital cultures and genexperts were E.coli, Klebsiella spp., and Mycobacterium tuberculosis. Behavior changes in antibiotics prescription and the development of local guidelines for antibiotics prescription is warranted to address this burden.

Keywords: Empirical antibiotic therapy, Antibiogram, Inappropriate antibiotic therapy, Antimicrobial resistance.

LIST OF ABBREVIATIONS

ADA: American Diabetes Association

AIDS: Acquired Immunodeficiency Syndrome

AMR: Antimicrobial Resistance

BSI: Bloodstream Infection

CHUB: University Teaching Hospital of Butare

CHUK: University Teaching Hospital of Kigali

CMHS: College of Medicine and Health Sciences

CRAG: Cryptococcal Antigen

CSF: Cerebral Spinal Fluid

GNB: Gram Negative Bacilli

HAART: Highly Active Antiretroviral Therapy

HIV: Human Immunodeficiency Viruses

HLOS: Hospital Length of Stay

ICU: Intensive Care Unit

IRB: Institutional Review Board

LMICs: Low and Middle-Income Countries

MDR: Multidrug resistance

TB: Tuberculosis

OPD: Outpatient department

OIs: Opportunistic Infections

PI: Principle investigator

SBP: Spontaneous Bacterial Peritonitis

USA: United States of America

UR: University of Rwanda

UTI: Urinary tract infection

WHO: World Health Organization

LIST OF TABLES

LIST OF FIGURES

TABLE OF CONTENTS

Contents

Chapter I: INTRODUCTION

I.1 Background

In both developed and low-middle income countries (LMICs), antimicrobial resistance (AMR) is a significant health threat that is linked to approximately 700,000 deaths per year and antibiotic misuse is one of the main causes.(1)

A cross-sectional study on antibiotic use before consultation or admission to the hospital in four LMICs such as Nepal, Cambodia, Sudan, and Democratic Republic of Congo-DRC (between January 2013 and October 2014) involving 1939 patients, has found that 22.1% patients have used antibiotics before consultations and among the antibiotics used, watch group antibiotics were more used. It was also found that 49.5% of antibiotics used were found inappropriate and discontinued at the time of consultation or admission. Hence, this has contributed to the AMR(2) although the AMR burden remains disproportionately higher in LMICs.(3)

Monitoring the usage of antibiotics is one of the five goals of the World Health Organization (WHO) Global Action Plan on AMR(4). However, given the broad range of diseases mostly those associated with fever that requires the use of antibiotics, antibiotics remain among essential drugs across different levels of medical care. “Fever is an elevation of body temperature that exceeds the normal daily variation and occurs in conjunction with an increase in the hypothalamic set point”, usually above 37.8°c (oral), 38.2°c (rectal), or 37.5°c (axillar)(5). It is among the predominant symptoms of patients who consult health facilities living in Sub-Saharan Africa.(6)

In a systematic review of forty-five studies involving a total of 54,578 patients from LMICs, 29,286(53.7%) were from Eastern Africa, overall the severe febrile illnesses were attributed to invasive bacterial or fungal infections, malaria, and viral infections.(7)

Another narrative literature review on fever etiology in Sub-Saharan Africa, apart from malaria, has found that bacterial zoonoses and bacterial blood-stream infection (BSI) are major causes of fever in admitted patients(6); Immunosuppression secondary to HIV and severe malnutrition has also been found to be a significant risk factor for bacteremia.(8)

In the pre-HIV treatment era, malaria and HIV-associated opportunistic infections (OIs) were found to be among the most common infectious diseases. However, after the initiation of highly active antiretroviral therapy (HAART), the HIV-related OIs decreased by 50 to 80%(9). The vastly increased access to HAART in Rwanda has led to a significant decrease of HIV patients hospitalized with severe immune depression, and AIDS-associated infections; therefore, an overall decrease in mortality rate. (10)(11)

In Sub-Saharan Africa, tuberculosis (TB) has emerged as the most frequent HIV-associated OI. In Rwanda, a country of nearly 13 million people, TB incidence is estimated at 57 patients per 100,000 populations (WHO report, 2020)

Malaria is still an important primary diagnosis to be ruled out in febrile patients even though its incidence at the tertiary level is not high because it is mainly treated at the primary and

secondary levels. In addition, the "Roll back malaria initiative" launched in Kigali in 2006, resulted in a dramatic decline in malaria cases.(12)

The laboratory investigations and management of febrile illnesses tend to be a challenge and can result in misguided treatments. A retrospective study done at Fletcher Allen Health care, USA comparing the yield of blood cultures before and during antibiotherapy in admitted patients with community-acquired infections or fever revealed that yield was predictable and only less than 1% isolated new pathogens from antibiotic blood cultures that had not previously been isolated from pre-antibiotic blood cultures. It has been shown that pre-antibiotic use decreases the yield of blood cultures(13). This corroborates with the findings of C.S Scheer et al who showed that culture positivity is reduced by 20% by pre-antibiotic therapy.(14)

At present, febrile disease due to bacteremia has been difficult to demonstrate in resource-limited settings. It necessitates blood culture facilities that are usually available in referral hospitals, and then, the supply of culture media and reagents is often unpredictable(15). This means that many patients with the suspected generalized bacterial disease are treated empirically. Empirical antibiotic therapy refers to the initially used antibiotic before identifying the pathogen.
Currently in our settings, there is no available data about the accuracy use of empirical antibiotic therapy. We, therefore, conducted this study to compare the empirical antibiotic therapy use and antibiogram results.

I.2 Literature review

Antimicrobial resistance is an emerging and global health burden, with inappropriate use of antibiotic therapy being one of the main causes(1). However, it has been observed that a large percentage of administrated antibiotics are prescribed with inappropriate indications.(16)

Globally AMR is among the major causes of death, LMICs being the most affected. In 2019, it was estimated that the highest rate of AMR burden was in Sub-Saharan Africa and it is believed that as many as 10 million people per year could die from AMR by 2050(17).
Regarding antibiotic misuse, a prospective observational study done in the university hospital Basel, Switzerland assessing the effectiveness of empirical and adjusted antibiotic therapy (before the culture results) for a period of nine months, has found they were inadequate at 22.4% and 27.4% respectively reasons being the use of antibiotic therapy with excessive broad spectrum and ineffectiveness of antibiotics against isolated germs.(18)

Another retrospective cohort study of 15,183 patients from 104 US hospitals with culture-positive community-onset sepsis over 7 years (January 2009 to December 2015) explaining the epidemiology of antibiotics-resistant pathogens and the result associated with both under- and over-treating those patients. It was discovered that most (81.6%) obtained adequate empirical antibiotics. Both inadequate and unnecessary broad-spectrum antibiotics were linked to high mortality.(19)

A review on AMR in East Africa, done by Lucas Ampaire et al, has disclosed that there's a high level of bacteria resistance among the frequently used antibiotics (ampicillin, gentamycin, and ceftriaxone) raising concern that these antibiotics may not be effective in

treating moderate to severe bacterial infection, this requires a review in empirical antibiotherapy based on the local analysis of AMR.(20)

In 2017, Vedaste N. et Al did a study in Gisagara district, Rwanda over a period of one year assessing the antibiotic therapy prescription suitability in outpatient consultations which revealed that 54.2% of 125,805 patients who consulted in the outpatient department (OPD) received antibiotics, only 38.6% were found to be suitable.(21)

A prospective observational study conducted at the University teaching hospital of Kigali (CHUK) over six months (July to December 2013), Rwanda determining the prevalence of AMR among bacterial pathogens associated with common infections in the medical wards has found that E.coli, Klebsiella, and Staphylococcus aureus are the most prevalent pathogens, from the cultured urine, blood, sputum, and wound swab, with multidrug-resistance (MDR) spectrum(22). In 2009, Muvunyi CM et al have done a prospective study which found that gram-negative bacilli (GNB), especially E.Coli, are the most common uropathogens in both in and out-patients and highly resistant to commonly used empirical antibiotics including quinolones, only fosfomycin-trometamol and imipenem were found to be most effective.(23)

Regarding the mortality with inadequate antibiotics use, there was a systematic review with a meta-analysis which revealed a very high incidence of inappropriate empirical antibiotic therapy and it was associated with a high mortality rate in patients with severe infection(24). Between June 2008-June 2009 in Chang Gung Memorial Hospital (Taiwan), a clinical database showed that among 937 patients with community-onset BSIs, 255 (27.2%) received inadequate empirical antimicrobial therapy and it was associated with a high 30-day mortality rate. The mortality rate was different according to patients' clinical severities.(25)

There is another study carried out in Palmetto Health Hospital Colombia, SC, USA from 1st January 2010 to 31st December 2013, intending to assess the impact of inappropriate empirical antimicrobial therapy on hospital length of stay (HLOS), which has shown that it was associated with prolonged HLOS in patients with both good and poor prognosis.(26)

I.3 Problem statement

In Rwanda, like other LMICs, febrile illnesses are among the predominant diseases in hospitals. CHUK is a referral hospital that receives patients referred from provincial and district levels for diagnosis and management of advanced diseases or complicated cases. Empirical antibiotics use and auto-medication are high due to countrywide limited access to specimen cultures, thus contributing to the possible risk of increasing AMR. However, there is limited evidence to guide the use of antibiotics. This study will contribute to show our current situation and inform the decision makers.

I.4 Research question

How accurate is the prescription of empirical antibiotics compared to the antibiogram results at the referral hospital, CHUK?

I.5 Objectives

I.5.1 General objective

- The overall objective of the study is to compare the empirical antibiotics use and the results of the antibiogram at CHUK.

I.5.2 Specific objectives

- To assess the discordance between the empirical antibiotics use and the antibiogram results
- To identify common germs isolated in positive cultures of patients with febrile illnesses from different biological specimens [blood, swabs, urine, sputum, cerebral spinal fluid (CSF), ascites, ...]
- To assess the in-hospital outcome (in-hospital mortality) of febrile ill patients with positive cultures.

I.6 Study significance

This study will provide significant information to the health system and the care providers, for future policy development and will serve as evidence on the current rational use of antibiotics in the general population. It will also give a hint on the potential germs that are resistant to the current antibiotics currently being used in the health system in Rwanda.

Chapter II: METHODOLOGY

II.1 Study type

This study was designed as a cross-sectional study for the patients with fever and exposed to empirical antibiotics prior to the culture results, and who have positive cultures.

II.2 Study site and period

This study was conducted at the University Teaching Hospital of Kigali (CHUK) the main referral hospital in Rwanda localized in Kigali city for the period of nine months from 1st August 2021 to 30th April 2022. CHUK was chosen because of its background of receiving referred patients from provincial and district hospitals of Rwanda as well as private clinics that are located in Kigali city, and it is one of the few sites where cultures of samples are done and expected to treat based on evidence.

II.3 Study population

The population included medical patients aged 15 years and above with fever who have been admitted to CHUK medical wards and ICU through emergency or internal medicine OPD.

II.4 Inclusion criteria

At the inclusion, all non-surgical patients (from emergency, ICU, and medical department) of 15 years old and above, admitted in a period between August 2021 to April 2022, who fulfilled the below criteria were enrolled:

- Consent to participate in the study and signed consent format. For people aged between 15 to 18 years, those in a coma and/or unable to sign the consent, the relative signed for them
- Having a history of fever before admission and whatever the time during the hospital stay
- Having at least positive culture from one of the body specimens or having positive genexpert results for Mycobacterium TB and having serum or CSF positive cryptococcal antigen (CRAG)
- Being treated with antibiotics empirically from lower level health facilities or empirical antibiotics initiated at CHUK.

II.5 Exclusion criteria

We have excluded all the below patients:

- All patients or relatives who refused to sign the consent or who have no next of kin, patients with disabilities, belonging to vulnerable populations like prisoners were also excluded
- Patients with fever but without culture done or samples judged contaminated
- Patients with an unclear history of antibiotics before admission

II.6 Sampling strategy and sample size

The sample size was determined based on the existing literature and recorded data from the CHUK statistics unit. In 2020 the CHUK records identified 240 positive cultures among all cases admitted to medical wards.

Using the **slovin's formula,** the sample size was calculated.

n = N / (1 + Ne^2)

n: Study sample size

N: Total number of patients with positive cultures results based on CHUK laboratory register for twelve months. It is estimated to be 240.

E: Error tolerance, which in our study will be 0.05

n = N / (1 + Ne^2) = $\frac{240}{1+240(0.05)2}$ = 150

II.7 Patients evaluation and data collection process

Using a predesigned questionnaire, patients were enrolled in our study after presenting 3 main criteria such as fever (either admitted with or acquired during the hospitalization) measured using axillary temperature, being treated with empirical antibiotic therapy, and having either positive cultures, positive genexperts, or positive CRAG. The empirical antibiotic therapy was checked either on the transfer sheet or in the medical file - treatment sheet (dose, route, and duration were also checked for accuracy). The principal investigator (PI) was following up on the requested cultures from the day of the request to the day of the culture results.

Once positive (here the PI got the results from the open clinic system or patient's medical file) patients were explained the purpose of the study (before the time of enrolment) and the reason for follow-up on their medical files. The antibiotics were changed according to the antibiogram results.

The informed consent form was written in three languages namely Kinyarwanda, English, and French. The patients were explained (by the researcher team) the right to accept or refuse participation in the study but also the right to withdraw at any time without consequences.

After fulfilling all inclusion criteria, patients were enrolled in the study and followed up during the course of hospitalization until the endpoint (discharge or in-hospital death). The cause of death was checked on the death certificate and the parameters preceding death were also recorded, the main diagnosis and HLOS were checked on the discharge form summary.

The created questionnaire for data collection included patient identification, medical history, clinical presentation, laboratory test results, and hospital outcome.

We defined acute fever as fever lasting less than seven days, subacute fever as fever lasting between seven to fourteen days, and chronic fever as fever lasting more than 14 days.

Auto-medication was defined as taking antibiotic therapy without a physician prescription.

In our study, antibiotic therapy was considered inappropriate when the bacteria isolated from the culture was resistant to the antibiotic being used.

The short-term outcome assessed in our study was the in-hospital mortality.

II.8 Data analysis

The data gathered on hard copies were entered into the software (Epidata version 3.1) for database creation and then exported to Stata version 13 for analysis. Descriptive data are presented as follows: categorical data are presented using frequencies and percentages in tables and continuous data are summarized by mean and median values depending on their distribution. The normality of continuous data was tested using the Shapiro-Wilk test.

The relationship between the outcome (in-hospital mortality) and potential predictors was studied using the Chi-square test and logistic regression (binary logistic regression analysis). Statistical significance for associations was taken at the level of $p < 0.05$.

II.9 Ethical consideration

Before conducting this study, the proposal was presented to the institutional review board of the College of Medicine and Health Sciences (CMHS) and the Kigali University Teaching hospital (CHUK) ethic committee members. Permission to carry out this study has been obtained from CMHS/IRB (N°224/CMHS IRB/2021) and CHUK/ IRB (Ref.: EC/CHUK/094/2021).

The aim of this study was fully explained to the participants or relatives before being included in the study and signed consent was obtained before enrolment; data regarding participants were kept confidential. The rights of patients were respected and participants were free to participate and leave the study at any time during the study period. No name of the patient or identification appeared before, during, or after reporting.

This research was conceived and is being submitted for partial fulfillment of the Master's degree in Internal Medicine of Bizimungu Olivier. This work will also be submitted to the hospital as recognition to have accepted to host the study and can be used in the initiation of the antibiotic stewardship program. It will be presented as an oral presentation at research days and conferences as well as workshops in the field of infectious diseases.
In addition, the findings of this study will be published in international journals for academic and clinical advancement.

Chapter III: RESULTS

III.1 Baseline clinical characteristics of study participants at recruitment

Over a period of 9 months, 150 patients met the eligibility requirements and were enrolled in the study. The median age was 48 years ranging from 15 to 98 years of age. There was a nearly equal distribution of gender among study participants with 52.7% made of females and 47.3% made of males. Around 90% of the participants had at least one comorbidity and the predominant comorbidity was diabetes mellitus (More details in Table 1).

Table 1: Baseline clinical characteristics of study participants at recruitment

Characteristics	Frequency (N=150)	%
Age in years		
Median (Q1-Q3)	48 (34-65)	
Gender		
Male	71	47.3
Female	79	52.7
Comorbidities		
Yes	135	90.0
Type of comorbidities		
HIV infection (n=35)		
New HIV infection	12	8.0
Existing HIV infection	23	15.3
Diabetes mellitus (n=52)		
Controlled (HbA1C <7)	12	8.0
Non controlled (HbA1C ≥7)	40	26.7
Hypertension	35	23.3
Stroke	10	6.7
CKD	17	11.3
Malignancies / Cancers	15	10.0
Cirrhosis	4	2.7

CKD: Chronic Kidney Disease, Q1: Quartile 1; Q3: Quartile 3

III.2 Disease characteristics and results of investigations

The median duration of the onset of fever was 9 days. Of all participants, 34% had acute fever while 29.3% had a chronic fever. Around 60.7% of the participants were admitted with fever while 39.3% developed fever during hospitalization. Among all participants, 31.3% of them had indwelling urinary catheters as a suspected source of infection and 14% had central lines while 42% did not have a clear source of infection (More details in Table 2).

Table 2: Disease characteristics and results of investigations

Characteristics	N	%
Duration of fever in days		
Median (Q1-Q3)	9 (6-15)	
Onset of fever		
Admitted with fever	91	60.7
In hospital fever	59	39.3
Time between onset of fever and empirical antibiotics		
Median (Q1-Q3)	5 (3-11)	
Time between onset of fever and sample collection		
Median (Q1-Q3)	5 (3-13)	
Time between onset of fever and antibiogram results		
Median (Q1-Q3)	7 (4-15)	
Duration of fever		
Acute (<7 days)	51	34.0
Sub-acute (7-14 days)	55	36.7
Chronic (>14 days)	44	29.3
Suspected source of infections		
Indwelling urinary catheter	47	31.3
Central lines	21	14.0
Tracheostomy	19	12.7
Unidentified	63	42.0
Laboratory measurements/parameters		
Hemoglobin (Mean ± SD)	11.55 ± 2.52	
Neutrophils [Median (Q1-Q3)]	7,331 (4,325-11,441)	
Lymphocytes [Median (Q1-Q3)]	1,404 (921-2,203)	
Monocytes [Median (Q1-Q3)]	706 (417-1,067)	
Platelets [Median (Q1-Q3)]	244 (161-370)	
ESR		
Increased (> 20 mm/h)	29	19.3
Normal (1- 20 mm/h)	7	4.7
Not requested	114	76.0
CRP		
Increased (> 5 mg/l)	60	40.0
Normal (0 – 5 mg/l)	1	0.7
Not requested	89	59.3

N= Total number of study participants

III.3 Main infection related diagnosis among study participants

Of all study participants, the treating team diagnosed UTI in 24%, followed by pneumonia and all type of tuberculosis (pulmonary, meningitis, and adenitis) at 20.7% and 17.3% respectively (More details in Table 3).

Table 3: Main infection-related diagnosis among study participants

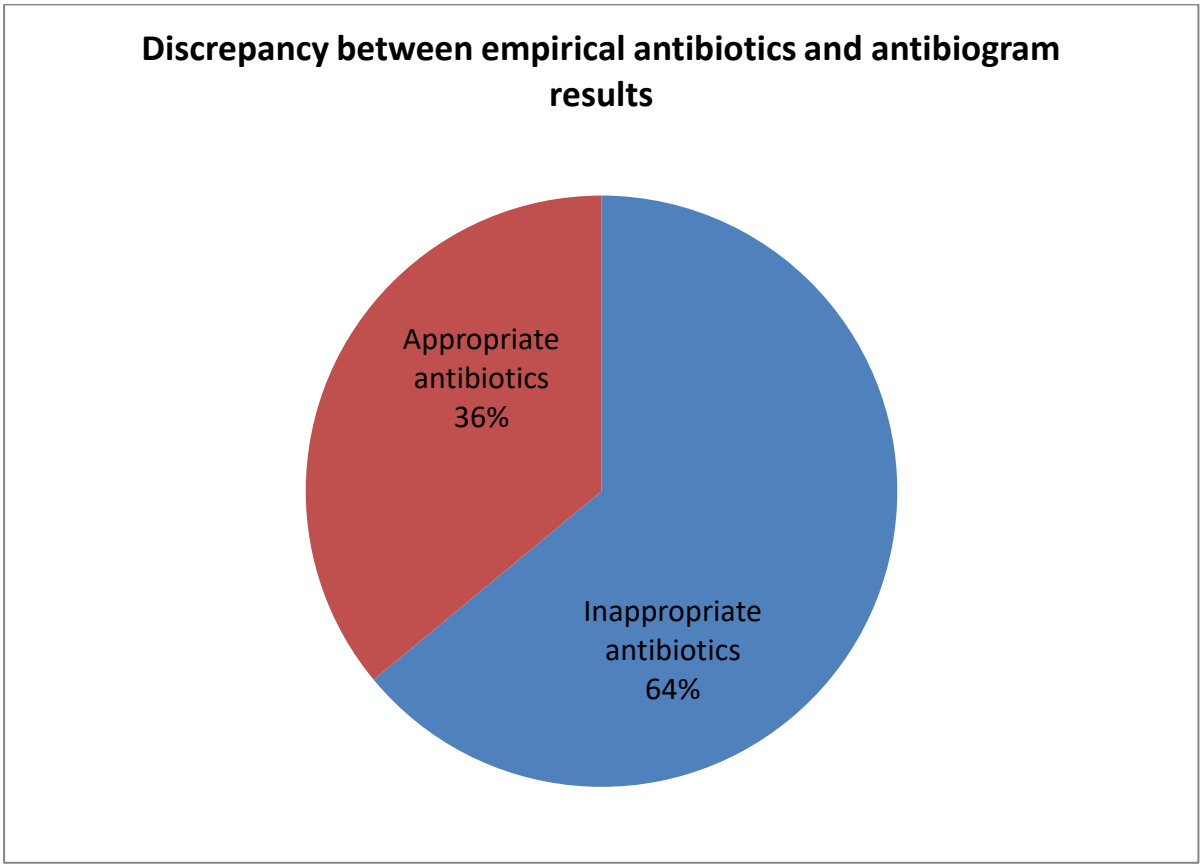
Diagnosis	N	%
UTI	36	24.0
Pneumonia	31	20.7
Tuberculosis	26	17.3
Meningitis	7	4.7
Bacteremia /Sepsis	11	7.3
Catheter-related blood stream infection	8	5.3
Diabetic foot	8	5.3
Abscess	5	3.3
SBP	4	2.7
Infected bedsore/ulcer	4	2.7
Cellulitis	4	2.7
Empyema thoracis	3	2.0
Thyphoid fever/perforation	3	2.0

N= Total number of study participants

III.4 Rate of inappropriate use of empirical antibiotics

The rate of discrepancy between the antibiogram results and the empirical antibiotics treatment was 64%, which indicates that 64% of the study population were on the wrong antibiotics before the results of the antibiogram, genexpert, and CRAG.

Figure 1: Rate of inappropriate use of empirical antibiotics



III.5 Common empirically administered antibiotics and their associated resistance

The most commonly administered empirical antibiotics were third-generation cephalosporin at 80.7% followed by metronidazole, tetracyclines, and penicillins at 24%, 14%, and 13.3% respectively.
The results of the antibiogram showed high resistance in third-generation cephalosporin, quinolones, and penicillins (mainly augmentin). (More details in Table 4)

Table 4: Most frequently used empirical antibiotics and their associated resistance.

Class/Antibiotics	Received empirically		Percentage of resistance per group	
	N=150	%	n	%
3rd generation cephalosporin (n=121)				
Ceftriaxone	121	80.7	74	61.2
Nitroimidazole (n=36)				
Metronidazole	36	24.0	-	-
Tetracyclines (n=21)				
Doxycycline	21	14.0	4	19.0
Penicillins (n=20)				
Augmentin	6	4.0	5	83.3
Cloxacillin	13	8.7	3	23.1
Ampicillin	1	0.7	0	0.0
Carbapenems (n=18)				
Meropenem	18	12.0	4	22.2
Glycopeptides (n=12)				
Vancomycin	12	8.0	2	16.7
Macrolides (n=5)				
Erythromycin	5	3.3	1	20.0
Quinolones (n=4)				
Ciprofloxacin	4	2.7	3	75.0
Bactrim (n=2)	2	1.3	0	0.0

n= number of participants with resistance per each group of antibiotic

III. 6 Common isolated germs in cultures of the study participants

Generally from all the types of samples that were cultured, E. coli was the most common grown germ at 28.7 followed by klebsiella pneumonia at 23.3% and Mycobacterium TB at 17.3% (Chart 2).

Specifically, Klebsiella pneumonia and Staphylococcus aureus were the most common isolated germs in 19 blood samples that were positive both at 31.6% each; E. coli was the most prevalent isolated germ in cultured urine samples at 63.9% followed by Klebsiella pneumonia at 19.4%;

Mycobacterium TB (confirmed by a sputum genexpert) was the most common isolated germ in sputum samples at 38.9% followed by Klebsiella pneumonia at 30.6% (More details in Table 5).

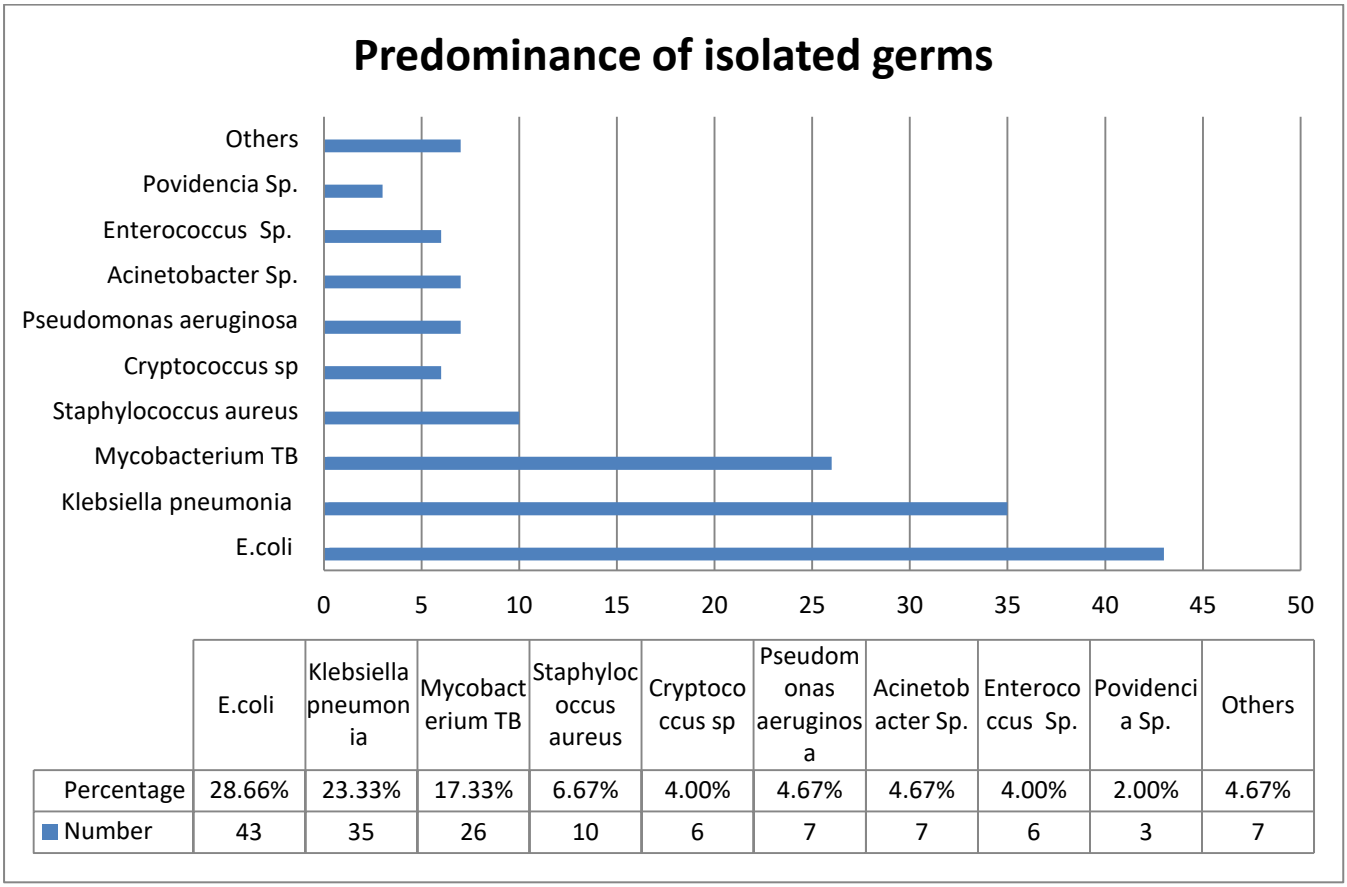
Table 5: Common isolated germs in cultures of the study participants

Sample	Isolated germ	Number	Percentage per group
Blood (n=19)			
	Klebsiella pneumonia	6	31.58
	Staph aureus	6	31.58
	E.coli	5	26.32
	Salmonella typhi	1	5.26
	Streptococcus sp	1	5.26
Urine (n=36)			
	E. coli	23	63.9
	Klebsiella pneumonia	7	19.4
	Enterococcus sp.	3	8.3
	Others*	2	5.6
	Staph aureus	1	2.8
Sputum (n=36)			
	Mycobactrium TB	14	38.9
	Klebsiella pneumonia	11	30.5
	Pseudomonas aeruginosa	3	8.3
	Others**	3	8.3
	Acinetobacter sp.	2	5.6
	E. Coli	2	5.6
	Staph aureus	1	2.8
Pleural fluid (n=7)			
	Mycobacterium TB	3	42.8
	Klebsiella pneumonia	1	14.3
	Pseudomonas aeruginosa	1	14.3
	Streptococcus pneumonia	1	14.3
	Streptococcus pyogene	1	14.3
Wound swab (n=21)			
	E. Coli	11	52.4
	Klebsiella pneumonia	7	33.3
	Staph aureus	2	9.5
	Proteus mirabis	1	4.8
CSF (n=13)			
	Mycobactrium TB	6	46.15
	Streptococcus species	1	7.70
	Cryptococcus sp	6	46.15

Tracheal aspirate (n=12)			
	Pseudomonas aeruginosa	3	25.0
	Klebsiella pneumonia	3	25.0
	Acinetobacter	3	25.0
	Mycobactrium TB	1	8.3
	Providencia Sp.	1	8.3
	E. coli	1	8.3
Ascitic fluid (n=4)			
	E. coli	1	25.0
	Providencia Sp.	1	25.0
	Acinetobacter Sp.	1	25.0
	Entrococcus Sp.	1	25.0
Lymph node (n=2)	Mycobactrium TB	2	100.0

Others*: Acinetobacter (n=1), Providencia sp (n=1); others**: Streptococcus viridans (n=1), Enterobacter sp (n=2);

Figure 2: Predominance of isolated germs among patients with positive cultures



	E.coli	Klebsiella pneumonia	Mycobacterium TB	Staphylococcus aureus	Cryptococcus sp	Pseudomonas aeruginosa	Acinetobacter Sp.	Enterococcus Sp.	Providencia Sp.	Others
Percentage	28.66%	23.33%	17.33%	6.67%	4.00%	4.67%	4.67%	4.00%	2.00%	4.67%
Number	43	35	26	10	6	7	7	6	3	7

III.7 Factors associated with mortality among study participants

Of all participants, 24 of them died (16%). Patients with discrepancy of antibiogram results and empirical antibiotics were 7 times more likely to die compared to patients without a discrepancy with a statistically significant difference (OR=7.73, 95% CI: 1.74-34.31, p=0.007). Patients who had persistent fevers after starting appropriate antibiotics appeared to have higher odds to die compared to patients who did not have persistent fever but the sample size was too small to generate reliable odds ratio estimates. Patients with chronic fever were 3.4 times more likely to die compared to patients who had acute fever (OR=3.46, 95% CI: 1.0-11.95, p=0.05). There was no statistically significant association between mortality, gender, presence of comorbidity, and the time between the onset of fever and the time of real antibiotics administration. (More details in Table 6)

Table 6: Factors associated with mortality among study participants

Predictors	In-hospital outcome		OR (95% CI)	P
	Died	Discharged alive		
Discrepancy of antibiogram and empirical antibiotics				
Yes	22 (22.9%)	74 (77.1%)	7.73 (1.74-34.31)	0.007
No	2 (3.7%)	52 (96.3%)		
Persistence of fever after starting appropriate antibiotics				
Yes	19 (95.0%)	1 (5.0%)	475 (52.59-4289)	<0.001
No	5 (3.9%)	125 (96.1%)		
Gender				
Male	13 (18.3%)	58 (81.7%)	1.38 (0.57-3.28)	0.466
Female	11 (13.9%)	68 (86.1%)		
Presence of any comorbidity				
Yes	22 (16.3%)	113 (83.7%)	1.26 (0.27-6.01)	0.767
No	2 (13.3%)	13 (86.7%)		
Diabetes				
Yes	7 (13.5%)	45 (86.5%)	0.74 (0.28-1.92)	0.538
No	17 (17.4%)	81 (82.6%)		
HIV status				
Positive	6 (17.1%)	29 (82.9%)	1.11 (0.40-3.07)	0.833
Negative	18 (15.6%)	97 (84.4%)		
Malignancy				
Yes	3 (20.0%)	12 (80.0%)	1.36 (0.35-5.22)	0.657
No	21 (15.6%)	114 (84.4%)		
Fever duration				
Acute (<7 days)	4 (7.8%)	47 (92.2%)		
Sub-acute (7-14 days)	10 (18.2%)	45 (81.8%)	2.61 (0.76-8.92)	0.126
Chronic (>14 days)	10 (22.7%)	34 (77.3%)	3.46 (1.0-11.95)	0.05
Time between onset of fever and administration of real antibiotics				
≤ 7 days	10 (11.9%)	74 (88.1%)		
> 7 days	14 (21.2%)	52 (78.8%)	1.96 (0.81-4.77)	0.135

Chapter IV: DISCUSSION

IV.1 Results discussion

AMR is considered an increasing global health concern, with inappropriate and irrational use of antibiotics being one of the leading causes(1). In LMICs the majority of febrile illnesses are treated empirically, one of the reasons being limited access to reliable diagnostic testing(15). Regular monitoring of appropriate antibiotic therapy use is mandatory to minimize AMR prevalence.

The findings from this study revealed that inappropriate use of empirical antibiotic therapy was high, 64%. The frequency of misuse found in this study was higher than the findings from a study done in Scotland at the Aberdeen teaching hospital by Y. Kumarasamy et Al, on "optimizing antibiotic therapy" where they concluded that inadequate use of empirical antibiotics was at 49%(27) and approximately similar finding of 47% was found in 8 medium-sized swiss hospitals(28). Our findings were also significantly higher than what was found in Taiwan and Switzerland at 27.2% and 22.4% respectively.(25)(18)
This difference can be explained by a lack of infectious disease local antibiogram protocols, policy, and specialized teams that lead the antibiotics prescriptions. It is also possible that there is a lack of regular AMR surveillance mechanisms to adapt to hospital prescriptions.

Of all cultures done in this study, we noticed that E.coli was the most frequently isolated germ at 28.7% followed by Klebsiella spp, Mycobacterium TB, and Staphylococcus aureus at 23.3%, 17.3%, and 6.7% respectively. The same pathogens were found in the study done by Makeda et Al titled "Five– year antimicrobial susceptibility trends among bacterial isolates from a tertiary health-care in Kigali, King Faisal Hospital, Rwanda 2009-2013", which revealed that of 5.296 isolates collected, E.coli was the most isolated germ 46.7% followed by Klebsiella spp, Staphylococcus aureus, and Enterococcus spp at 18.4%, 11.7% and 10.3% respectively(29). Similar findings were also observed in the studies done by Ntirenganya et Al and Mpirimbanyi C et Al where E.Coli and Klebsiella sp. were the most cultured isolates(22)(30).
E.coli and Klebsiella sp. were the commonest germs isolated in the above-mentioned studies probably due to several admissions of patients with different comorbidities. The difference in germs percentages was possibly due to some factors such as study sites, duration, and sample size. In our study, including patients from ICU could be the reason for the high proportion of Klebsiella sp.

Furthermore, in our study, each urine and sputum culture yielded 24% of bacterial isolates. Wound swabs, blood, cerebral spinal fluid (CSF), tracheal aspirate, pleural fluid, lymph node, and ascitic fluid culture isolates made up 14%, 12.7%, 8.7%, 8%, 4.7%, 1.3% and 2.6% respectively and 99,3% were monomicrobial.

In urine, E.coli was the most frequent pathogen isolated followed by klebsiella pneumonia at 63.9% and 19.4% respectively. Those findings are almost similar to those reported in the study done by Claude Mambo et Al (2009) where E.coli and Klebsiella pneumonia were the most common uropathogen at 60.7% and 18.9% respectively(23). This finding corroborates

with the findings of Ntirenganya et Al (2013) which showed E.coli and Klebsiella pneumonia as the most frequent pathogens isolated in urine specimens.(22)
Similarly, another prospective study done in Bagamoyo hospital, Tanzania in 2019 investigating on outpatients with UTIs has found similar results where E.coli and Klebsiella are the most uropathogens found.(31)
DIBUA et al also had the same findings which showed that E.Coli is the most urinary pathogen isolated in patients from three medical centers in ENUGU state in southeast Nigeria.(32)

In sputum, Mycobacterium TB was the most finding at 38.9% (confirmed by a positive genexpert) followed by Klebsiella pneumonia at 30.5%, and pseudomonas sp. at 8.3%. Apart from genexpert which was added, Klebsiella pneumonia was the most commonly isolated bacteria from previous studies in Ethiopia (31.0%)(33), Tanzania (29.9%)(34), and China (27.4%)(35). However, our results were higher compared to the studies reported in Tripura, north-eastern India (20.4%)(36) and Bangladesh (13.3%)(37).

In terms of hospital outcome, the findings from this study showed that there was an association between inappropriate use of empirical antibiotic therapy and in-hospital mortality (OR=7.73, 95% CI: 1.74-34.31, p=0.007); this prevalence corroborates with previous systematic review with a meta-analysis of studies from Asia, Northern America, Europe, and the Middle East which revealed that appropriate use of empirical antibiotic therapy reduces in-hospital mortality (RR 0.67, 95% CI 0.56 to 0.80) and 30- day mortality (RR 0.71, 96% CI 0.62 to 0.82).(24)
Similar findings were seen in a study done in Taiwan by Chen et Al in 2008 – 2009 which showed that in adult patients with community-onset BSIs at ED, inappropriate empirical antibiotic therapy is linked to an increased risk for 30-day all-cause mortality (HR 1.64, 95% CI 1.19-2.26)(25). The same findings were observed in a retrospective cohort analysis of electronic health record data from 131 hospitals in the USA by S Kadri et Al. (2005 – 2014) where they demonstrated that discordant empirical antibiotic therapy was highly associated with mortality (OR= 1.46 95% CI, 1.28-1.66; p<0.0001).(38)

IV.2 Study limitations

Our study had some limitations. First, the pre-admission antibiotics were missing due to poor transfer information notes or incomplete patient information (history not clear and lack of records and prescription). Second, stock-out of culture media and tubes was frequent which may have led to inconsistencies in the data collected. Third,lack of budget to invest in materials.

Chapter V: CONCLUSION AND RECOMMENDATIONS

V.1 Conclusion

There is an inappropriate use of antibiotic therapy in tertiary hospital settings and this may be associated with high hospital mortality. The majority of admitted patients received third-generation cephalosporins, which have a high resistance rate, and the most common germs isolated in hospital cultures and genexperts were E.coli, Klebsiella spp., and Mycobacterium TB.

V.2 Recommendations

As this study was a single-centered-hospital based with a short period of 9 months, further multi-centered-based hospital studies with a larger sample size are recommended.

➢ To the Ministry of health and managers of hospitals

- To initiate infectious disease sub-specialty in Rwanda

- Development and implementation of hospitals based antibiotics prescription guidelines

- To provide appropriate and sufficient laboratory materials for cultures in hospitals

- To organize seminars and workshops on AMR and the appropriate use of antibiotics for all health care providers

➢ To the health care professionals

- Behaviour changes in antibiotics prescription and develop a local guideline for antibiotics prescription

- To timely request cultures in febrile patients as they guide in the appropriate use of antibiotics

➢ To the general population

- Population awareness about the high rate of AMR due to inappropriate use of antibiotics and avoidance of auto-medication.

Chapter VI: REFERENCES

1. Baekkeskov E, Rubin O, Munkholm L, Zaman W. Antimicrobial Resistance as a Global Health Crisis. Oxford Res Encycl Polit. 2020;(February):1–24.

2. Ingelbeen B, Koirala KD, Verdonck K, Barb B, Thong P, El S, et al. Antibiotic use prior to seeking medical care in patients with persistent fever: a cross-sectional study in four low- and middle-income countries by Mukendi. 2020;(xxxx).

3. By C, Neill JIMO. TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS THE REVIEW ON. 2016;(May).

4. Global action plan on antimicrobial resistance.

5. Bleeker-Rovers CP, van der Meer JWM, Beeching NJ. Fever. Medicine (Baltimore). 2009;37(1):28–34.

6. Maze MJ, Bassat Q, Feasey NA, Mandomando I, Musicha P, Crump JA. The epidemiology of febrile illness in sub-Saharan Africa: implications for diagnosis and management. Clin Microbiol Infect [Internet]. 2018;24(8):808–14. Available from: https://doi.org/10.1016/j.cmi.2018.02.011

7. Prasad N, Murdoch DR, Reyburn H, Crump JA. Etiology of severe febrile illness in low- and middle-income countries: A systematic review. PLoS One. 2015;10(6):1–25.

8. Mayer KH, Huson MAM, Stolp SM, Van Der Poll T, Grobusch MP. Community-acquired bacterial bloodstream infections in HIV-infected patients: A systematic review. Clin Infect Dis. 2014;58(1):89–92.

9. Palella F. Declining Morbidity and mortality among patients with advanced HIV infection. N Engl J Med. 1998;571–96.

10. Biomedical R. Rwanda AIDS Update 2014 UNAID. 2014;(March).

11. MOH. Republic of Rwanda Ministry of Health NATIONAL HIV / AIDS TARGETS. 2019;1–29.

12. Karema C, Wen S, Sidibe A, Smith JL, Gosling R, Hakizimana E, et al. History of malaria control in Rwanda: Implications for future elimination in Rwanda and other malaria-endemic countries. Malar J [Internet]. 2020;19(1):1–12. Available from: https://doi.org/10.1186/s12936-020-03407-1

13. Grace CJ, Lieberman J, Pierce K, Littenberg B. Usefulness of blood culture for hospitalized patients who are receiving antibiotic therapy. Clin Infect Dis. 2001;32(11):1651–5.

14. Scheer CS, Fuchs C, Gründling M, Vollmer M, Bast J, Bohnert JA, et al. Impact of antibiotic administration on blood culture positivity at the beginning of sepsis: a prospective clinical cohort study. Clin Microbiol Infect [Internet]. 2019;25(3):326–31. Available from: https://doi.org/10.1016/j.cmi.2018.05.016

15. Petti CA, Polage CR, Quinn TC, Ronald AR, Sande MA. Laboratory medicine in Africa: A barrier to effective health care. Clin Infect Dis. 2006;42(3):377–82.

16. Embrey M. Promoting rational prescribing. Manag Access to Med Heal Technol [Internet]. 2012;(3):24. Available from: http://apps.who.int/medicinedocs/documents/s19606en/s19606en.pdf

17. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629–55.

18. Mettler J, Simcock M, Sendi P, Widmer AF, Bingisser R, Battegay M, et al. Empirical use of antibiotics and adjustment of empirical antibiotic therapies in a university hospital: A prospective observational study. BMC Infect Dis. 2007;7:1–10.

19. Rhee C, Kadri SS, Dekker JP, Danner RL, Chen HC, Fram D, et al. Prevalence of Antibiotic-Resistant Pathogens in Culture-Proven Sepsis and Outcomes Associated With Inadequate and Broad-Spectrum Empiric Antibiotic Use. JAMA Netw open. 2020;3(4):e202899.

20. Ampaire L, Muhindo A, Orikiriza P, et al. A review of antimicrobial resistance in East Africa. Afr J Lab Med. 2016;5(1), a432. http://dx.doi. org/10.4102/ajlm.v5i1.432

21. Nkurunziza et al. Antibiotic Prescription Suitability Assessment in Health Centers of Gisagara District , Rwanda. *Rw. Public Health Bul. 2020. 2 (3): 19-24*

22. Ntirenganya C, Manzi O, Muvunyi CM, Ogbuagu O. High prevalence of antimicrobial resistance among common bacterial isolates in a tertiary healthcare facility in Rwanda. Am J Trop Med Hyg. 2015;92(4):865–70.

23. Muvunyi CM, Masaisa F, Bayingana C, Mutesa L, Musemakweri A, Muhirwa G, et al. Decreased susceptibility to commonly used antimicrobial agents in bacterial pathogens isolated from urinary tract infections in Rwanda: Need for new antimicrobial guidelines. Am J Trop Med Hyg. 2011;84(6):923–8.

24. Marquet K, Liesenborgs A, Bergs J, Vleugels A, Claes N. Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: A systematic review and meta-analysis. Crit Care. 2015;19(1).

25. Chen HC, Lin WL, Lin CC, Hsieh WH, Hsieh CH, Wu MH, et al. Outcome of inadequate empirical antibiotic therapy in emergency department patients with community-onset bloodstream infections. J Antimicrob Chemother. 2013;68(4):947–53.

26. Battle SE, Bookstaver PB, Justo JA, Kohn J, Albrecht H, Al-hasan MN. Association between inappropriate empirical antimicrobial therapy and hospital length of stay in Gram-negative bloodstream infections. J Antimicrob Chemother: stratification by prognosis. 2016;1–6.

27. Kumarasamy Y, Cadwgan T, Gillanders IA, Jappy B, Laing R, Gould IM. Optimizing antibiotic therapy — the Aberdeen experience. 2003.

28. Bugnon-Reber A V., De Torrenté A, Troillet N, Genné D, Christin L, Chuard C, et al. Antibiotic misuse in medium-sized Swiss hospitals. Swiss Med Wkly. 2004;134(33–34):481–5.

29. Carroll M, Rangaiahagari A, Musabeyezu E, Singer D, Ogbuagu O. Five-year antimicrobial susceptibility trends among bacterial isolates from a tertiary health-care facility in Kigali, Rwanda. Am J Trop Med Hyg. 2016;95(6):1277–83.

30. Sutherland T, Mpirimbanyi C, Nziyomaze E, Niyomugabo JP, Niyonsenga Z, Muvunyi CM, et al. Widespread antimicrobial resistance among bacterial infections in a Rwandan referral hospital. PLoS One. 2019;14(8):1–15.

31. Schmider J, Bühler N, Mkwatta H, Lechleiter A, Mlaganile T, Utzinger J, et al. Microbiological Characterisation of Community-Acquired Urinary Tract Infections in Bagamoyo, Tanzania: A Prospective Study. Trop Med Infect Dis. 2022;7(6):100.

32. Dibua UME, Onyemerela IS, Nweze EI. Perfil da frequência, análise urinária e suscetibilidade de patógenos causando infecções do trato urinário no estado de Enugu, Sudeste da Nigéria. Rev Inst Med Trop Sao Paulo. 2014;56(1):55–9.

33. Assefa M, Tigabu A, Belachew T, Tessema B. Bacterial profile, antimicrobial susceptibility patterns, and associated factors of community-acquired pneumonia among adult patients in Gondar, Northwest Ethiopia: A cross-sectional study. PLoS One [Internet]. 2022;17(2 February):1–18. Available from: http://dx.doi.org/10.1371/journal.pone.0262956

34. Kishimbo P, Sogone NM, Kalokola F, Mshana SE. Prevalence of gram negative bacteria causing community acquired pneumonia among adults in Mwanza City, Tanzania. Pneumonia. 2020;12(1).

35. Luan Y, Sun Y, Duan S, Zhao P, Bao Z. Pathogenic bacterial profile and drug resistance analysis of community-acquired pneumonia in older outpatients with fever. J Int Med Res. 2018;46(11):4596–604.

36. Paul DM, Majumdar DT, Bhowmik DP. Antimicrobial Susceptibility Pattern of Community Acquired Pneumonia among Adults in Tripura, North-Eastern India. Sch J Appl Med Sci. 2020;8(8):1901–7.

37. Akter S, Shamsuzzaman SM, Jahan F. Community acquired bacterial pneumonia: Aetiology, laboratory detection and antibiotic susceptibility pattern. Malays J Pathol. 2014;36(2):97–103.

38. Kadri SS, Lai YL, Warner S, Strich JR, Babiker A, Ricotta EE, et al. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. Lancet Infect Dis [Internet]. 2021;21(2):241–51. Available from: http://dx.doi.org/10.1016/S1473-3099(20)30477-1

Chapter VII: APPENDICES

VII.1 Consent form

English version

Patient identification number: ……..

I am Dr. Olivier BIZIMUNGU, an Internal Medicine Resident at the University of Rwanda who is carrying out a study on **"ASSESSMENT OF DISCREPANCY BETWEEN EMPIRICAL ANTIBIOTICS AND CULTURES RESULTS IN FEBRILE PATIENTS AT CHUK"**

You will be required to understand its purpose, benefits, and risks before you agree to participate in it.

- **Aim:**

To compare the empirical antibiotics and the results of antibiogram of febrile patients admitted at CHUK and their short-term outcomes

- **Risks to the participants:**

To get blood, the procedure can be painful but we will try not to harm you.

- **Benefits:**

Participation is completely voluntary and there is no financial support for the research participants. The findings of this study will help in the appropriate management of patients with febrile illnesses.

- **Confidentiality:**

The principal investigator will keep all information strictly confidential.

- **Questions:**

Participants are free to look for any clarifications about the study when they wish. My phone number: **0788258271**.

For questions regarding the participant rights, please contact:

1. The CMHS/IRB acting chairperson on **0784575900**
2. The Director of CHUK ethics committee on **0785466254**

- **Rights to leave the study:**

You are free to leave the study at any time even if you have consented to participate and this will not affect the care we will be giving to you.

- **Statement of approval:**

I have read and understood all of the above information. I received a detailed explanation in understandable language of the nature, purpose, risks, and benefits of the study. I am aware that I have the right to leave the study at any time. By signing this informed consent form, I acknowledge my consent to participate in this study.

Thus, I sign for myself /next of kin …… as a confirmation to participate in the study.

Signature: ……Date: ……

I explained to the participant, to the best of my knowledge and belief, the purpose of the study. The participant had a clear understanding of objectives, benefits, and risks.

Signature: …… Date of signed consent: ……

Kinyarwanda version

Nimero y'umurwayi …….

Nitwa BIZIMUNGU Olivier ndi umuganga wiga ibirebanye n'indwara zo mu mubiri muri Kaminuza y'u Rwanda, ubushakashatsi bwanjye bwerekeye ku **"ISUZUMA RYO KUREBA UKUDAHURA HAGATI YA ANTIBIYOTIKE ZITANGWA MBERE NA NYUMA Y'IBIZAMINI N'IBISUBIZO MU BARWAYI BAFITE UMURIRO MU BITARO BYA CHUK"**

Urasabwa kubanza gusobanukirwa intego y'ubu bushakashatsi, inyungu n'ingaruka zabwo mbere y'uko wemera kubugiramo uruhare.

- **Intego:**

Kugereranya antibiyotike zitangwa mbere na nyuma y'ibizamini n'ibisubizo mu barwayi bafite umuriro mu bitaro bya kaminuza i Kigali CHUK

- **Ingaruka:**

Kubera amaraso azafatwa muri ububushakashatsi ,uzaba aburimo ashobora kubabazwa n' urushinge ruzakoreshwa . Gusa ni ububare bw' akanya gato kandi buhita bushira hatagombye guhabwa umuti

- **Inyungu:**

Umuntu wese wagize uruhare muri ubu bushakashatsi nta nyungu y'amafaranga azakuramo. Ubumenyi tuzakuramo buzadufasha kurushaho kuvura neza abarwayi bafite umuriro mu bitaro bya CHUK.

- **Ibanga:**

Umushakashatsi azabika mu buryo bw'ibanga amakuru yose ya buri muntu.

- **Ibibazo:**

Umuntu wese uzagira uruhare muri ubu bushakashatsi, mu gihe cyose yifuza ibindi bisobanuro, yemerewe kubaza ibibazo. Nimero ya telefoni yanjye ni: **0788258271**.

Ku bibazo birebana n'uburenganzira bw'umuntu wagize uruhare mu bushakashatsi wakitabaza numero zikurikira:

1. Ushinzwe uburenganzira bw'abakorerwaho ubushakashatsi: **0784575900**
2. Umuyobozi mukuru wa komite ishinzwe ubushakashatsi muri CHUK: **0785466254**

- **Uburenganzira bwo kwikura mu bushakashatsi:**

Ufite uburenganzira n'ububasha bwo kwikura mu bakorerwaho ubushakashatsi igihe cyose ubishakiye kandi ntankurikizi ku buvuzi uri gukorerwa zibayeho.

Amasezerano yo kwemera gukorerwa ho ubushakashatsi:

Maze gusoma byimbitse ibyanditse hejuru kandi nabyumvise cyane. Nasobanuriwe neza mu rurimi numva intego z'ubu bushakashatsi, inyungu ndetse n' ingaruka zabwo. Nasobanuriwe kandi ko nemerewe kuva mu mubare w'abakorerwaho ubushakashatsi ku bushake bwanjye igihe mbishakiye kandi nta nkurikizi zindi.

Nshyize umukono kuri aya masezerano kandi nemeye ko nkorerwaho/umurwayi wanjye akorerwaho ubushakashatsi.

Nyewe Umurwayi / umurwaza ……. Nsinye nk'ikimenyetso cy'uko nemeye kugira uruhare muri ubu bushakashatsi.

Umukono wanjye / umurwaza ……Itariki: ……

Nsobanuriye umurwayi/umurwaza mu buryo bwimbitse intego z'ubu bushakashatsi, inyungu ndetse n'ingaruka zabwo.

Umushakashatsi: ……. Itariki: ……

VII.2 Data collection tool

English version

1. IDENTIFICATION

Study number	
Initials	
Hospital ID	
Date of enrollment	
Mobile phone/ contact	**1.** **2.**

2. SOCIAL DEMOGRAPHIC

Age	
Gender	o Male o Female
Residence	o Province o District
Onset of symptoms	o In days:
Admitted from OPD CHUK	o No o Yes
Consulted the health center	o No o Yes When (In days): o Antibiotics used (if known):
Referring Hospital(if any)	o No o Yes When(In days): o Antibiotics used (if known):

3. PAST HISTORY

Comorbidities

- No
- Yes If yes: One □ More than one □

- HIV status
  - Negative
  - Positive If Yes,
    - Newly diagnosed: YES / NO
    - Last CD4 count / HIV V.L , if known:
    - Line and regimen, if known:
- Diabetes mellitus
  - No
  - Yes Last HBA1C (If known) □

- Other Co-morbidities
  - Malignancies YES / NO
    - If yes, which type:
  - Cirrhosis YES / NO
  - CKD YES / NO
  - Other(s):
- Auto-medication with antibiotics
  - No
  - Yes When:
  - Antibiotics used (if known):

4 .CLINICAL PRESENTATION

- Duration of the fever
  - Acute (less than 7 days):
  - Sub acute (7 – 14 days)
  - Chronic (More than 14 days)

- Antibiotics received prior to sample cultures withdraw (during admission)
    - No
    - Yes If yes, Ward :
        - Which antibiotics: Duration (in days):

- Recent Anti malaria drugs use
    - NO
    - Yes Before admission □ During admission □

- BMI INTERPRETATION
    - Obese
    - Normal
    - Undernourished

- Indwelling urinary catheter
    - No
    - Yes

- Central lines
    - No
    - Yes

- Prosthetic valves
    - No
    - Yes

- Other risk of infection
    - No
    - Yes Which one:

5. LABORATORY RESULTS

5.1 Routine laboratory exams

- Hemoglobin (g/dl) :

- WBC:
    - Absolute neutrophils counts:
    - Absolute lymphocytes count:
    - Absolute monocytes count:

- Platelets:

- Malaria smear:
  - Positive
  - Negative
  - Not available
- ESR:
  - Normal (1-20 mm/h):
  - Increased:
  - Not available
- CRP:
  - Normal (0-5 mg/l)
  - Increased:
  - Not available

- **SAMPLES FOR CULTURES**

RESULTS / SAMPLES	**Negative culture**	**Positive culture**			**Genexpert results**
		Isolated germ	**Antibiogram**	**Time(days) required**	
Blood					
Urine					
Sputum					
Wound swab					
Cerebral Spinal Fluid (CSF)					
Tracheal aspirate					
Pleural fluid					
Lymph node					

Note: Please mention below the culture samples which were requested but not done

-

- After how long the culture sample was requested from the fever onset (days):
- After how long the empirical antibiotics were initiated from the fever onset (days):
- After how long the real antibiotics were initiated from the fever onset (days):
- Ultrasound findings:
- Radiological findings:

5.2 Other laboratory exams when clinically indicated

-

6. FINAL DIAGNOSIS:

7. IN-HOSPITAL OUTCOME:

- Fever disappearance after starting the antibiotics (in days):
- Persistence of fever after completion of antibiotics
  - No
  - Yes
- Cured at the time of discharge
  - Time of the hospital stay(in days):
- Improved at the time of discharge
  - Time of the hospital stay(in days):
- Discharged
    - With oral antibiotics
    - Without oral antibiotics
- Died
  - No
  - Yes, On which day of hospitalization:
  - Retained cause of death

Kinyarwanda version

1. UMWIRONDORO

Numero y'ubushakashatsi	
Inyuguti zitangira Amazina	
Numero yo mu bitaro	
Itariki yinjiriye mu bushakashatsi	
Numero za telephoni	**1.** **2.**

2. SOCIAL DEMOGRAPHIC DATA

Imyaka	
Igitsina	o Gabo o Gore
Aho atuye	o Intara o Akarere
Igihe yatangiriye kugira ibimenyetso	o Mu minsi:
Yinjiye mu bitaro avuye mu bivuza bataha kuri CHUK	o Oya o Yego
Yivurije mu kigo nderaburezi	o Oya o Yego Ryari (Mu minsi): o Antibiyotike yanyweye (Niba zizwi):
Ibitaro byamwohereje	o Ntabyo o Birahari Ryari(Mu minsi): o Antibiyotike yanyweye (Niba zizwi):

3. PAST MEDICAL HISTORY

Izindi ndwara usanganywe

- Ntazo
- Zirahari Imwe □ Hejuru y'imwe □

➢ Ubwandu bw'agakoko gatera SIDA
  - Ntabwo
  - Burahari - Wanduye vuba: Yego / Oya
    - Abasirikare ufite mu maraso / Ingano ya virusi (Niba bizwi):
    - Imiti igabanya ubukana, Niba izwi:

➢ Diyabete
  - Oya
  - Yego HBA1C ya nyuma (Niba izwi) □

➢ Izindi ndwara
  - Kanseri Yego / Oya
    - Niba ari yego, Ni ubuhe bwoko bwa kanseri:
  - Indwara y umwijima (Cirrhosis) Yego / Oya
  - Indwara y'impyiko (ESRD) Yego / Oya
  - Izindi ndwara:

➢ Yanyweye antibiyotike atahawe na Muganga
  - Oya
  - Yego Ryari:
  - Antibiyotike yanyweye (Niba zizwi):

4 .CLINICAL PRESENTATION

➢ Igihe umuriro wamaze
  - Munsi y'iminsi 7:
  - Hagati y'iminsi 7 na 14:
  - Hejuru y'iminsi 14:

- Antibiyotike yanyweye mbere yo gufata ibizamini (Mu gihe ari mu bitaro)
    - Ntazo
    - Zirahari Ni izihe: Iminsi yazinyoye:

- Uheruka kunywa imiti ya Malariya
    - Oya
    - Yego Mbere yo kujya mu bitari □ Mu gihe uri mu bitao □

- Ingano y'ibiro ku burebure
    - Umubyibuho ukabije
    - Umubyibuho usanzwe
    - Ananutse

- Ufite agapira ko mu ruhago
    - Oya
    - Yego

- Central lines
    - Oya
    - Yego

- Prosthetic valves
    - Oya
    - Yego
- Ibindi byago byo kugira infegisiyo
    - Ntabyo
    - Birahari Ibihe:

5. IBISUBIZO BYA LABORATWARI

5.1 Ibizamini bisanzwe byo muri laboratwari

- Hemoglobin (g/dl) :
- WBC:
    - Absolute neutrophils counts:
    - Absolute lymphocytes count:
    - Absolute monocytes count:
- Platelets:
- Ikizamini cya Malariya:
    - Arayifite
    - Ntayo afite
    - Ntago cyasabwe
- ESR:
    - Ni nzima (1-20 mm/h):
    - Iri hejuru:
    - Ntago yasabwe
- CRP:
    - Ni nzima (0-5 mg/l)
    - Iri hejuru:
    - Ntago yasabwe:
    -

- **IBIZAMINI BYO GUHINGWA MURI LABORATWALI**

IBISUBIZO / **IBIZAMINI**	**Ntacyo byerekanye**	**Hari icyo byerekanye**			**Ibisubizo bya Genexpert**
		Microbe zabonetse	**Antibiogram**	**Iminsi byatwaye**	
Amaraso					
Inkari					

Igikororwa					
Swabu ku gisebe					
Cerebral Spinal Fluid (CSF)					
Tracheal aspirate					
Lymph node					

Note: Ibizamini byasabwe bwo guhingwa ariko ntibikorwe.....

- Ni nyuma y'iminsi ingahe ibizamini byasabwe kuva umurwayi agize umuriro:
  -
- Ni nyuma y'iminsi ingahe wanyweye antibiyotike(za mbere yo gufata ibizamini) kuva umurwayi agize umuriro:
- Ni nyuma y'iminsi ingahe wanyweye antibiyotike za nyazo(hagendeye ku bisubizo by'ibizamini byasabwe) kuva umurwayi agize umuriro:
- Ibisubizo bya Ultrasound:
- Ibisubizo by'izindi radio:

5.2 Ibindi bizamini bya labotatwari byasabwe

6. FINAL DIAGNOSIS:

7. IN-HOSPITAL OUTCOME

- Nyuma y'iminsi ingahe umuriro wagiye nyuma yo gutangir antibiyotike:
- Gukomeza kugira umuriro nyuma yo kurangiza kunywa antibiyotike
  - Oya
  - Yego

- Gutaha wakize
    - Iminsi yamaze mu bitaro:

- Gutaha worohewe

  Iminsi yamaze mu bitaro:
- Wasezerewe:
    - Ufite antibiyotike zo kunywa
    - Nta antibiyotike zo kunywa afite
- Yarapfuye
    - Oya
    - Yego, Nyuma y'iminsi ingahe agiye mu bitaro:
    - Icyateye urupfu

VII.3 Time framework

Activity	**Period**
Presentation of the proposal to department	May, 2021
Presentation of proposal in research committee at UR	June, 2021
Presentation of proposal in ethic committee at CHUK	July, 2021
Data collection and follow up	August, 2021 to end April, 2022
Data processing and analysis	May, 2022 to June, 2022
Redaction of the report	June - July, 2022
Publication of the results	August, 2022

VII.4 Budget

	ITEM	QUANTITY	UNIT PRICE Rwf	TOTAL PRICE Rwf
1.	Printing of consent forms	155 x 2pages	50	15 500
2.	Printing of questionnaires	155 x 5pages	50	38 750
3.	Communication expenses (4G monthly data)	9 months	10 000	90 000
4.	Peridem for Data collectors	1 x 9 months	50 000 / month	450 000
5.	Statistical data analysis by a consultant statistician	1	500 000	500 000
6.	Printed copies of the draft/ proposal, 25 pages each	5 copies	1 250 / copy	6 250
7.	Printed copies of the proposal, 25 pages each	3 copies	1 250 / copy	3 750
8.	Printed copies of the draft / dissertation, 50 pages each	10 copies	2 500 / copy	25 000
9.	Final printed copies of the dissertation , 50 pages each	5 copies	2 500 / copy	12 500
10.	Book binding	5 copies	5 000 / copy	25 000
11.	Sub total			1 166 750
12.	Miscellaneous 20%			233 350
13.	**TOTAL**	**1 400 100 rwf**		

VII.5 Ethical approval

UNIVERSITY of RWANDA

COLLEGE OF MEDICINE AND HEALTH SCIENCES

DIRECTORATE OF RESEARCH & INNOVATION

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 22nd /June /2021

Olivier BIZIMUNGU
School of Medicine and Pharmacy, CMHS, UR

Approval Notice: No 224/CMHS IRB/2021

Your Project Title ***"Assessment Of Discrepancy Between Empirical Antibiotics And Cultures Results In Febrile Patients At CHUK "Prospective, observational cohort study in admitted patients with febrile illness""*** has been evaluated by CMHS Institutional Review Board.

		Involved in the decision		
		Yes	No (Reason)	
Name of Members	**Institute**		**Absent**	**Withdrawn from the proceeding**
Prof Kato J. Njunwa	UR-CMHS	X		
Dr Stefan Jansen	UR-CMHS	X		
Dr Brenda Asiimwe-Kateera	UR-CMHS	X		
Prof Ntaganira Joseph	UR-CMHS	X		
Dr Tumusiime K. David	UR-CMHS	X		
Dr Kayonga N. Egide	UR-CMHS	X		
Mr Kanyoni Maurice	UR-CMHS		X	
Prof Munyanshongore Cyprien	UR-CMHS	X		
Mrs Ruzindana Landrine	Kicukiro district		X	
Dr Gishoma Darius	UR-CMHS	X		
Dr Donatilla Mukamana	UR-CMHS	X		
Prof Kyamanywa Patrick	UR-CMHS		X	
Prof Condo Umutesi Jeannine	UR-CMHS		X	
Dr Nyirazinyoye Laetitia	UR-CMHS	X		
Dr Nkeramihigo Emmanuel	UR-CMHS		X	
Sr Maliboli Marie Josee	CHUK	X		
Dr Mudenge Charles	Centre Psycho-Social	X		

After reviewing your protocol during the IRB meeting of where quorum was met and revisions made on the advice of the CMHS IRB submitted on 18th June 2021, **Approval has been granted to your study.**

Email: researchcenter@ur.ac.rw P.O Box 3286 Kigali, Rwanda www.ur.ac.rw

Please note that approval of the protocol and consent form is valid for **12 months**.

You are responsible for fulfilling the following requirements:

1. Changes, amendments, and addenda to the protocol or consent form must be submitted to the committee for review and approval, prior to activation of the changes.
2. Only approved consent forms are to be used in the enrolment of participants.
3. All consent forms signed by subjects should be retained on file. The IRB may conduct audits of all study records, and consent documentation may be part of such audits.
4. A continuing review application must be submitted to the IRB in a timely fashion and before expiry of this approval
5. Failure to submit a continuing review application will result in termination of the study
6. Notify the IRB committee once the study is finished

Sincerely,

Date of Approval: The 22nd June 2021

Expiration date: The 22nd June2022

Dr. Stefan Jansen
Chairperson Institutional Review Board,
College of Medicine and Health Sciences, UR

Cc:

- Principal College of Medicine and Health Sciences, UR
- University Director of Research and Postgraduate Studies, UR

CENTRE HOSPITALIER UNIVERSITAIRE
UNIVERSITY TEACHING HOSPITAL

Quality Health Care
Training & Research

Ethics Committee / Comité d'éthique

23rd Aug,2021 Ref.:EC/CHUK/094/2021

Review Approval Notice

Dear Olivier BIZIMUNGU,

Your research project: ***"Assessment of discrepancy between empirical antibiotics and cultures results in febrile patients at CHUK "***

During the meeting of the Ethics Committee of University Teaching Hospital of Kigali (CHUK) that was held on 23rd Aug,2021 to evaluate your request for ethical approval of the above mentioned research project, we are pleased to inform you that the Ethics Committee/CHUK has approved your research project.

You are required to present the results of your study to CHUK Ethics Committee before publication by using this link:www.chuk.rw/research/fullreport/?appid=423&&chuk.

PS: Please note that the present approval is valid for 12 months.

Yours sincerely,

Dr Emmanuel Rusingiza Kamanzi
The Chairperson, Ethics Committee,
University Teaching Hospital of Kigali

ETHICS COMMITTEE
CHUK

Scan code to verify.

" University teaching hospital of Kigali Ethics committee operates according to standard operating procedures (Sops) which are updated on an annual basis and in compliance with GCP and Ethics guidelines and regulations "