



UNIVERSITY of
RWANDA

COLLEGE OF MEDICINE & HEALTH
SCIENCES
SCHOOL OF MEDICINE & PHARMACY

SEASONAL TRENDS IN THE DIAGNOSIS OF TUBERCULOSIS AT KIGALI UNIVERSITY TEACHING HOSPITAL, RWANDA

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Registration number: 10107665

A dissertation submitted for partial fulfillment of the requirements for the degree of
MASTER OF MEDICINE IN EMERGENCY AND CRITICAL CARE.

In the College of Medicine and Health Sciences

School of Medicine and Pharmacy

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DECLARATION

I declare that this Dissertation contains my own work except where specifically acknowledged

UWAMAHORO Doris Lorette

Signature



Approval for submission by Supervisors:

Dr. MBANJUMUCYO Gabin



Signature..... Date 12/04/2019

Associate Professor MINDI Guptill



Signature..... Date.....March 18, 2019.....

DEDICATION

To God the Almighty,
To my lovely husband and children
To my Beloved Parents, Brother and sisters,
To my Friends and Relatives,
To my Supervisors,
To my Patients

This piece of work is dedicated with great pleasure.

ACKNOWLEDGEMENT

This dissertation for the award of a Masters' degree would not have been successful if there were no joint efforts in terms of moral support and guidance from various persons to whom I am addressing my heartfelt recognition.

I would like to extend my sincere gratitude and genuine appreciation to God, the Almighty for abundant blessings and protection.

I am grateful to the Government of Rwanda for the scholarship they offered me at University of Rwanda, College of Medicine and Health Sciences, School of Medicine and Pharmacy, in collaboration with Ministry of Health through Human Resource for Health program.

I would like to thank the KUTH in collaboration with the University of Rwanda, College of Medicine and Health Sciences, School of Medicine and Pharmacy for having granted us the permission to conduct the present study.

My special thanks go to supervisors of this work, **Dr Mindi Guptill, Dr Joseph Becker, Dr Gabin Mbanjumucyo**. Their contributions have greatly improved this work and my overall knowledge in research.

I also want to recognize the inputs of **Vinay Sharma, Dr Stephanie Chow Garbern** and **Michael Henry** for their contribution in improving the quality and relevance of this work.

I would like to thank the staff of the University Teaching Hospital of Kigali, for having taught me a lot during my training in Emergency Medicine.

Last but not least, my sincere thanks go to all my colleagues, friends and relatives for their support and being by my side throughout my life.

Dr.UWAMAHORO Doris Lorette

LIST OF SYMBOLS AND ACRONYMS

KUTH: Kigali University Teaching Hospital

HIV: Human Immunodeficiency Virus

WHO: World Health Organization

TB: Tuberculosis

DOT: Directly Observed Therapy for Tuberculosis

CMHS: College of Medicine and Health Sciences

IRB: Institutional Review Board

EC/CHUK: Ethics Committee/Centre Hospitalier Universitaire De Kigali

OR: Odd Ratio

CI: Confidence Interval

P: P value

ABSTRACT

INTRODUCTION

Tuberculosis (TB) is a serious global health problem with an estimated 9. 6 million new cases and 1.5 million deaths in 2014 alone. Research in several countries reveals there might be an association between seasons and the presentation and diagnosis of patients with TB.

METHODS

This was a retrospective chart review performed at the tertiary level care center, Kigali University Teaching Hospital (KUTH); from January 2016 to December 2017.

We documented patient demographics in addition to TB status, time of season (rainy or dry), HIV status and culture status.

RESULTS

In the overall population, Males made up 58.2% of included patients. More positive TB results occurred in the dry season compared to the rainy season ($OR= 1.35$). Adults were more likely to be diagnosed with TB compared to children ($OR= 14.7$, $p=<0.001$). There was no relationship between HIV and TB status ($p=0.73$).

CONCLUSION

TB is a deadly infectious disease and is prevalent in almost every part of the world. Our study confirms that TB detection does vary with season with more diagnoses occurring in the dry season. This study might help physicians to plan for which period of the year they would expect more TB patients, and, therefore set protective measures and establish guidelines on how to properly handle patients. The government should also strengthen education about TB awareness at the level of the community.

CHAPTER1.INTRODUCTION

Tuberculosis (TB) is a serious global health problem with an estimated 9.6 million new cases and 1.5 million deaths in 2014 alone¹. More than 95% of deaths occur in low to middle income countries with the highest incidence of TB cases being in the Western Pacific Regions and South-East Asia, which bear 58% of cases worldwide. The burden is great in Africa with an estimated 281 TB cases² per 100,000 in 2014³. In 2016, 2.5 million people contracted TB in Africa alone accounting for a quarter of new TB cases worldwide. Furthermore, over 25% of worldwide deaths due to TB occur in Africa⁴.

Rwanda is actively preventing and managing communicable diseases such as HIV and TB. The country's first TB sanatorium opened in Rwamagana in 1954 where TB infected patients from all over the country were isolated and managed until 1989⁵. In 1990, the Ministry of Health implemented a six-point Stop TB Strategy through a program known as "Rwanda National TB Control Program (NTP). TB management and treatment was decentralized to the local health facility level where the WHO Directly Observed Therapy for TB (DOT) strategy was implemented. DOT is a specific strategy endorsed by the WHO to improve medication adherence by requiring health workers, community volunteers or family members to observe and record patients taking each dose⁶.

Between 1990 and 2013, the mortality rate fell by 81%; prevalence and incidence fell by 75% and 76% respectively. In 2014, 6,024 all-forms TB cases were reported, with a consistent 2.3 % annual decrease since 2006². Thus, Rwanda is close to achieving the WHO targets for TB treatment and management.

Research done in Asia, South-America and Africa reveals a possible association between seasons and the presentation and diagnosis of patients with TB. A systematic review in 2011 reviewed studies looking at TB seasonality. The review included twelve descriptive studies conducted in 11 countries around the world between 1971-2006. This review revealed a seasonal pattern of TB presentation and diagnosis with predominant peaks in spring and summer in temperate climates; those countries include South Africa, India, Hong Kong, Japan, Kuwait, Spain, UK, Ireland, Russia and Mongolia⁷. Four seasons are recognized in these countries: spring, summer, autumn, winter. The literature suggests that TB incidence peaks during spring and summer, which could be a consequence of TB transmission during winter months (possibly due to overcrowding in poorly ventilated settings, diminished amount of natural UV light and delays of health care seeking behavior)⁸.

In contrast, a study done in Cameroon assessed TB seasonality in the rainy season versus dry season⁹. Cameroon, which has a similar climate to Rwanda, has variability in TB presentation

depending on the season with more TB cases diagnosed in the rainy season compared to the dry season. In Cameroon, TB was more prevalent in males than females ($p=0.034$), with the most affected age group being 21-30 years old ($p=0.002$)¹⁰.

Rwanda has two seasons, each repeating once throughout the year. There are two rainy seasons (the first from February to June and the second from September to December) separated by two dry seasons (the major one from June to September and a less severe one from December to February)¹¹. There has not been research conducted in Rwanda assessing the impact of seasons on TB incidence. Additionally, the Rwandan climate is quite different from most of the countries where TB seasonality research has been completed. This fundamentally limits our ability to apply research from other countries to Rwanda. Despite the decreasing numbers of TB in Rwanda, 6,024 TB cases still represent a significant burden. As a result, better understanding TB in a Rwandan context and assessing seasonality may yield clues that could help with prevention, management and treatment of this disease. This study will help us not only know the TB incidence at Kigali University Teaching Hospital (KUTH), but also help us determine what times of the year we can expect more TB patients. Lastly, this research may benefit East African countries or others with a similar rainy/dry climate.

1.1. Aims and objectives

1.1.1. Aim

To determine the impact of rainy and dry season on TB (all forms) presentation at KUTH.

1.1.2. Objectives

- To determine the most affected age group and gender.
- To determine the type of samples analysed by the laboratory.

CHAPTER 2.METHODOLOGY

2.1 Research design

We conducted a retrospective chart review from January 2016 to December 2017 of 2762 patient charts which indicated a need for TB testing and had laboratory tests requested and analyzed for diagnosis.

2.2. Research approach

We created a database in Microsoft Excel and collected data from laboratory records. Data included patient demographics, TB status, HIV status, and culture status. There are two dry seasons and two rainy seasons throughout the year in Rwanda. The first dry season is from January 1st to January 31st and the second dry season is from June 16th to August 31st. In between are two rainy seasons: February 1st to June 15th and September 1st to December 31st.

2.3. Research setting

This study was performed at a tertiary level care center in Kigali University Teaching Hospital (KUTH), from January 2016 to December 2017, in Kigali; Rwanda. KUTH is an urban referral hospital with approximately 560 inpatient beds and 40 beds in the Emergency Department. It also has outpatient services where patients from different district hospitals and private clinics can consult for further evaluation and more advanced laboratory testing. Typical disease profiles of patients presenting to KUTH include trauma and infectious disease. At KUTH, if sampling sites are pulmonary, diagnosis is mainly done with GeneXpert. If sampling sites are extrapulmonary, diagnosis is still commonly achieved with GeneXpert; however, sometimes the diagnosis is purely clinical.

2.4. Study population

We included all patients with suspected TB who had laboratory tests requested and analyzed for diagnosis. There were no exclusion criteria. We documented patient demographics (eg gender, age) in addition to TB status, time of season (rainy or dry), HIV status and culture status.

2.5. Sampling

2.5.1. Sample size

We estimated that 5 patients are tested every day for TB, and over a period of 2 years, this resulted in a calculated sample size of 3650 patients. We reviewed in total 2762 patient charts whose samples were sent to KUTH laboratory for analysis from January 2016 to December 2017.

2.6. Validity and reliability of research instruments

No research instruments were utilized for this study.

2.7. Outcomes

2.7.1. Primary Outcomes

The primary outcome for this study is to assess the impact of rainy and dry season on TB presentation at KUTH. A positive TB finding was determined using the Genexpert lab test.

2.7.2. Secondary Outcomes

Secondary outcomes for this study are assessing associations between HIV status, age, and gender with TB status.

2.8. Data collection

Data collection consisted of reviewing patient charts from January 2016 to December 2017. Variables included patient demographics, HIV status, TB status, culture status, and Genexpert results. Data was entered into a password-protected Excel spreadsheet.

2.9. Data analysis

Data analysis was performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive analyses were completed for the overall cohort. Data with any missing entries were eliminated and analysis consisted of logistic regression analysis to calculate odds ratios (ORs) with 95% confidence intervals. A significance level of $p < 0.05$ was utilized in our analyses.

2.10. Ethical consideration

The research study has been approved by the CMHS Institutional Review Board (IRB) No 090/CMHS IRB/2018 and the KUTH Ethics Committee No EC/CHUK/585/2018.

2.11. Data management

Only study investigators had access to the KUTH laboratory registers. We collected data in a pre-designed excel sheet using a password protected computer.

CHAPTER 3.RESULTS

3.1. Patient Demographics

Among 2,762 reviewed patient charts, 1,570 charts contained sufficient data to be included in the study (Figure 1). In the overall population, male patients made up 58.2% of included patients (Table 1). The mean age for male patients was 37.5 years (SD=21) and the mean age for female patients was 40(SD=20) (Table 1). Furthermore, males were mostly aged between 20 to 30 years while females were between 30 to 40 years (Figure 2). 17.7% of patients were found to be HIV + and TB was confirmed in 13.9% of the total patients (Table 1). In terms of sampling procedures for TB testing, most samples were obtained from extrapulmonary sites (53.5%), with the most common being pleural effusions (39.1%). The most common pulmonary site sampled for testing was the sputum (61.8%) (Table2).

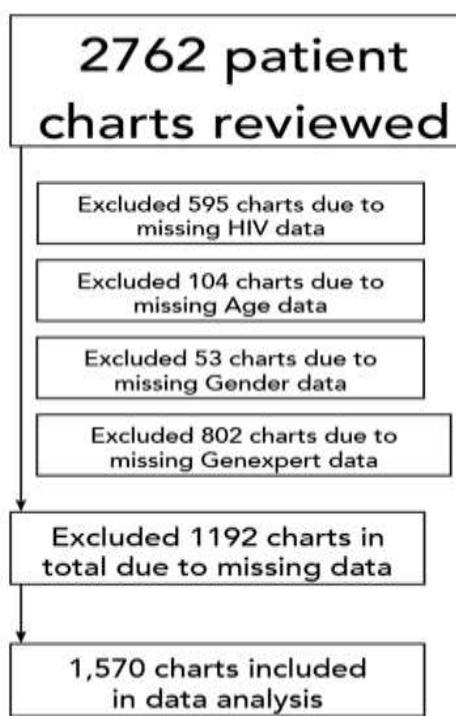


Figure 1 Study flow chart

Characteristics	n (%)
Gender	
Male	915(58.2)
Female	655(41.7)
Age (years)	
Male	37.5 ± 21
Female	40 ± 20
HIV Status	
Positive	278 (17.7)
Negative	1292 (82.2)
TB Status	
Positive	219(13.9)
Negative	1351(86)
Children(<18yrs)	227 (14.4)
Adults(≥ 18yrs)	1343 (85.5)

Table 1 Patient Demographics

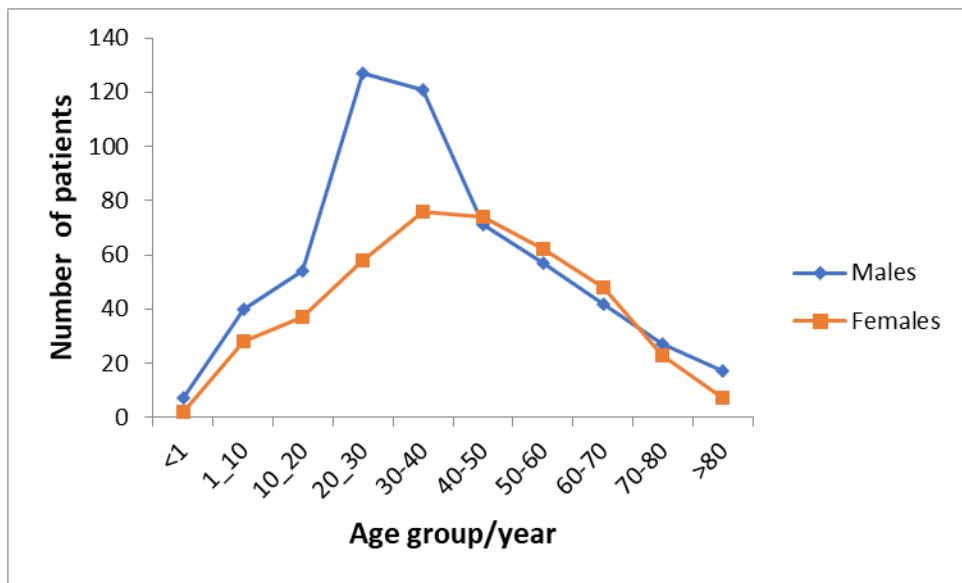


Figure 2 Age Distribution of Patients Enrolled in the Study

3.2. Primary Outcomes

More positive TB tests occurred in the dry season compared to the rainy season ($OR = 1.38$, 95% CI: 1.01, 1.89, $p=0.03$) (Table 3). Although more positive TB cases occurred during the rainy season (Figure 3), the proportion of positive cases in the dry season (0.2) exceeded the rainy season (0.13) (Table 3). For the most part, TB testing increased in the rainy season compared to the dry season during both 2016 and 2017 (Figure 3). Furthermore, more TB testing was completed in 2017 compared to 2016. There was no relationship between the month of the year and positive TB diagnosis (Figure 4).

3.3. Secondary Outcomes

Adults were more likely to be diagnosed with TB compared to children ($p<0.001$, $OR=14.7$, 95% CI: 5.6 – 60.4) (Table 3). There was no relationship between TB status and HIV status ($p=0.73$).

Type of Sample		
Pulmonary (P) or Extra pulmonary (E)	Specific Sample Site	Number of Samples
P	BAL	163
P	Sputum	275
P	Tracheal aspirate	7
E	Articular fluid	2
E	Aspirate	1
E	Biopsy	17
E	Biopsy LN	1
E	Bloody	3
E	Bone marrow	3
E	Cerebrospinal Fluid	1
E	Cervical swab	1
E	Empyema	4
E	Gastric aspirate	40
E	Hand aspirate	1
E	Joint fluid	13
E	KFH	4
E	Knee aspirate	1
E	Ocular fluid	1
E	Pericardial fluid	9
E	Peritoneal Fluid	92
E	Pleural effusion	201
E	Pus	29
E	Pus swab	4
E	Pyothorax	1
E	Semen	2
E	Stool	7
E	Swab	3
E	Testicular pus	1
E	Urethra pus	1
E	Urine	70

Table 2 Sites of TB sampling, extrapulmonary or pulmonary

Season	TB positive	Total tested	Ratio
Rainy	147	1138	0,13
Dry	72	432	0,2

Table 3 TB status as it relates to the season

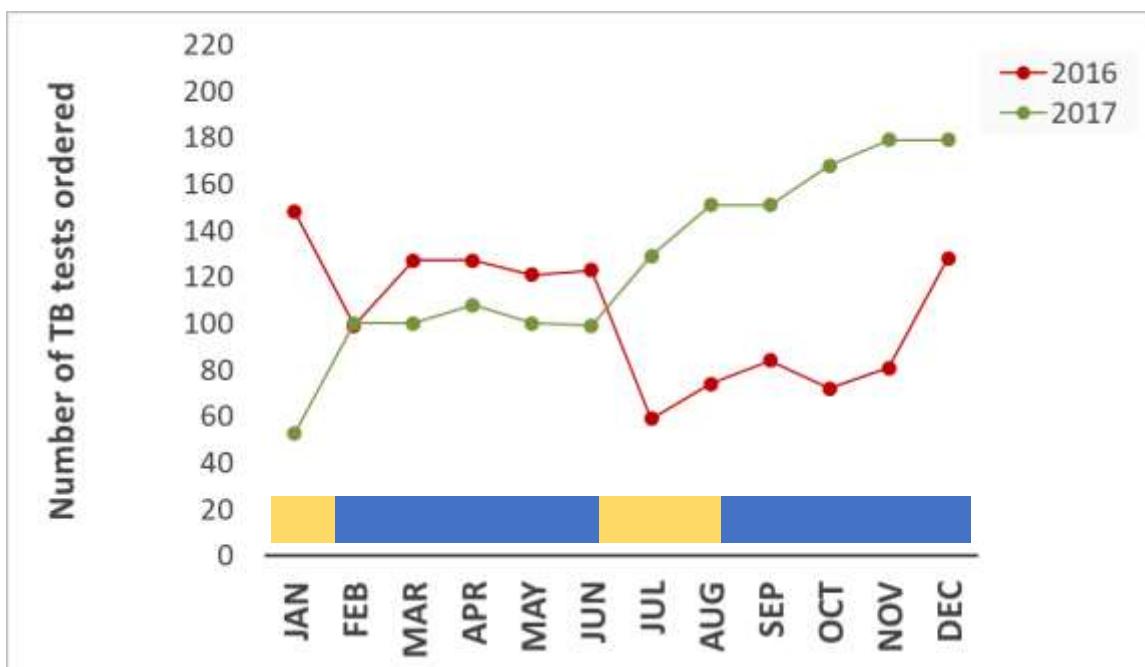


Figure 3 Number of TB tests ordered throughout the year. The yellow shading corresponds to the dry season and the blue shading corresponds to the rainy season.

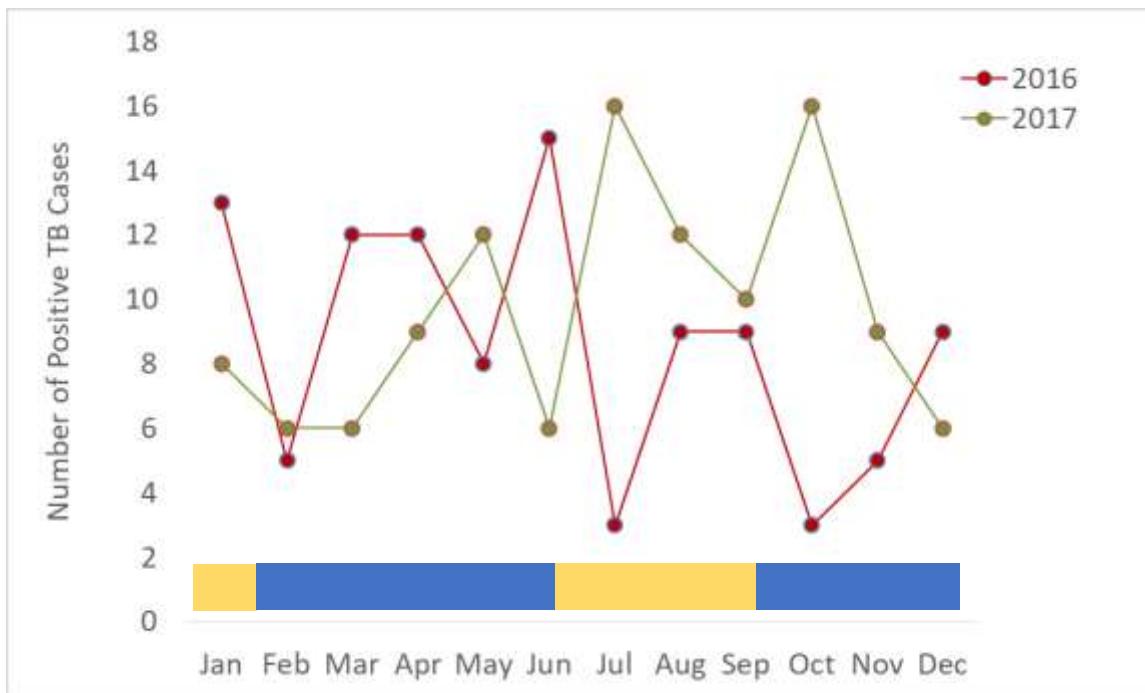


Figure 4 Occurrence of positive tests throughout the year. The yellow shading corresponds to the dry season and the blue shading corresponds to the rainy season.

CHAPTER4. DISCUSSION AND CONCLUSION

4.1. Discussion

This study was a single center, retrospective chart review done at a tertiary care center in Kigali, Rwanda assessing seasonal trends of TB. In our study, TB diagnosis occurred more often during the dry season (OR = 1.38) compared to the rainy season. This finding differs from a study done in Cameroon which showed more diagnoses were made in the rainy season¹⁰. Additionally, in our study, TB testing tended to increase in the rainy season compared to the dry season during both 2016 and 2017 (Figure 3). Considering the above findings, it suggests TB testing should be conducted all the time in Rwanda. However, during the rainy season, people are sometimes less inclined to present to the hospital thus, while they may contract the disease in the rainy season, it is not confirmed until much later. This delay in diagnosis could result in poorer outcomes for the patient.

Furthermore, among the 1570 patients' charts reviewed, adult men predominated in the study population (Table 1) and were mostly affected at 52.8%. Prior studies have also shown that men were mostly affected, and this could be partly explained by their social interactions (drinking, smoking...) and less immune function compared to women^{7,10,12}. Our study findings are consistent with other studies done in Africa looking at TB epidemiology, however, risk factors and associated behaviors for why men are contracting TB is not well understood in the Rwandan context. Further research can help to understand these social factors and allow for informed public health recommendations.

Overall, adults were more likely to contract TB compared to children. This is consistent with other studies looking at TB. A systematic review done in 2011 revealed the prevalence of TB in adults increases with age reaching 80% at 80 years⁷. However infection in children is reported to be recent. Our findings, however, may be an overestimate as it is very difficult to diagnose TB in children and our equipment may not be accurate in a pediatric population. Nonetheless, with efforts to reduce TB in the Rwandan population, public education of adults discussing initial symptoms and when to see a physician can be critical in attaining this goal.

In terms of sampling procedures for TB testing, most samples were obtained from extra-pulmonary sites, with the most common being pleural effusions. This differs from other studies which have often relied on pulmonary sites for TB diagnosis. A study in Israel revealed that the majority of confirmed laboratory cases were from pulmonary sites in 82.9% and 16.9% from extrapulmonary sites¹. We did not specifically look at the positivity of TB depending on the sample sent but the variety of sample sites that can diagnose TB is of interest and warrants further research.

4.2. Limitations

- We had a lot of missing data entries and incomplete charts as this was a retrospective study.
- We only studied patients who presented at KUTH missing patients who consulted at district hospitals.
- Some body fluid samples sent to the laboratory were not enough/not adequate for analysis and were rejected.
- No patients' files reviewed in order to tell if they presented in rainy or dry season

4.3. Conclusion

TB is a deadly infectious disease and is prevalent in almost every part of the world. Seasonal variation in TB diagnoses has been reported in different regions, suggesting that various geographic and demographics are involved in seasonality. Our study confirms that TB detection does vary with season with more diagnoses occurring in the dry season. This study might help physicians to plan for which period of the year they would expect more TB patients, and, therefore set protective measures and establish guidelines on how to properly handle patients. The government should also strengthen education about TB awareness at the level of the community.

4.4. Recommendations

A prospective study is highly recommended so as to understand well TB trends with regards to seasons.

Identify risk factors for TB contraction in the Rwandan population

There should be an improvement regarding data recording in order to avoid a lot of undocumented information.

A similar study might be conducted in District Hospitals so that we can get an overview for the whole Country.

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APPENDICES

VISION	A world free of tuberculosis – zero deaths, disease and suffering due to tuberculosis			
GOAL	End the global tuberculosis epidemic			
INDICATORS	MILESTONES		TARGETS	
	2020	2025	SDG 2030	END TB 2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100 000)	50% (<55/100 000)	80% (<20/100 000)	90% (<10/100 000)
TB-affected families facing catastrophic costs due to TB (%)	Zero	Zero	Zero	Zero

Who report, 2015



UNIVERSITY OF RWANDA

COLLEGE OF MEDICINE AND HEALTH SCIENCES

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 23rd April 2018

Dr. Elisee Lorette UWAMAHORO
School of Medicine and Pharmacy, CMHS, UR

Approved Notice No.000-CMHS IRB/2018

Your Project Title "Seasonal Trends In The Diagnosis Of Tuberculosis At Kigali University Teaching Hospital, Rwanda" has been evaluated by CMHS Institutional Review Board.

Name of Member	Institute	Involved in the decision	
		Yes	No (Reason)
Prof. Jean J. Musingo	UR-CMHS	X	
Prof. Jean Bosco Niyitegeka	UR-CMHS	X	
Dr. Bonaventure Kammer	UR-CMHS	X	
Prof. Ngapira Joseph	UR-CMHS	X	
Dr. Umuhoza K. Désiré	UR-CMHS	X	
Dr. Kageruka N. Ngabo	UR-CMHS	X	
Mr. Kanyanya Musanze	UR-CMHS	X	
Prof. Mutesera Jeanne Cyprien	UR-CMHS	X	
Mrs. Mutesera Cyprien	Kicukiro district	X	
Dr. Gishoma Eliezer	UR-CMHS	X	
Dr. Dossoula Soukamena	UR-CMHS	X	
Prof. Kyomera Jean Paul	UR-CMHS	X	
Prof. Casper Dossou Soukamena	UR-CMHS	X	
Dr. Mutesera Jeanne	UR-CMHS	X	
Dr. Mutesera Cyprien	Centre Psycho-Social	X	

After reviewing your protocol during the IRB meeting of where question was met and revision made on the issue of the CMHS IRB submitted on 12th April 2018. Approval has been granted to your study.

REVIEWED: 12 APRIL 2018 APPROVED: 23 APRIL 2018 APPROVAL NUMBER: 000-CMHS IRB/2018

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 23rd April 2018

Expiration date: The 23rd April 2019

[Signature]

Professor Kato J. NJUNWA
Chairperson Institutional Review Board,
College of Medicine and Health Sciences, UR



[Signature]
Chair
Chair

Cc:

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

EMAIL: researchcenter@ur.ac.rw P.O. Box: 3286, Kigali, Rwanda WEBSITE: <http://cmhs.ur.ac.rw/> www.ur.ac.rw



CENTRE HOSPITALIER UNIVERSITAIRE
UNIVERSITY TEACHING HOSPITAL

Ethics Committee / Comité d'éthique

May 28th, 2018

Ref.: EC/CHUK/585/2018

Review Approval Notice

Dear Uwamahoro Doris Lorette,

Your research project: "Seasonal trends in the diagnosis of tuberculosis, CHUK"

During the meeting of the Ethics Committee of University Teaching Hospital of Kigali (CHUK) that was held on 28/05/2018 to evaluate your protocol of the above mentioned research project, we are pleased to inform you that the Ethics Committee/CHUK has approved your protocol.

You are required to present the results of your study to CHUK Ethics Committee before publication.

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

Yours sincerely,

Dr. Rusingiza Emmanuel
The President, Ethics Committee,
University Teaching Hospital of Kigali



<<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>>

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CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 11th February, 2019
No 069 /CMHS IRB/2019

Dr.Doris Lorette Uwamahoro
School of Medicine, CMHS, UR

Re: Amendment Request for Research Protocol

Dear Dr.Doris Lorette Uwamahoro

We thank you for submitting your request for research project amendments in the project titled
"Seasonal trends in the diagnosis of tuberculosis at Kigali University Teaching Hospital, Rwanda".

After reviewing your protocol, the amendments have been approved with a change in the expansion of the research team as follows:

1. Dr Vinay Sharma of University of Michigan, USA as Co investigator
2. Dr.Mbanjumurey Gabin as a co supervisor

We wish you success in this important study.



Cc:

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