EPIDEMIOLOGICAL PROFILE OF FEBRILE NEUTROPENIA IN CHILDREN AT THREE REFERRAL HOSPITALS IN RWANDA

A 5-year retrospective study

By:

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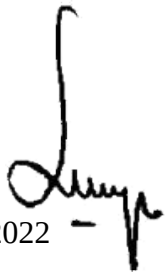

Date:31st/08/2022

Aimable Kanyamuhunga MD, MMED

DEDICATION

To the Almighty God, I thank you for the courage and determination to realize the completion of this work.

To my lovely husband, Dunia Jean Marie Vianney

To our children, Evan Manzi Lael, and Evy Rugwiro Anael

To my mother Nyaminani Suzanne

To my brothers and sisters and in laws family.

I dedicate this work.

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GLOSSARY ITEMS

CHUK: Centre Hospitalise Universitaire de Kigali

RMH: Rwanda Military Hospital

KFH: King Faisal Hospital

FN: Febrile Neutropenia

SSA: Sub-Saharan África

ANC: Absolute Neutrophil Count

UK: United Kingdom

USA: United State of America

HSCT: Hematopoietic Stem Cell Transplantation

HICs: High Income Country

LICs: Low Middle-Income Country

BSI: Bloodstream Infection

HIV: Human Immunodeficiency virus

HSCT: hematopoietic stem cell transplantation

BSI: bloodstream infection

RCWMCH: Red cross war memorial children hospital

SCOPE: Surveillance and Control of Pathogens of Epidemiologic Importance Project

%: percentage

RSV: Respiratory syncytial virus

HHV6: Human Herpes virus

EBV: Epstein Bar-virus

CLSI: Clinical laboratory standard Institute.

API-20E: Analytical profile Index

IDSA: Infectious Disease Society of America

MSSA: Methicillin- Sensitive staphylococcus aureus

MRSA: Multidrug resistant staphylococcal aureus

ABSTRACT

Introduction: Febrile neutropenia (FN) is an oncological emergency and requires prompt intervention. Recommended management of febrile neutropenia is based on local epidemiology of microorganisms in developed countries which has improved mortality and morbidity associated with FN. Rwanda lacks data on local epidemiology for Febrile neutropenia.

Objectives: This study intends to highlight the epidemiology of bacteraemia in pediatric population diagnosed with hemato-oncologic diseases presenting with febrile neutropenia at CHUK, RMH, and KFH for 5 years period.

Methodology: This was a cross-sectional retrospective study over a period of 5 years at 3 referral hospitals (RMH, CHUK and KFH) which included all patients with Febrile neutropenia aged less than 15 years. After data collection, Stata version 13 was used for analysis.

Results: This is the 1st study describing epidemiology of microorganism in Neutropenic cancer patients in our country.138 children were included in this study; 92 patients (67%) had hemato-oncology diseases with ALL predominance at 50%, while 46 (33%) were non cancer patients. Overall prevalence of febrile neutropenia in our study was 0.42%. Prevalence in hemato-oncology was 36%. The rate of bacteremia was 37.6% (52/138). The main predominant micro-organism was Gram negative which constitute 65.4% of all isolates with *Escherichia coli* predominance, followed by *Klebsiella spp* while most common gram-positive isolates were *Staphylococcal aureus*. Concerning antibiotic susceptibility, our study has showed that gram negatives were largely resistant to 3rd generation cephalosporins. However, 67% of S. aureus was mainly MRSA, though All *E. coli* isolated in our study were 100% sensitive to carbapenem. The 30-day all-cause mortality rate was 21% in all Febrile neutropenic patients. The 30-day all-cause mortality rate in cancer patients with FN was 19%. Patients with severe neutropenia were at increased risks of dying comparing to those with mild or moderate neutropenia.

Conclusion: Gram negative bacteremia was more common in febrile neutropenic pediatric patients. Antibiotic resistance to3rd generation cephalosporins and gentamicin suggest that carbapenems are needed for empiric treatment of febrile neutropenia. Antibiotic stewardship and microbial surveillance in our institutions need to be emphasized.

key words: febrile neutropenia, haematology, Rwanda

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CHAPTER 1: INTRODUCTION

1.1 Background

Febrile Neutropenia (FN) is a life threatening condition occurring in oncology (1). It is characterised by a temperature of 38^0 Celsius with an absolute neutrophil count (ANC) of less than 0.5 x 109/L (2). In neutropenic patients, fever is defined as a single oral temperature of ≥38.3°C (101°F) (3). Severity of neutropenia is classified by The American Society of Clinical Oncology as: severe, moderate or mild. Severe neutropenia is considered when ANC is less than 0.5×10^9/L.
(4).

Febrile neutropenia can result from the cancer itself, or administration of chemotherapy, radiotherapy and immunosuppressants(5). FN is most common in hematological malignancy; it can occur at the time of diagnosis or at the end stage diseases. Patients on chemotherapy have higher risk for FN episodes (6). 80% of the patients diagnosed with hematological malignancy undergoing chemotherapy are likely to develop FN comparing to those with solid malignancies with a likelihood of 10%-50%.

FN is associated with a higher mortality rate of 24% in high income countries (HIC) and 33% in lower income countries (LIC)(7,8).Regardless of progress in management, FN is associated with delayed hospital stays and increased health care cost(9). Timely and adequate empirical antibiotic treatment has shown to improve the prognosis(10,11).

Empirical usage in cancer patients is from the United States and European recommendations based on microbial isolates which have changed from gram negative to gram positive over the last 40 years (7).The epidemiology of bacterial isolates differs between HICs and LICs. In HICs, gram positives predominate and the treatment is based on bacterial isolates rather than empirical treatment alone, this was shown in studies conducted in Spain, Italy and the United States of America (12–15). Although data from low income countries mostly showed predominance of gram negatives in studies from Mexico, Ghana, Uganda and Tunisia (7,11,16,17).This trend differs in some African countries. Knowledge of bacterial isolates is of medical concern as it helps in management of Febrile neutropenia but also reducing bacterial resistance(20).

Rwanda still treats FN empirically based on study findings from HICs. There are no local epidemiologic studies on FN in Rwanda, therefore this study aims at identifying the causative microorganisms of FN in children with hemato-oncology diseases in three referral hospitals (CHUK, KFH, RMH) in Rwanda.

1.2 Problem statement

There is a marked shift of micro-organism causing infection in neutropenic patients as reported by European study, where around 70% of bacteraemia was related to Gram-positive organisms by the late 1980s and in early 1990s(21–23). Death related to FN episodes in high income countries(HICs) is ranging from 0.7–3.9% comparing to death rate observed in low income countries(LICs) which is considerably higher at 4–13.2%(24).

Neutropenic fever is a burden for children with newly diagnosed haematological cancer and for children receiving chemotherapy or radiotherapy. It is associated with prolonged hospital stay, high morbidity and mortality, higher hospital costs, and affects quality-of-life(24,25). HICs treat FN based on their local epidemiology, while LICs have minimal data concerning local epidemiology in FN. Nevertheless the majority of HICs use empirical therapy which has been shown to increase antimicrobial resistance(26,27). Identifying the causative microorganisms has helped in guiding antibiotherapy choices, thus improving the quality of life in children with neutropenic fever (6,8,10).

There is no data concerning local epidemiology in Rwanda although we receive many patients with FN. And this will be the first study among Rwandan children, The goal of this study aims to shed light on bacterial etiology and antibiotic sensitivity of febrile neutropenia in children with and without hemato-oncology diseases at three tertiary Rwandan hospitals over a 5 years period.

1.3. Research question

- What are the microbiological patterns in neutropenic fever in paediatric patients with and without hemato-oncologic malignancies at CHUK, RMH, and KFH?

1 .4. Aims and objectives

1.4.1. General objectives

This study generally sought to describe the epidemiology of bacteraemia in children with and without hemato-oncologic diseases presenting with febrile neutropenia at CHUK, RMH, and KFH.

1.4.2. Specifics objectives

- To assess socio-demographic status of children with Febrile neutropenia with and without hemato-oncology diseases.
- To describe the microorganism isolates in children with neutropenic fever with and without hemato-oncologic diseases.
- To determine short-term outcomes associated with neutropenic fever in children with and without hemato-oncology disease (30-day all mortality).
- To identify the prevalence of febrile neutropenia in among children with and without hemato-oncology diseases
- To describe antibiotic sensitivity in febrile neutropenic patient with or without hemato-oncology diseases.

CHAPTER 2: LITERATURE REVIEW

2.1. Definition & causes of neutropenic fever

Definition: FN is happened when there is decreased circulating white cell in blood characterised by a temperature of 38^{o} Celsius with an absolute neutrophil count of less than 0.5 x 109/L (2).FN is common in paediatric populations mostly in patients receiving chemotherapy or other myelosuppressive treatment and It is associated with poor outcome (30). But there are other causes of FN outside of oncological patients; those FN can be inherited or acquired.

The inherited causes of FN are many but the most severe one is Kostmann syndrome which is an autosomal recessive with HAX1 mutations associated with poor regulation of myeloid homeostasis at early promyelocyte stage, it's a rare condition occurring in the neonatal period. For the acquired causes of FN, the most common causes can be infections: like viruses (e.g., RSV, EBV, Parvovirus, HHV6, etc.), bacteria, and fungi. Other causes of FN include drug-induced, autoimmune, and chronic idiopathic, in clinical practice inherited causes of FN are rare (31,32).

FN can be identified either microbiologically when an organism has been identified, or clinically documented FN based on physical examination and radiology with a negative microbiology work up(26). The bacteraemia rate of FN can be identified microbiologically in only 20-30% of the cases(24,33).

2.2. Infections and febrile neutropenia in immunocompetent children

Many studies have demonstrated the codominance of virus in causing FN in immunocompetent children where respiratory syncytial virus (RSV) was found to be the most isolate in the immunocompetent children as shown by a retrospective study done in Japan (2012-2019) where RSV infection was observed in 31(11%) (34). Other study done from 2013 to 2015 in Israel in non-immunocompromised infants and young children < 2years, found that viruses like Adenovirus, RSV, Parainfluenza virus 1,2,3 and Influenza A, EBV, and CMV were the primary cause of FN(29).

The bacterial infections causing neutropenia in immunocompetent children was found in different studies ranging 5.3%-48.9% of patients(35).For example, a study done in Israel showed

bacteremia of 2.3% where *Staphylococcus aureus*, Enterobacter spp, Brucella spp, Salmonella spp., and E. *coli* were the isolated microorganism(29). Sergienko et al demonstrated bacterial isolates in 3.7 % where *Brucella melitensis and Streptococcus viridans* were mostly isolated .pneumonia, impetigo, cellulitis and otitis media were the most common diagnoses (28).
FN in otherwise healthy children is transient with low risk of bloodstream infection (BSI) and has good clinical outcome, therefore conservative management could be carried out in most of them(36).

2.3. Febrile neutropenia in oncologic patients

Infections are a remarkable contributing factor poor outcome observed in paediatric oncology(18). Its prevalence ranging from 11% to 38%(22,37) . FN in cancer patients is a common complication, and is associated with higher death rate, especially in LICs, it requires a high index of suspicion and immediate empiric antibiotic treatment (38,39).

Patients with hematological malignancies have an increased risk for developing FN, a greater number of FN in hematology malignancy occur at initial diagnosis or during chemotherapy phase, Fever being an exclusive sign of infection secondary to suppressed inflammatory responses in FN (6).The percentage of bloodstream infections among neutropenic fever episodes ranges between to 20% to 33% (40).

In an analysis acute mortality rate related to FN was 3.2%,with a noticeable rate of 24% in 30days after the bacteraemia onset (41).FN in oncology department has been showed to be associated with high mortality even in developed countries, as it was reported to be 9.5% in USA in 2000 and 33% in lower income countries (LIC)(7,42).However general death rate in FN patients still reach 20% to 30%.(42) , crude mortality in FN patients with hematological malignancy reach 40% (9).

2.4. Bacterial infections in febrile neutropenia in oncology

The epidemiology of pathogens which causes bacteraemia in FN is dynamic. The Infectious Diseases Group of the European Organization for Research and Treatment of Cancer (EORTC-IDG) trials have demonstrated a change of bacteraemia rate causing FN that had dropped to 22% in 1994 from 32% in 1973 Between 1973-1978, The proportion of Gram-negative and Gram-

positive pathogens went from 71% and 29%, respectively, while in the period of 1992–1994 , it switched to 33% and 67% (23).

Data from developed countries on epidemiology of febrile neutropenia showed predominance of gram positives, The studies conducted in the United States of America and Europe highlighted Gram-positive microorganisms as the main causative of bacteraemia in FN patients(12). The other study done in Italy, showed predominance of gram positives at 57% (14). Isolates in one U.S. city of Memphis, showed predominant of gram positives; Streptococcus viridans being mostly isolated at 29% (13). Gram-positive microorganisms reported in developed countries have been linked to use of semi-permanent central venous catheter ,skin contamination during sampling and difference in clinical practices observed in different studies (13,18,43,44).

Recent update showed that 40 to 50% are related to gram negative infections (8,45). Gram negative mortality reaches 18%(46).Different studies have demonstrated gram negative predominance in FN with hemato-oncology patients. The results from systematic review for cancer patients showed predominance of gram negative bacteremia range from 24.7 to 75.8%,Escherichia coli being the most isolated microorganism at a rate of 32.1%(45).

From January 2007 to December 2017, in 247 patients at Shanghai were reported as being infected by Gram-negative bacteria, with ALL predominance, most isolated microorganisms were Escherichia coli (40%), followed by Klebsiella pneumoniae (8). In a cross-sectional study done in hemato -oncology department in Turkey between 2010 and 2015 for patients with FN showed that FN was most commonly identified in patients having leukemia mostly acute lymphoblastic leukemia (33.8%),with a predominance of gram-negative bacteria at 60.5%, Escherichia Coli being the most isolated bacteria at 16.7%(15).

Gram negative bacteremia in FN patients with hemato-oncology conditions has been observed also in different studies from developing countries. In southern India, a study conducted by James V, Prakash, Et al. evaluating the microbiology pattern of bacteria isolates in FN in pediatric oncology found that bacteremia rate was 24% with gram negative bacteria co-dominate at 52.2% , Escherichia coli predominated in 20.6% of all isolates(27).

Other study done in Ghana by Nkrumah NO, et al. highlights a rate of bacteremia of 22% with a predominance of gram-negative at 52.6%. (16). Data from 2 studies done in children with FN with cancer (one in Tunisia, and another in Uganda) have shown gram negative predominance at 48.1% and 66.8% ,rate of bacteremia were 28.7 and 14.1% , respectively(7,17).While the rate of bacteremia in cancer patients in South Africa was 13.8% (18).

2.5. Sepsis in sub-Saharan Africa

Sepsis is still a main cause of death; prolonged hospital stays and morbidity among children living in Sub-Saharan Africa. A study conducted in East Africa showed that in Kenya 25% of hospital deaths in children were due to community acquired bacteraemia (47). In Tanzania among children with laboratory confirmed bacteraemia 34.9% died.(48). In Rwanda, 23.8% of the children with laboratory confirmed bacteraemia died (48)(49).

Causative bacteria in African in paediatric populations differ from country to country. In two urban hospitals in Gambia, a study done between January 2013 and September 2015 in children presenting with severe infection revealed that Gram positive organisms were more commonly isolated with *Staphylococcal aureus* being the most isolated microorganism(49). A study done in Ghana by Nkrumah. et al. found that the major cause of bacteraemia was gram negatives, with the most common bacteria isolated being non-typhoidal salmonellae (NTS) (53.3%) (50).
In 2018, Ishimwe E, and Rogo T conducted also a study in Rwanda where they showed that the most common cause of bacteraemia was *Klebsiella spp* (30%), *S.aureus* (27.5%), and *E.coli* (22.5%)(48).

2.6. Empirical antibiotics for febrile neutropenia

Early initiation of empirical antibiotics in children with Febrile neutropenia diagnosed with malignancies is crucial in oncology department. Knowledge of the prevalent microorganism causing FN in cancer patients and drug susceptibility is necessary to decide appropriate empirical therapy.

Guidelines by the Infectious Diseases Society of America (IDSA) recommend that High-risk patients need hospitalization for intravenous empirical antibiotic therapy with a monotherapy of an anti-pseudomonal b-lactam agent. High risk patients were defined as prolonged neutropenia,

Temperature greater than 38.3^{o}C, hemodynamic instability and other comorbidities. When multidrug resistance is suspected or in hemodynamic instability ,IDSA suggest addition of Aminoglycosides, fluoroquinolones, vancomycin to the initial therapy(3).

IDSA recommends use of vancomycin in FN cancer patients when there is an evidence of MRSA but If there is a negative blood culture ,IDSA recommends discontinuing vancomycin after 3days (3). The Rwanda Pediatric guidelines recommend use of 3rd generation cephalosporins in pediatric patients with sepsis(51).We generally use third generation cephalosporins and Gentamicin mostly used at CHUK and RMH although KFH prefer to use Tazobactam and Amikacin or combination of carbapenem and vancomycin for patients with FN with oncology conditions

Different approaches for managing FN in cancer patients using empirical anti-microbials has been successful in last 50years ago and it has been shown to decrease the adverse outcomes associated with FN. However, there is increase of antimicrobial resistance in bacteria where gram negative bacteria have been more often identified as causative agents of FN-related infections which requires a switch in empirical treatment used(7,8,45).

In a systematic review evaluating antimicrobial resistance among gram-negative bacteria, in 10 studies evaluated, *E. coli* and Klebsiella isolates showed high susceptibility to carbapenems(45). Although vancomycin usage in FN has been proved safe patients having MRSA (3).

2.7. Cancer in Rwanda

Rwanda has high cancer burden exceeding 3000 cases annually by 2018(52). High incidence of leukemia was observed between 2012-2017 with 318 cases of ALL in Rwandans where approximately 68% of patients were <15years of age at diagnosis (53). There is a limited data in our country concerning microbiologic isolates in Neutropenic fever amongst paediatric hemato-oncology patients. Although bloodstream infection is an important contributor to hospitalization, no published study has been done specifically in hemato-oncology patients. There is only one study describing the cause of bacteraemia in paediatric patients in Rwanda(48). Therefore, our study aims to highlight the epidemiology of bloodstream infection in paediatric hemato-oncology patients at three referral hospitals in Rwanda.

CHAPTER 3: RESEARCH METHODOLOGY

3.1. Study design

This was a retrospective cohort study for a period of 5 years from January 2016 until December 2021.

3.2. Study site

Three paediatric tertiary canters (hospitals) which provide paediatric hemato- oncologist services in Rwanda were considered: University Teaching Hospital of Kigali (CHUK), Rwanda Military Hospital (RMH) and King Faisal Hospital, Kigali (KFH).

The University Teaching Hospital of Kigali is the largest academic tertiary referral hospital in Kigali-Rwanda, Nyarugenge District. It has a capacity of 560 total beds. There are 86 beds located in paediatrics from which 10 are for oncology. The oncology ward is staffed by one paediatric hemato-oncologist, one paediatric resident and one registered nurse in daily basis. The hospital has a level 3 laboratory, is not accredited, and does not use an automated system for blood cultures.

Rwanda Military hospital is a public tertiary care level to the general population with national centre for Radiotherapy and specialized personnel in oncology and in radiotherapy. With 406 bed capacity, where 81 is for pediatric. Their laboratory has Kenya accreditation system (KENAS) Level 3, and does not use an automated system for blood cultures. RMH has 81 pediatric beds.

King Faisal Hospital is a private governmental hospital located in Kigali which provides paediatric oncology services including chemotherapy with two permanent oncologists. The KFH laboratory is level 3, not accredited, and is without an automated system. With 160 bed capacity, 20 pediatric beds.

All the hospitals do not have an automated system for doing blood culture. They use the Analytical Profile Index (API) 20E for bacterial identification. Antibiotic susceptibility testing is performed using disk diffusion (Kirby-Bauer testing) and interpretation is per the Clinical and Laboratory Standards Institute (CLSI).

3.3. Study population

Participants aged below 15 years diagnosed with neutropenic fever who consulted the respective hospitals during the study period.

3.4. Selection of study population

3.4.1. Inclusion criteria

All participants aged below age 15 years diagnosed with neutropenic fever who consulted the respective paediatric departments under the study period.

- Objective fever must be present, defined as temperature greater than 38 degrees Celsius.
- The absolute neutrophil count must be Below 1500cells/microliter.

3.4.2. Exclusion criteria

- Neutropenia without fever.
- Children with FN in whom blood cultures were not obtained.

3.5. Sample enrolment and calculation

The sample size calculation was done using the Fischer's formula which is used to estimate a proportion from the population and the sample size was calculated as follows:

$n = Z^2 \frac{p\,(1-p)}{e2}$

n= the minimum required sample size.

Z^2= the standard normal value corresponding to 95% confidence interval equalling to 1.96.

p= the estimated proportion or prevalence of neutropenic fever calculated at 4.7% from the pilot study conducted for participants of a 3-month period.

E= level of precision set at 5%.

Thus,

$n= 3.84\frac{0.047\,(1-0.047)}{0.0025}= 76$

The study used consecutive sampling and the minimum required sample from our population is 76 participants.

3.6. Study procedures

3.6.1. Sampling and enrolment

Principal investigator (PI) reviewed existing patient files and the electronic health data base to collect patient data on children admitted with fever and neutropenia in the scope of the study period. The PI extracted patients who presented with fever and low absolute neutrophil count, defined as a temperature greater than 38 degrees Celsius and ANC <1500 cells/microliter whose blood culture had been drawn. The PI reviewed demographic data; medical history including

underlying diseases; vital signs especially Temperature; empirical treatment on admission; treatment adjusted after antibiogram all this information was retrieved from the patient files while Full blood count, microbiological results and drug sensitivity were retrieved from laboratory. Data was collected after getting the Institutional Review Board (IRB) approval.

3.6.2. Laboratory methodology

Standard practice at CHUK, RMH and KFH is that blood cultures were sent to the microbiology laboratory in culture medium bottles. Growth time were approximately 7 days at 35 degrees Celsius. Blood culture bottles were manually checked daily for evidence of microbial growth Isolated bacteria were sub-cultured using an appropriate media guided by gram stain results as follows. gram-positive cocci used mannitol salt agar and blood agar as their media for gram stain whereas MacConkey agar and Xylose Lysine Deoxycholate agar media were used during the isolation of gram-negative bacilli. Catalase and coagulase tests were used in identifying gram-positive species. Genus and species identification of gram-negative bacilli used colony morphology. During the study period all hospitals were not having an automated system. Antibiotic susceptibility testing was carried out by using disk diffusion (Kirby-Bauer testing) and interpreted as per Clinical and Laboratory Standards Institute (CLSI).

3.7. Outcome of the study

The main outcome of the study is:

- To identify microorganisms causing bacteraemia in Neutropenic fever in three referral hospitals.
- To describe the antibiotic sensitivity among children with FN
- Identify the patient who are at risk for developing FN
- The second goal were to look short term outcomes defined as 30-day all-cause mortality.

3.8. Data management and analysis

Data collection was done using a drafted questionnaire as there was no standard tool. After, data were entered into the Epidata version 3.1 then Stata version 13 was used for data analysis. Descriptive data were presented as follows: categorical data were presented using frequencies and percentages in tables and charts. Continuous data were summarized by mean and median

values depending on their distribution. Chi-square test and logistic regression (binary logistic regression and multivariable logistic regression analysis) were utilised to study the relationship among the outcomes and possible predictors. Statistical significance for associations was taken at the level $p < 0.05$.

3.9. Compensation/reimbursement

No compensation was given in this study.

3.10. Ethical consideration

3.10.1. Confidentiality

Participant's confidentiality was maintained by keeping all data in a secured area and in a password protected computer. Each participant was re-identified and given a study number. Only members of the research team had access to the data.

3.10.2. Consent form

Waiver of consent was used as this was a retrospective study.

3.10.3. Ethical approval

The research proposal was reviewed and approved by the University of Rwanda, College of Medicine and Health Sciences institutional review board, Approval Notice No:228/CMHS IRB/2022(Appendix 2) and institutional board review of CHUK, RMH and KFH Rwanda (See Appendix 3,4 and 5)

3.10.4. Conflict of interest

No conflicts of interest to notify.

3.10.5 Funding and sponsors

No funding has been sought for this project

CHAPTER 4: RESULTS

4.1. Flow chart for study participants' recruitment

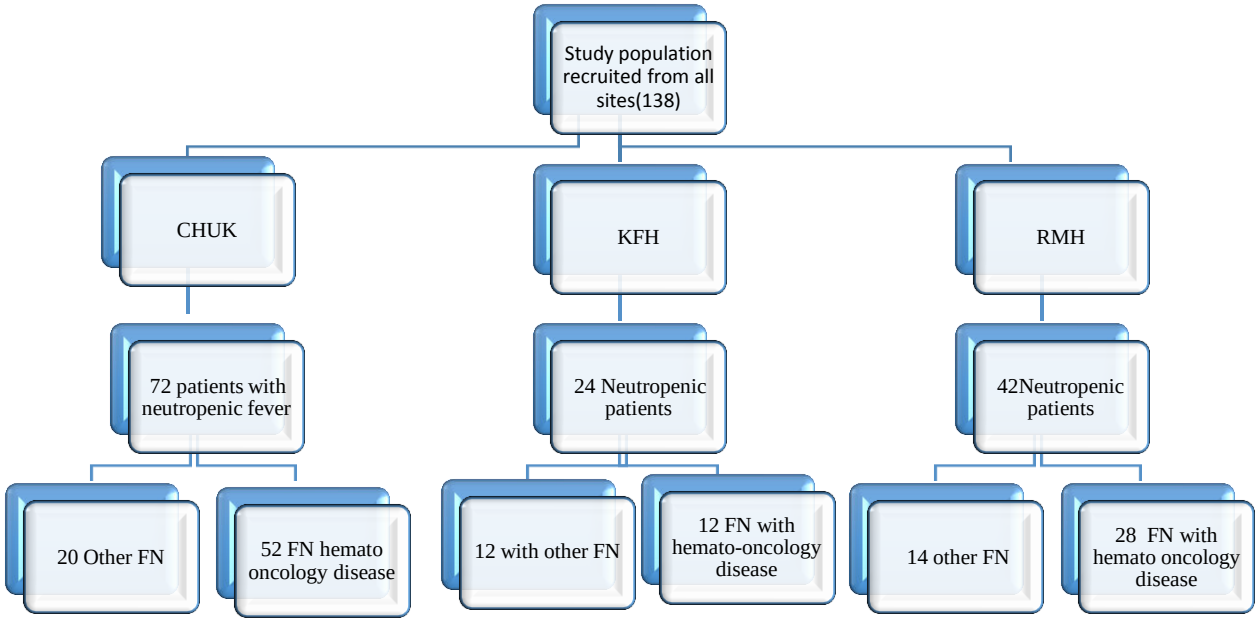


Figure 1:Flow chart for study participant enrolment

A total of 32518 medical records of children admitted over the 5-year period at the study sites were reviewed and these included 250 children with haemato-oncological disease. A total of 138 children under 15 years with FN were identified 92 with haemato-oncological disease and 46 with other conditions as shown in **(Flow chart 4.1).**

4.2. Prevalence of febrile neutropenia

In 5years period, we have recruited138 patients with FN out of 32518 children admitted in the study sites representing an overall prevalence of 0.42% (420 per 10,000 children. Prevalence in hemato-oncology was 36% (92/250) (250 patients had hemato-oncology conditions during the study period).

4.3. Sociodemographic and clinical characteristics of children with febrile neutropenia

The mean age of patients who were recruited in the study was 7.9 years (SD=4.15), ranging from 1 year to 15 years. Fifty-five percent of the participants were males and 32.6% of the total number of patients resided in Kigali City. 68% of the patients had severe neutropenia. **(Table 1)**

Table 1: Sociodemographic and clinical characteristics of children with febrile neutropenia

Characteristics	N	%
Age (Mean ± SD)	7.92 ± 4.15 years	
Age range		
1-5 years	47	34.06
6-11 years	55	39.86
12-15 years	36	26.09
Gender		
Male	76	55.07
Female	62	44.93
Residence		
Kigali	45	32.61
South	29	21.01
Est	24	17.39
West	21	15.22
North	18	13.04
Outside of Rwanda	1	0.72
ANC	94	68.11
Severe	30	21.74
Moderate	14	10.14
mild		

4.4. Distribution of diagnosis among participants with febrile neutropenia

Hemato-oncologic causes occupied 67% of all causes of FN where (ALL) was the most common in 50 % (46/92), while non hemato-oncology causes were 33% causing FN where the most common diagnoses were malnutrition (75%) and sepsis (50%) **(Table 2)**

Table 2:Distribution of the diagnosis among participants with febrile neutropenia

Variables	N	%
Hemato&oncologic causes	92	67
ALL	46	50
AML	12	13.04
Burkitt lymphoma	6	6.52
Anaplastic LC Lymphoma	2	2.17
Non-Hodgkin's lymphoma	1	1.08
Chronic myeloid leukemia	1	1.08
Aplastic anemia	15	16.3
Solid tumor	9	9.8
Wilms tumor	6	66.67
Brain tumor	2	22.22
Ewing sarcoma	1	11.11
Non hemato-oncologic causes	46	33
Infectious	30	65
Sepsis	15	50.00
Typhoid fever	6	20.00
Pneumonia	5	16.67
Other	4	13.33
Non-infectious	16	35
Malnutrition	12	75
Nephrotic syndrome	4	25

4.5. Treatment modalities for patients with hemato-oncology diseases

There were 92 patients with hemato-oncologic disease and febrile neutropenia. Considering the management modalities, 19/92 patients (20.65%) were on chemotherapy. 11/92 of them were on chemotherapy for malignancy other than ALL classified as unknown while 71/92 (77.2%) were not on treatment as they were newly diagnosed. (**Table3)**

Table 3: Distribution of the diagnosis among participants with febrile neutropenia

Treatment modalities for patients with hemato-oncology diseases

Management	**n**	**%**
Malignancy-related management		
Chemotherapy	19	20.65
Maintenance phase	3	15.7
Induction phase	5	26.3
Unknown	11	57.9
Radiotherapy	2	2.17
Others (without treatment)	71	77.17

4.6. Distribution of isolated microbes among participants with febrile neutropenia

During the study period, of 138 participants with febrile neutropenia, 52 (37%) yielded positive blood cultures. Of the 52 isolates 18(34.7%) were gram positive and 34(65.3%) were gram negative. Over all 29 patients with oncologic conditions had a bacterial isolate while there were 23 isolates among those with non-oncologic disease. The only gram-positive organism isolated in these patients was *Staphylococcus aureus*. The prevalence of a gram-positive isolates was 8 (27.5%) among the 29 haemato-oncology patients with a bacterial isolate and 10 (43.5%) among the 23 other patients with bacterial isolates. The prevalence of a gram-negative isolates was 21 (72.5%) among the 29 haemato-oncology patients with a bacterial isolate and 13 (55.5%) among the 23 non-haemato-oncology patients with bacterial isolates. These differences between patients with haemato-oncologic conditions and those without are not significant (p=0.23).

Escherichia coli and *Staphylococcus aureus* were mostly isolated in malignancy-related cases, while Salmonella and *Staphylococcal aureus* were common in non-malignant causes of FN **(table 4).**

Table 4: Distribution of the diagnosis among participants with febrile neutropenia

Diagnosis	Salmonella	E. coli	Klebsiella	Staph aureus	Acinetobacter	Pseudomonas	Total
Malignancy causes							
Hematological	0	10	5	8	2	2	27
Solid tumors	0	1	1	0	0	0	2
Non-malignancy causes							
Infectious	6	1	2	8	0	1	18
No-infectious	0	0	3	2	0	0	5
Total	**6**	**12**	**11**	**18**	**2**	**3**	**52**

4.7. Antibiotic sensitivity

"50% of Salmonella spp. were resistant to ceftriaxone, polymyxin B and piperacillin tazobactam,33% of salmonella spp showed resistance to carbapenems and amikacin,83% susceptible to cefotaxime and ciprofloxacin, 100% of salmonella were susceptible to gentamycin" "Gram negative bacilli showed wide resistance to 3rd generation cephalosporins and only E. coli was 100% to ceftriaxone. *E. coli* was 100% susceptible to carbapenems while klebsiella spp showed 82%sensitivity to carbapenems".

"100% of Acinetobacter showed susceptibility to amikacin and polymyxin B, only 50% of Acinetobacter were sensitive to Gentamycin, ciprofloxacin and tazobactam."

"Only 75% of pseudomonas showed susceptibility to ceftazidime,33% of pseudomonas showed resistance to carbapenems, amikacin and ciprofloxacin."

"Only 33% of S. aureus was MSSA" **(Table 5).**

Table 5: Antibiotic sensitivity

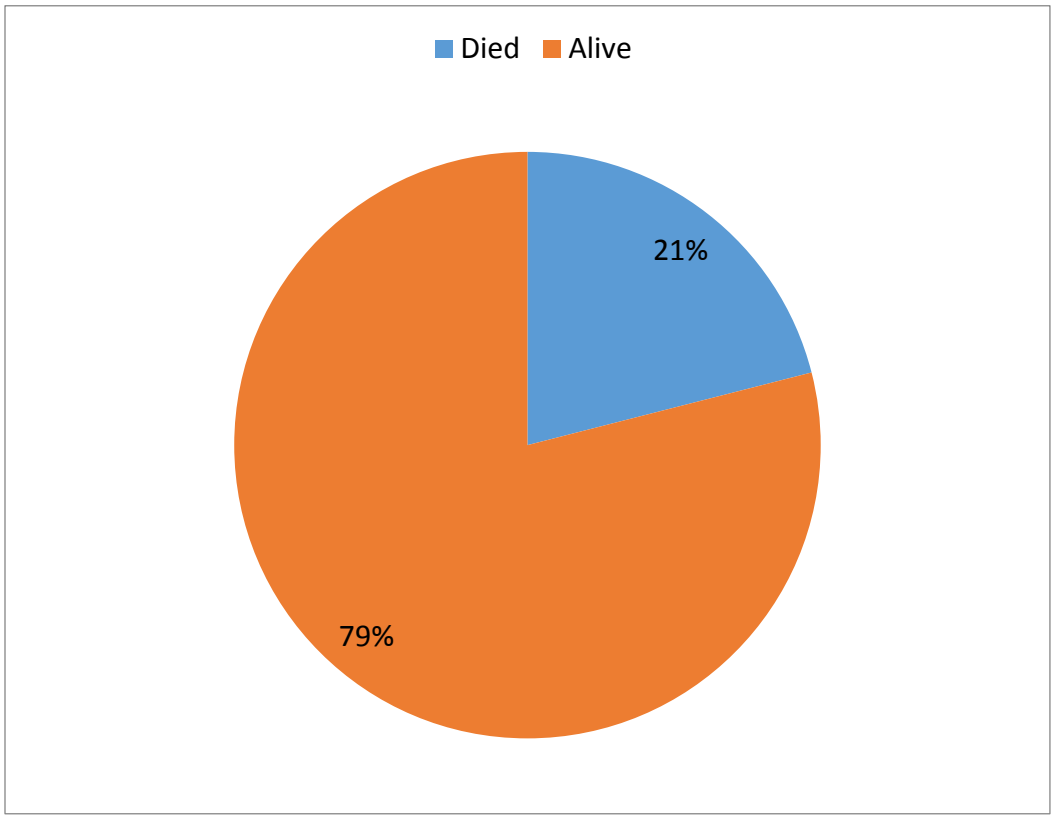
Antibiotics sensitive to	Isolated microorganisms					
	Salmonella* typhi n=6 (%)	***E. Coli n=12(%)**	**Klebsiella* sp n=11(%)**	**Staph aureus n=18(%)**	**Acinetobacter n=2(%)**	**Pseudomonas *n=3(%)**
Oxacillin	0	0	0	33	0	0
Amoxiclav	17	0	0	6	0	0
Cephalotin	17	0	0	11	0	0
Cefotaxime	83	16	0	0	0	0
Cephalotin	17	0	0	11	0	0
Gentamycin	100	8	36	0	50	67
Amikacin	67	67	45	0	100	67
Chloramphenicol	17	16	18	0	0	0
Tetracycline	0	8	0	55	0	0
Colistin	0	0	0	33	0	0
Erythromycin	0	0	0	50	0	0
Cotrimoxazole	0	0	9	0	0	0
Ciprofloxacin	83	58	27	33	50	67
Imipenem	67	100	82	0	0	67
Clindamycin	0	0	0	72	0	0
Ceftazidime	75	25	25	0	0	75
Cefuroxime	0	0	0	6	0	0
Ceftriaxone	50	0	9	0	0	0
Piperacillin-tazobactam	50**	0	50**	0	50**	0
Vancomycin	0	0	0	89	0	0
Meropenem	67	100	82	0	0	67
Polymyxin B	50	8	9	22	100	33

Legend 1. *Only 4 isolates were tested for ceftazidime sensitivity.

Legend 2. ** only 2 isolates were tested to piperacillin/tazobactam

4.8. Short term outcome associated with febrile neutropenia

Figure 2: Short-term outcomes associated with neutropenic fever (30-day all-cause mortality



Of 138 patients who were recruited with neutropenic fever,29 died within 30days of hospitalization giving an overall case fatality of 21%. Among 92 febrile neutropenic patients with hemato-oncologic disease,19 patients died within 30days of admission with a case fatality of 20%.

(Chart 2)

4.9. Factors associated with mortality among patients with neutropenic fever

Overall, 29(21%) of the 138 patients died by the 30th day of admission.

Patients with severe ANC have increased risk of dying compared to those with mild or moderate ANC (OR=3.62; 95% CI: 1.17-11.16; p=0.025) and no other associated risks factors was linked to death found due to limited sample size. majority of death was due to acute lymphoblastic leukemia and malnutrition **(Table 6)**

Table 6:Factors associated with mortality among patients with neutropenic fever

Predictors	30 days Outcome		OR (95% CI)	P value
	Died	Alive		
Age				
1-5 years	11 (23.40%)	36 (76.60%)	1.35 (0.44-4.14)	0.599
6-11 years	12 (21.82%)	43 (78.18%)	1.54 (0.52-4.53)	0.426
12-15 years	6 (16.67%)	30 (83.33%)	Ref	
Sex				
Male	19 (25.00%)	57 (75.00%)	1.43 (0.62-3.33)	0.395
Female	10 (16.13%)	52 (83.87%)	Ref	
Blood culture result				
Positive	14 (25.93%)	40 (74.07%)	1.34 (0.58-3.08)	0.48
Negative	15 (17.86%)	69 (82.14%)	Ref	
Gram				
Positive	4 (20%)	16 (80.00%)	Ref	
Negative	9 (26.47%)	25 (73.53%)	1.44 (0.37-5.47)	0.592
Hematological malignancies				
Yes	17 (25.00%)	51 (75.00%)	Ref	
No	12 (17.14%)	58 (82.86%)	1.61 (0.70-3.69)	0.26
Solid tumors				
Yes	2 (22.2250	7 (77.78%)	1.08 (0.21-5.49)	0.927
No	27 (20.93%)	102 (79.07%)	Ref	
ANC				
Severe	25 (26.60%)	69 (73.40%)	3.62 (1.17-11.16)	0.025
Moderate/Mild	4 (9.09%)	40 (90.91%)	Ref	
Isolated germ				
Salmonella	1 (16.67%)	5 (83.33%)	Ref	
E. Coli	5 (41.67%)	7 (58.33%)	3.5 (0.31-40.7)	0.306
Klebsiella	3 (27.27%)	8 (72.73%)	1.87 (0.15-23.4)	0.625
Staphylococcus aureus	4 (22.22%)	14 (77.78%)	1.42 (0.13-16.02)	
Acinetobacter	0 (0.00%)	2 (100%)	-	
Pseudomonas	0 (0.00%)	3 (100%)	-	

CHAPTER 5: DISCUSSION

5.1. Socio demographic and clinical characteristics of the patients

During the 5year period, the mean age of patients who were recruited in the study was 7.9 years (SD=4.15), ranging from 1 year to 15 years (Table 1). Fifty five percent of the participants were males 68% of the patients was having severe absolute neutrophil counted patients, comparable results has been observed in other study(54).

5.2. Distribution of diagnosis among participants with febrile neutropenia and prevalence

In our study, 67% had hematological-oncology diseases, while 33% were for other FN not related to hemato-oncology diseases. Hematological causes were the most underlying diagnosis, with ALL most common at 50% (Table 2). This can be explained by the high incidence of ALL in Rwanda(53).Similar findings have been observed elsewhere(7,8,15,26).

Overall prevalence of febrile neutropenia in our study was 0.42%. Prevalence in hemato-oncology was 36%, similar to other studies which report prevalence ranging from 11% to 38%(22,37). This high incidence of FN in hemato-oncology patients gave awareness of severity of FN in those patients, thus screening and isolation from the general ward are recommended.

We have found that malnutrition and sepsis were the most non hemato-oncology causes. Other studies demonstrated bronchiolitis and inherited conditions as the most common causes of FN (31,34,35),explained by high incidence of malnutrition in our country where 38% of under 5years are stunted.

5.3. Distribution of isolated microbes among participants with febrile neutropenia

To our consideration, of 138 patients with FN, blood culture was positive in 52 patients (37.6%). Gram negative bacteria was most commonly isolated at 65.4%. The most commonly isolated microorganism in non-hematological causes of FN was salmonella and *Staphylococcal aureus* (Table 4). This differs to what was found in a systematic review , where the most common micro-organism identified in non hemato-oncology children were mostly virus RSV,EBV, Parvovirus, HHV6. (31),same results with viral predominance was observed in other studies (34,35,54).This co-dominance of virus in immunocompetent children can be explained by advanced diagnostic capability in viral screening in developed countries which is lacking in our country.

Nevertheless, in our study of 138 FN recruited, 92 patients were found to have hemato-oncology conditions. Microbiologically confirmed BSIs were observed in 37.6%. Literature has showed microbiology can be identified in 20-30% of patients with FN (24,33). Comparable results has been observed elsewhere (9,16,55),but lower in studies done in South Africa and Uganda, 13.8% and 14.1% respectively(7,18). Gram negative bacilli being highest in our study; with *Escherichia coli***(**Table4) the same results has been observed in those studies (8,15,27,45). Our findings confirms emerging gram negative bacteria observed in previous local study done at CHUK in pediatric patient.(48)

Studies from developing countries has also showed gram-negative bacteria to be the main etiology of bloodstream infection (7,16,17,27). Empiric antibiotic use in peripheral facilities before referral may select out for the gram-negative organisms

Gram-positive bacteria were reported as the main micro-organisms isolate in developed countries, probably due to use of semi-permanent central venous catheters and skin contamination during sampling(13,18).

The small percentages of Gram-positive bacteremia observed in our study might be linked to dissimilarities in manner of our clinical practice compared to developed countries, including unavailability of long-term indwelling catheters, which are the main source of Gram-positive bacteremia.(43,44).

5.4. Antibiotic sensitivity

Our study has showed that gram negatives were largely resistant to 3rd generation cephalosporins.67% of S. aureus was mainly MRSA. It is concerning that 11% of S. *aureus* isolates were resistant to vancomycin. Only three quarters of isolated pseudomonas showed sensitivity to commonly used empirical antibiotic in FN(Ceftazidime). (Table 5)

In our study *E.coli* and klebsiella spp showed 100% and 82% sensitivity to carbapenems respectively, the Same results have been showed in systematic review where in 10 studies, *E.coli* and *Klebsiella spp* showed over 90% susceptibility to carbapenems .(45), IDSA support use of carbapenems and vancomycin in FN cancer patients with high risk (3). Our study confirm wide resistance of gram negative to 3rd generation cephalosporins which was also observed in

local study conducted by Tanya Rogo et Al.(48). Our study has shown high prevalence of MRSA at 67% (Table 5) but also showed emerging resistance to vancomycin ,confirming the existing data where 60%of tested S.aureus were MRSA in a study by Ishimwe et Al(48).

By comparison, Our research showed increased MRSA and increased resistance to cefotaxime and gentamicin on the preexisting data from CHUK done Ishimwe et Al(48).

The most commonly isolated microorganism in non hemato-oncology patients with FN was Salmonella and *S. aureus*. Salmonella was 100% sensitive to gentamicin and 83% sensitive to cefotaxime and ciprofloxacin, while *S. aureus* was 89% sensible to vancomycin and 70% to clindamycin (Table5), there are limited data on antibiotic sensitivity in patients with FN out of oncology.

5.5. Short term outcome of febrile neutropenia

FN is associated with high mortality and morbidity. The 30-day all-cause mortality in our study was 21% in all Febrile neutropenic patients. The mortality observed in non-cancer patients can be explained by poor outcome associated with malnutrition in general pediatric patients.as recent data reports high prevalence of malnutrition in our country,38% of children under 5years being malnourished. The 30-day all-cause mortality rate in cancer patients with FN was 19%. Our mortality rate was similar to another study where the overall mortality rate within 30 days after the onset of bacteraemia was found to be 24%(33).A study in low-income countries reported mortality of 33% which is high comparable to mortality observed in USA which was9.5%.(42)(7). This can be explained by unavailability of data on epidemiology of microorganisms causing FN in resource-limited countries. Patients with severe neutropenia have increased risk to die compared to those with mild or moderate neutropenia (OR=3.62; 95% CI: 1.17-11.16; p=0.025) (Table 6). No other factors were associated with mortality in our study, and this can likely be explained by the relatively small sample size.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

6.1. Conclusion

This study highlights that patient with neutropenia and underlying hematological malignancy are susceptible to develop bloodstream infection, study has responded to our objectives. Overall, it has shown local epidemiological data causing FN in general pediatrics, with emphasize in hemato-oncology patients. *Escherichia* coli was mostly gram negative isolated in hemato-oncology diseases and was highly sensitive to carbapenems. Antibiotic selectivity based on local epidemiology data will help us improve clinical outcome among cancer patients with FN in our institutions.

6.2. Recommendation

- ✓ Further study on drug resistance in FN is advised in the future
- ✓ To elaborate antibiotics stewardship in pediatric patients especially in oncology patients with FN
- ✓ use of Meropenem and vancomycin in FN with cancer to patients with severe neutropenia Is advised
- ✓ increase the capacity of our laboratory to do screening of viral causes of Febrile neutropenia.
- ✓ To do study on Febrile neutropenia at Butaro District hospital (where there are many pediatric patients on chemotherapy)

6.3. Study limitation

- ✓ Being retrospective design and small sample size was a hindrance to our study
- ✓ Stock out of blood culture bottles resulting in long period of not doing blood culture
- ✓ Inability to do viral testing among other causes of febrile neutropenia

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APPENDICES

APPENDIX 1: DATA COLLECTION SHEET

TOPIC: "epidemiological profile of febrile neutropenia in children at referral hospitals in rwanda: (a 5 years' retrospective study) chuk, kfh, and rmh"

1.Participant identification and demographic data

Date: ……/……. /…..

Participant initials: …

Age: ☐

Sex: male ☐ female ☐

Place of Residency: ☐ Kigali ☐ North ☐ South

☐ East ☐ West ☐ other:specify…….

District: ……

Nationality: ☐ Rwandese ☐other: specify…….

2.Patient's diagnosis

☐ hematological malignancies ☐ solid tumours ☐ other: specify….

Specify……

Specify:……

☐ radiotherapy ☐ chemotherapy: ☐ others…..

Specify phases……. specify phases.....

☐ Infections: ☐ Non infectious

Specify:…… specify:……

3.clinical and laboratory characteristics

Temperature ☐

ANC ☐

Febrile neutropenia episode ☐

Blood culture: Positive ☐

Negative ☐

If positive: gram negative ☐ gram positive ☐

Specify…… specify……

empiric antibiotics before blood culture result

Specify:…… Antibiotics tailored after antibiogram

Specify :…….

4.Antibiotic sensitivity

Isolated germ:		
Antibiotics	**Sensitivity**	**Resistance**
Penicilline G		
Oxacillin		
Ampicillin		
Amoxyclav		
Cephalotin		
Cefotaxim		
Gentamycin		
Amikacin		
chloremphenicol		
Tetracyclin		
Colistin		
Erythromycin		
Cotrimoxazol		

Nitrofuran		
Ciprofloxacin		
Imipenem		
Clindamycine		
Ceftaxidim		
Cefuroroxim		
Ceftriaxon		
Piperacilline tozobactam		
Tetracycline		
Vancomycine		
Meropenem		
Polymyxin B		

5.short term outcome

Mortality within 30days Yes ☐ No ☐

APPENDIX 2: INSTITUTION REVIEW BOARD ETHICAL APPROVAL

UNIVERSITY of RWANDA

COLLEGE OF MEDICINE AND HEALTH SCIENCES

DIRECTORATE OF RESEARCH & INNOVATION

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 21st /March /2022

Dr Tuyisingize Marie Aimee
School of Medicine and Pharmacy, UR

Approval Notice: No 228/CMHS IRB/2022

Your Project Title ***"Epidemiological profile of febrile neutropenia in children in three referral hospitals in Kigali, Rwanda", A 5years retrospective study"*** has been evaluated by CMHS Institutional Review Board.

Name of Members	Institute	Involved in the decision		
		Yes	No (Reason)	
			Absent	Withdrawn from the proceeding
Prof Kato J. Njunwa	UR-CMHS	X		
Prof 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	
Prof Gishoma Darius	UR-CMHS	X		
Prof 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 March 2022, **Approval has been granted to your study.**
Please note that approval of the protocol and consent form is valid for **12 months**.

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

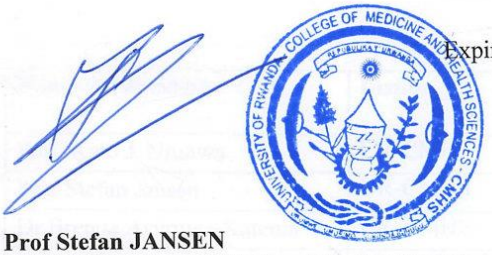
You are responsible for fulfilling the following requirements:

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 21st March 2022

Expiration date: The 21st March 2023



Prof Stefan JANSEN
Ag. 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

APPENDIX3: CHUK ETHICAL APPROVAL

CENTRE HOSPITALIER UNIVERSITAIRE
UNIVERSITY TEACHING HOSPITAL

Quality Health Care
Training & Research

Ethics Committee / Comité d'éthique

13th May,2022 *Ref.:EC/CHUK/083/2022*

Review Approval Notice

Dear TUYISINGIZE Marie Aimee,

Your research project: ***"epidemiological profile of febrile neutropenia in Children at three referral hospital "***

During the meeting of the Ethics Committee of University Teaching Hospital of Kigali (CHUK) that was held on 13th May,2022 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=590&&chuk.

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

Yours sincerely,

Prof. Florence MASAISA
The Vce Chair, Ethics Committee,
University Teaching Hospital of Kigali

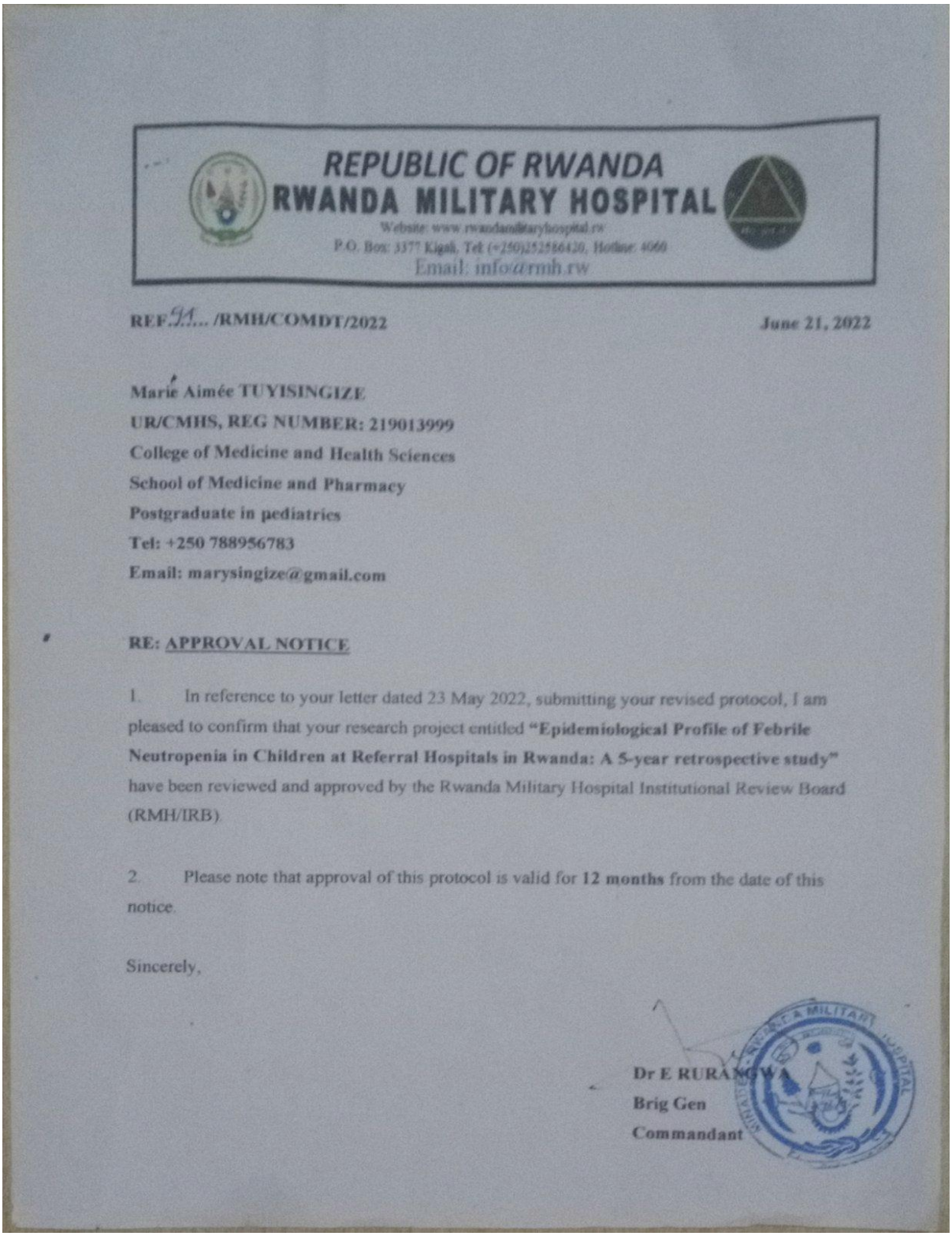
ETHICS COMMITTEE
CHUK

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 "

Web Site : www.chuk.rw ; B.P. 655 Kigali- RWANDA Tél.: 00 (250) 252575462. E-Mail: chuk.hospital@chuk.rw

APPENDIX 4: RMH ETHICAL APPROVAL



REPUBLIC OF RWANDA
RWANDA MILITARY HOSPITAL
Website: www.rwandamilitaryhospital.rw
P.O. Box: 3377 Kigali, Tel: (+250)252586420, Hotline: 4060
Email: info@rmh.rw

REF.71.../RMH/COMDT/2022 June 21, 2022

Marie Aimée TUYISINGIZE
UR/CMHS, REG NUMBER: 219013999
College of Medicine and Health Sciences
School of Medicine and Pharmacy
Postgraduate in pediatrics
Tel: +250 788956783
Email: marysingize@gmail.com

RE: APPROVAL NOTICE

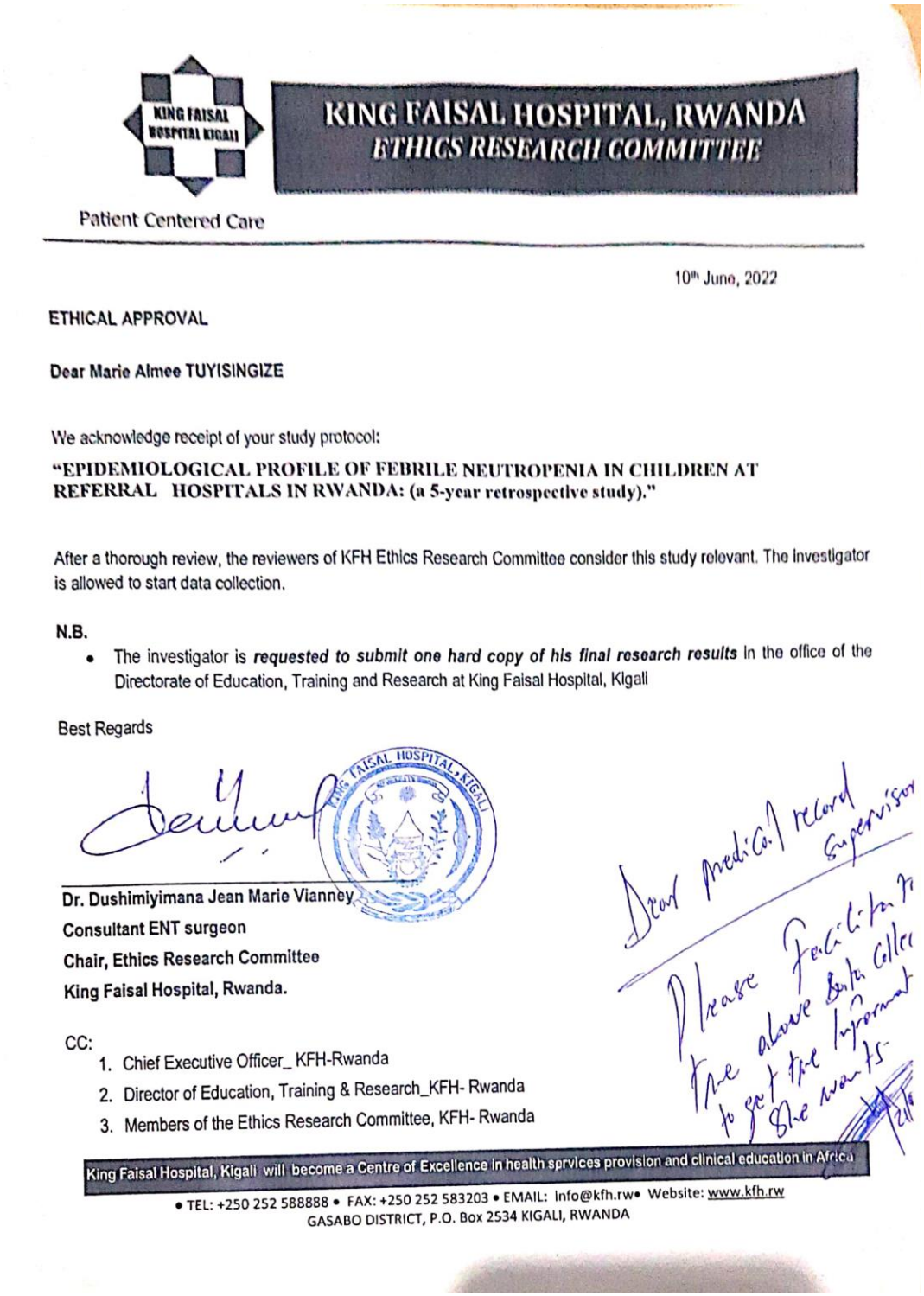
1. In reference to your letter dated 23 May 2022, submitting your revised protocol, I am pleased to confirm that your research project entitled **"Epidemiological Profile of Febrile Neutropenia in Children at Referral Hospitals in Rwanda: A 5-year retrospective study"** have been reviewed and approved by the Rwanda Military Hospital Institutional Review Board (RMH/IRB).

2. Please note that approval of this protocol is valid for **12 months** from the date of this notice.

Sincerely,

Dr E RURANGWA
Brig Gen
Commandant

APPENDIX 5: KFH ETHICAL APPROVAL



KING FAISAL HOSPITAL, RWANDA
ETHICS RESEARCH COMMITTEE

Patient Centered Care

10th June, 2022

ETHICAL APPROVAL

Dear Marie Aimee TUYISINGIZE

We acknowledge receipt of your study protocol:

"EPIDEMIOLOGICAL PROFILE OF FEBRILE NEUTROPENIA IN CHILDREN AT REFERRAL HOSPITALS IN RWANDA: (a 5-year retrospective study)."

After a thorough review, the reviewers of KFH Ethics Research Committee consider this study relevant. The investigator is allowed to start data collection.

N.B.

- The investigator is ***requested to submit one hard copy of his final research results*** in the office of the Directorate of Education, Training and Research at King Faisal Hospital, Kigali

Best Regards

KING FAISAL HOSPITAL KIGALI

Dr. Dushimiyimana Jean Marie Vianney
Consultant ENT surgeon
Chair, Ethics Research Committee
King Faisal Hospital, Rwanda.

CC:

1. Chief Executive Officer_ KFH-Rwanda
2. Director of Education, Training & Research_KFH- Rwanda
3. Members of the Ethics Research Committee, KFH- Rwanda

Dear medical record Supervisor
Please facilitate
the above Data Collec
to get the Informat
She wants

King Faisal Hospital, Kigali will become a Centre of Excellence in health sprvices provision and clinical education in Africa

• TEL: +250 252 588888 • FAX: +250 252 583203 • EMAIL: info@kfh.rw• Website: www.kfh.rw
GASABO DISTRICT, P.O. Box 2534 KIGALI, RWANDA