International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Chest Radiographic Features and Factors Associated with Smear Negative, Culture Positive Pulmonary Tuberculosis in Uganda. A Population Based Study

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ABSTRACT

Pulmonary Tuberculosis (PTB) remains a significant cause of morbidity and mortality worldwide. Early, accurate detection and treatment of active cases is vital for good clinical outcomes and disease control. Although sputum smear microscopy is commonly used for diagnosing PTB, 30-60% of all PTB cases are smear negative pulmonary tuberculosis. The objective of this study was to determine the social demographic, clinical and radiographic factors associated with SNPTB in Ugandan communities and describe the chest radiographic features of smear negative culture positive PTB.

Methods: This retrospective study used data collected by the school of public health and the National Tuberculosis and Leprosy Program (NTLP) in the 2013/2015 Uganda National TB prevalence survey. Case control study design was used. Social demographic, clinical and radiographic variables of the 93 cases who had SNPTB were matched against randomly selected controls in the same age bracket and analysed by logistic regression using STATA 13, to find factors associated with SNPTB. Descriptive statistics were used to summarize the categorical characteristics of the study participants in form of percentages. Continuous variables such as age were summarized into median and inter quartile range. Median and interquartile range were used because the data was not normally distributed.

Results: Factors male sex (AOR= 2.48, 95CI=458-4.213, p=0.001), being single (AOR=2.05, 95%CI=1.250-3.371, p=0.004), current smoking (AOR= 2.39, 95%CI=1.302-4.391, p=0.005) and urban setting were positively associated with SNPTB. Among the clinical features, cough ≤ 2 weeks (AOR=2.92, 95%CI=1.548-5,535, p=0.001), a positive HIV result (AOR=2.54, 95%CI=1.437-4.496, p=0.001), being on current PTB treatment (AOR=14.67, 95%CI=1.675- 128.517, p=0.015) were positively associated with SNPTB. Radiographically 87% of the cases had abnormal chest radiographs. 75.2% of the cases had features that were highly suggestive of active PTB. 63.4% of the cases had features of active post primary PTB, whereas 11.8% had features of atypical PTB. 13% of the cases had

normal chest radiographs. Consolidations, nodules, and pleural effusion were positively associated with developing SNPTB, however the study had low power.
Conclusion: Chest radiography is able to identify features suggestive of active pulmonary tuberculosis in more than half of the patients with negative sputum smears.

CHAPTER ONE

1.0 Introduction

Tuberculosis(TB) in 2015, was one of the top 10 causes of death worldwide, ranking even above HIV/AIDS, as one of the leading causes of death from an infectious disease(1). In 2015, there were more than 10.4 million new cases globally with more than two thirds of the global TB burden being reported in Africa and Asia (1). Inadequate case detection has been identified as one of the reasons for high burden of TB in the world especially in resource limited countries of Africa and Asia(2). Uganda was listed among the 30 most burdened countries globally in the 2015 global TB report(3), and although progress has occurred (1), HIV infection remains the strongest risk factor for TB infection in Uganda.
Currently, WHO recommends initial smear microscopy for the detection of acid-fast bacilli(4). However, 30–60% of all Pulmonary tuberculosis (PTB) cases are smear negative inspite of the clinical picture and radiological findings being consistent with diagnosis of PTB (4, 5).The mortality of SNPTB patients can reach 25% in populations with high prevalence of HIV infection, especially in the absence of Gene Xpert, which is also limited, since it only detects one strain of Mycobacterium tuberculosis complex (MTBC) namely M.tuberculosis (6).
Studies have found that the numbers of smear negative PTB are usually more than the smear positive numbers (7, 8). And although patients with SNPTB are less contagious than patients with sputum smear–positive TB(9), 10–20% of PTB transmission at the population level is as a result of SNPTB(4, 10). Therefore, persons in contact with patients with SNPTB are at risk of infection due to MTBC and the subsequent development of active PTB unless diagnosed by either culture, chest radiography(CXR) or treated empirically (11). Especially since literature has shown that HIV infection is associated with of development of SNPTB(12).
Chest radiography (CXR) is a rapid imaging technique that uses X-rays to visualize the internal structures of a patient and allows lung abnormalities to be identified. For many years, WHO has recommended chest radiography (CXR) as a diagnostic tool to be used as a complementary part of the clinical diagnosis of SNPTB, and as such, CXR has previously been placed at the end of diagnostic algorithms. The 2008 handbook for National Tuberculosis control programmes (13), as well as the third edition of the International standards for Tuberculosis care in 2014 suggested the use of CXR directly after an initial negative bacteriological test, and not just for people living with HIV (14). This was because numerous national TB prevalence surveys have demonstrated that CXR is the most sensitive screening tool for SNPTB(14), since a significant proportion of people with TB are asymptomatic, at least early in the course of the disease. Furthermore, there is the increased availability of radiography, including digital radiography with its lower running costs.

1.1 Problem statement

Whereas Uganda has taken positive steps and is no longer considered a high TB burdened nation(1), WHO estimates that about one third of all incident cases of active TB are either missed diagnoses, delayed diagnoses or sometimes wrong diagnoses(1).Unfortunately, microscopic examination of sputum smear samples, is often the only available bacteriological test for PTB, and it does not diagnose SNPTB.

In the 2015 Uganda National TB prevalence survey, 41156 individuals from communities in 57 districts in Uganda were screened for PTB with symptoms and chest radiography. ZN sputum analysis, gene expert and culture studies were done on two sputum samples collected from the 5143 presumptive PTB cases. 186 cases of PTB were confirmed bacteriologically of which, 93 had SNPTB, and out of which, only 6 were detected by Gene Xpert. Radiography was able to detect suspicious abnormalities in 74 of the SNPTB cases.

This showed that the incidence of SNPTB is relatively high. And whereas chest radiography is more often able to identify abnormalities suggestive of SNPTB, information detailing the chest radiographic features of confirmed SNPTB, as well as the social and clinical factors associated with SNPTB in East Africa is limited. And due to the low bacillary load, the radiographic and clinical presentation of SNPTB may not be typical but rather mimic other pulmonary infections resulting in missed or wrong diagnoses

1.2 Study justification

In the setting of a negative sputum smear result and no access to gene Xpert or culture, chest radiography takes on a vital role. This study will generate information on the social demographic, clinical and radiographic factors associated with SNPTB as well as features of SNPTB on chest radiography. This information will ultimately aid the clinical and radiographic diagnosis of SNPTB in resource limited settings. This will ultimately reduce the morbidity, mortality as well as the community transmission of smear negative PTB, which will be in keeping with the sustainable development goal number three which aims to promote health and wellbeing by increasing life expectancy and reducing the proficiency of common killers such as infectious diseases.

1.3 Research questions

1. What were the social demographic factors associated with SNPTB among persons aged 15 and above in Ugandan communities in 2014?
2. What were the clinical factors associated with SNPTB among persons aged 15 and above in Uganda in 2014?
3. What were the chest radiographic features of smear negative PTB and the radiographic factors associated with SNPTB among persons aged 15 and above in Ugandan communities in 2014?

1.4 General objective

To determine the social demographic, clinical and radiographic factors associated with SNPTB as well as describe the chest radiographic features of SNPTB among Ugandans aged 15 and above in 2014.

1.4.1 Specific objectives

1. To determine the social demographic factors associated with SNPTB among persons aged 15 and above in Ugandan communities in 2014.
2. To determine the clinical factors associated with SNPTB among persons aged 15 and above in Ugandan communities in2014.
3. To describe the chest radiographic features of smear negative PTB and determine the radiographic factors associated with SNPTB among persons aged 15 and above in Ugandan communities in 2014.

1.5 Conceptual frame work

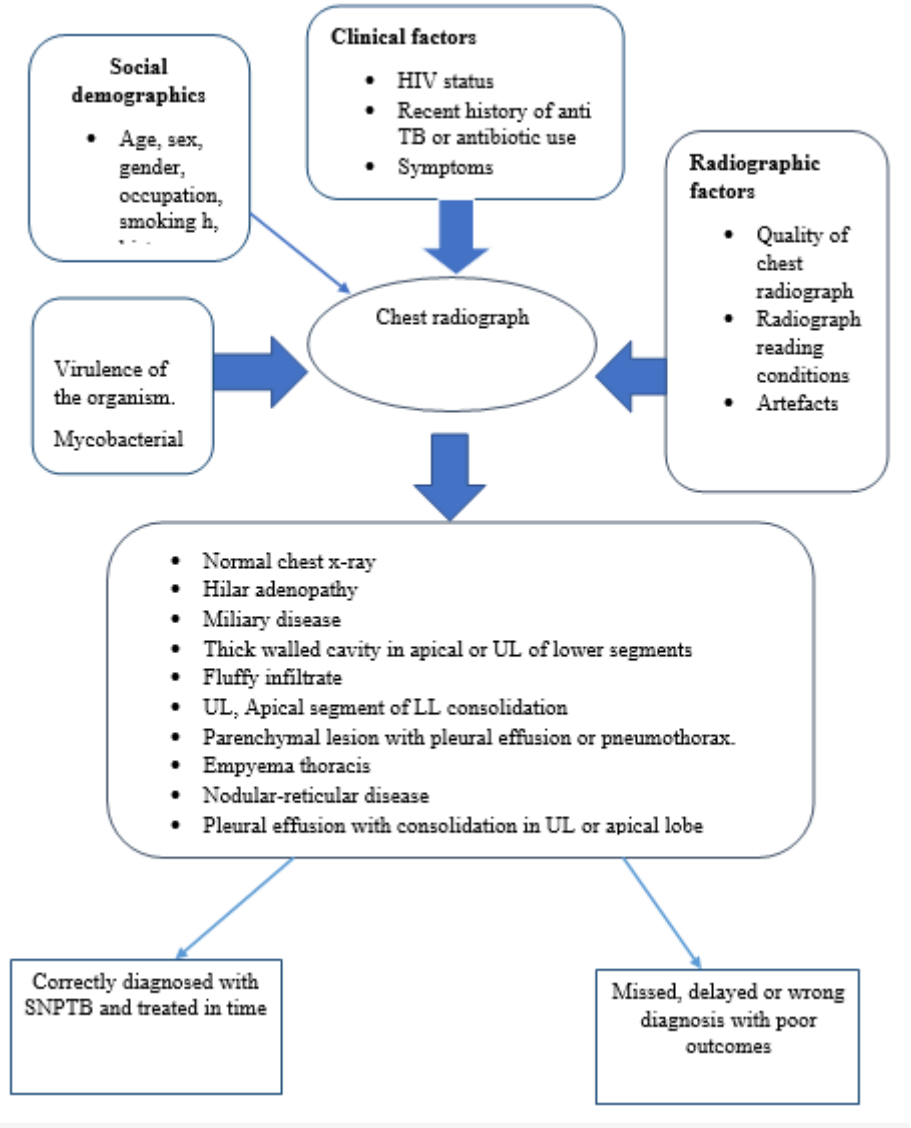

Figure 1: A conceptual framework for the study.

CHAPTER TWO: LITERATURE REVIEW

2.1 Background

Mycobacteria are aerobic, non-motile organisms that appear positive with acid-fast alcohol stains. They have a lipid rich, hydrophobic cell wall, which is substantially thicker than most other bacteria(15). Mycobacterium Tuberculosis Complex, the causative pathogens of tuberculosis, comprise of M. Tuberculosis, M. Bovis, M. Africanum, M. Canetti, M. Microti, and M. Pinnipedii.

Though the global prevalence of TB and death rates from the disease are steadily declining(1), WHO estimates that about one third of all incident cases of active TB are not properly diagnosed(16). National surveys have concluded that the pool of undetected PTB cases especially SNPTB remains large in many countries despite the scaling up and decentralizing of TB diagnosis and treatment, particularly in certain risk groups, such as people living with HIV(17).

WHO defines, a SNPTB case as a patient with two negative sputum smears, but growth positive cultures, or a patient who shows no response to a course of broad-spectrum antibiotics and yet has

clinical and chest radiological findings consistent with active pulmonary tuberculosis, in whom treatment with antituberculosis medication has been initiated(18).

2.2 Mechanism of infection

The organism is transmitted via the airborne route and spreads from person-to-person. When an infected individual coughs, sneezes or speaks, tiny droplets each containing between 1-5 TB bacilli are released into the air. They are so minute, that they are able to remain airborne in any indoor space for up to 4 hours, and even longer in poorly ventilated buildings. The tubercle bacillus is extremely sensitive to direct sunlight, but can survive in the dark for several hours(11). The infectious dose of tuberculosis is between 1 and 10 bacilli. Left untreated, a person with active TB can infect an average of 10-15 people each year. Once an individual has been infected with the mycobacterium, progression to active tuberculosis depends on the person's immune status. Disease will develop in only 10% of person's with normal immunity; half the cases will occur within 2 years after infection(19). People at the extremes of life – children under the age of 5 years and the elderly – are most at risk (20). Conditions associated with immunosuppression also increase the risk of progression to active disease. Conditions which predispose exposed individuals to developing active disease include HIV infection, diabetes mellitus, smoking, alcohol consumption, children, poverty and overcrowding(21).

2.3 Pathophysiology of PTB

The pathogenesis of the disease is described in two stages – primary infection followed by secondary (post-primary) disease in some individuals(22). Between these two stages is usually a latent phase lasting months to years.

2.3.1 Primary infection

Primary infection occurs on first exposure to the mycobacterium. In environments where tuberculosis is endemic this usually occurs in childhood, but can occur at any age in a previously unexposed individual(23). TB organisms inhaled in droplet nuclei activate the cellular immune response to induce an inflammatory area, usually in the upper lobe, called the Ghon focus. The bacilli in the primary focus gradually lose their viability and multiply less. The inflammatory area in the primary focus is replaced by fibrous scar tissue, sometimes with calcification, in which the macrophages containing bacilli are isolated and die. Some dormant bacilli in the primary focus can survive for months or years: these are known as "latent bacilli" and are not infectious.

Primary infection is usually asymptomatic and a positive tuberculin skin test (TST) 4-6 weeks after infection is the only evidence of infection(24). In a few cases, the immune response is not strong enough to isolate and prevent multiplication of bacilli and these may spread from the lymphatics into the bloodstream and throughout the body causing disease within a few months(24).

2.3.2 Secondary or post-primary TB

Secondary or post-primary TB occurs after a latent period of months or years following primary infection(25). It happens either through reactivation of latent bacilli or by re-infection with Tuberculosis. Reactivation occurs when dormant bacilli, persisting in tissues for months or years after primary infection, start to multiply because of immunosuppression as a result of HIV infection, diabetes or certain medications such as steroids(25). Re-infection occurs when a previously sensitized individual (a person who had primary TB) is exposed to an infectious contact(25). Post-primary TB usually affects the lungs but can involve any part of the body. The characteristic features of post-primary PTB include upper lobe involvement with cavitation and extensive lung destruction(26).

Pulmonary MTBC infections do not show any age or racial predilection. They are however more common among persons with immunosuppressed states and people of poor socioeconomic who dwell in overcrowded settings (27, 28).

2.4 Clinical presentation of PTB

Pulmonary tuberculosis is the most common form of TB disease in humans occurring in over 80% of cases. Tuberculosis may, however, affect any part of the body.

The main symptoms of pulmonary tuberculosis are:

- Persistent cough of 2 weeks or more or any duration if HIV positive (29, 30) . The cough may be productive with sputum which may be blood stained(29).
- Fever for more than 2 weeks(31).
- Drenching night sweats(31).
- Unexplained weight loss (more than 1.5 kg in a month)(29).

These main symptoms may be accompanied by one or more of the following: chest pain; loss of appetite and weight, tiredness; fever, particularly with a rise in temperature in the evening and shortness of breath(32). Coughing up blood (haemoptysis) may occur in complicated cases(32).

2.5 Diagnostic criteria for smear negative PTB

Clinical, radiographic, and microbiologic criteria are all equally important and all must be met to make a diagnosis of smear negative PTB lung disease**.**

2.5.1 Laboratory studies

WHO recommends that two sputum specimens should be obtained for microscopic examination from all patients suspected of having pulmonary TB(33). Microbiological diagnosis is confirmed by gene Xpert or culturing M. tuberculosis from any suspected site of disease. However, in many settings where resources are limited, neither culture nor rapid amplification methods are currently available or feasible. In such circumstances, WHO recommends that the diagnosis of TB may also be confirmed by the presence of acid-fast bacilli (AFB) in sputum smear examination(34). Repeated sputum smear microscopy may diagnose pulmonary TB in up to two-thirds of active cases. Sputum should be collected in the early morning on 2 consecutive days. Early-morning gastric aspirate may also produce a good specimen, especially in children. Ziehl-Neelsen staining of sputum is a simple 5-step process that takes approximately 10 minutes to accomplish. While highly specific for mycobacteria, this stain is relatively insensitive (35), and detection requires at least 10,000 bacilli per ml. Most clinical laboratories currently use a more sensitive auramine-rhodamine fluorescent stain (auramine O).The absence of a positive smear result does not exclude active mycobacterial infection.

2.5.2 Imaging studies

Primary PTB typically presents with, a pneumonia like picture of infiltrative process in middle or lower lung regions with hilar adenopathy, miliary disease, and pleural effusions(31).

Reactivation TB: The radiologic manifestations of active secondary pulmonary TB include: Cavity formation in apical segments, miliary disease, and empyema thoracis, consolidations in the apical segments of the upper lobe or lower lobes, pleural effusions and fibrosis.

TB associated with HIV disease: Frequently atypical lesions that can mimic primary PTB depending on the CD4 cells or can have normal chest radiographic findings(28) (36) .

Healed and latent TB: Homogeneously calcified nodules (usually 5-20 mm) are tuberculomas, representing old infection.

In immunodeficiency syndrome, mediastinal or hilar adenopathy is the most common radiographic finding (36).

Studies have shown that reactivation SNPTB can radiographically present with absence of cavitation or absence upper lobe infiltrates as well as a normal chest radiograph (32).

2.6 Factors associated with a negative sputum smear result.

Numerous studies have revealed that clinical factors linked to AFB smear negativity include HIV seropositivity as well as absence of cough, dyspnoea, haemoptysis and expectoration (37-39). Furthermore, antibiotic use prior to testing has been found to be associated with a negative smear result possibly due to reduction in mycobacterial load(40). The social demographic factors of age, smoking history, alcohol use as well as marital status have not been strongly linked to development of SNPTB(39).

Other factors linked to SNPTB include a low mycobacterial burden as well as poor quality smear microscopy from inadequate sputum collection, not to mention storage, staining and reading errors (37).

2.7 Effect of HIV on PTB

HIV infection causes reduced immune competence and the consequent loss of ability to prevent the spread of the tubercle bacilli from localized granulomas due to a decline in the number of CD4+ T cells. Rapid progression from initial infection to TB disease may also occur in markedly immunosuppressed patients.

In the early stages of HIV infection, before host immunity is significantly compromised, patients with TB have the typical symptoms of TB, and smear microscopy is usually positive. With more advanced HIV infection and compromised immune status, TB symptoms are atypical and the smear is often negative (41, 42). Paucibacillary smears are also more frequent in HIV-infected TB patients. In the absence of Gene Xpert or culture, HIV-positive patients with smear-negative TB are more likely to die during or before diagnosis than HIV-negative smear-positive patients.

HIV infection also diminishes the reliability of chest radiographs for the diagnosis of pulmonary TB because the disease commonly presents with an atypical pattern (43). Furthermore, the chest radiograph may be normal in a proportion of HIV-infected patients with sputum culture-positive TB(43).

However, chest radiography remains an important adjunct to the diagnosis of smear-negative pulmonary TB in people living with HIV.

2.8 Treatment and prophylaxis for PTB

Although vaccination with Mycobacterium Bovis bacillus Calmette-Guérin (BCG) protects against TB disease and mortality in some populations, its efficacy is suboptimal and clearly not adequate for disease control(44).

The standardized regimens for anti-TB treatment recommended by WHO include five essential medicines designated as “first line”: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) and streptomycin (S).

For treatment of new cases of pulmonary, WHO recommends a standardized regimen consisting of two phases. The initial (intensive) phase uses four drugs (rifampicin, isoniazid, pyrazinamide and ethambutol) administered for two months. This is followed by a continuation phase with two drugs (rifampicin and isoniazid) for four months or, exceptionally, with two drugs (isoniazid and ethambutol) for six months when adherence to treatment with rifampicin cannot be ensured. Supervised daily administration of medicines in the initial phase of treatment of all new cases is recommended.

The ministry of health in Uganda under the 2014 isoniazid preventive therapy guidelines recommends that all children under 5 years who have history of contact with a person having PTB and have no symptoms of PTB should be initiated on isoniazid prophylaxis for six months. In addition WHO has recommended that all newly diagnosed HIV patients in whom tuberculosis has been excluded be initiated on isoniazid prophylaxis for six months (45).

2.9 Prognosis

Without adequate treatment, TB is rapidly fatal especially in HIV-positive patients, usually within months(46). Among treated TB patients, death rates are higher in HIV positive than in HIV-negative patients Case fatality is higher in HIV-positive patients with smear-negative pulmonary TB, as these patients are generally more immunosuppressed than those with smear-positive TB(47).

CHAPTER THREE: METHODOLOGY

3.1 Study design

This was a retrospective nested case control study, which used data collected by the School of Public Health Makerere University, and the National TB and Leprosy Program, during the 2013-2015 population based PTB prevalence survey in Uganda. The PTB prevalence survey was a systematic prospective cross sectional survey.

3.2 Study site

Clusters of villages selected from all over Uganda in a single stage systematic cluster sampling strategy with probability proportionate to population size (PPS) as in EPI survey methodology (Lemeshow, 1985). In the mother study, the villages were stratified by rural and urban settings to ensure a representative and precise overall estimate of prevalence.

Uganda is a landlocked country in East Africa. It is bordered to the east by Kenya, to the north by South Sudan, to the west by the Democratic Republic of the Congo, to the south-west by Rwanda, and to the south by Tanzania. A 2014 population census estimated the population of Uganda to be 34,634,650 people.

3.3 Study population

The study involved use of socio-demographic and clinical data as well as the chest radiographs of participants on the National TB prevalence survey, of either gender, aged 15 and above, who had SNPTB or a smear negative culture negative result. There was no contact with human subjects in this study.

3.4 Sample Size.

The minimum sample size of the cases was supposed to be calculated using the Charan and Biswas formula for case control studies(48).

$$\text{Sample size for cases} = \frac{r+1}{1} \times \frac{(P^{*})(1-P^{*})(Z_{\beta}+Z_{\alpha/2})^2}{(P_1-P_2)^2}$$

Where

r = Ratio of control to cases (which is 3 in this study)

p^{*} = Average proportion exposed= (proportion of exposed cases+ proportion of exposed controls)/2.

Z_{β} =standard normal variate for power

$Z_{\alpha/2}$ = standard normal variate for level of significance

P_1-P_2 =proportion in cases- proportion in controls.

In this study the exposure was considered to be having both cough for more than two weeks and an abnormal chest radiograph.

However since this was a retrospective nested case control, all the 93 SNPTB cases were included and a minimum case to control ratio of 1:3 was used making the total sample size 372.

✘ Includes 30 cases of Mycobacteria other that Tuberculosis (MOTT).

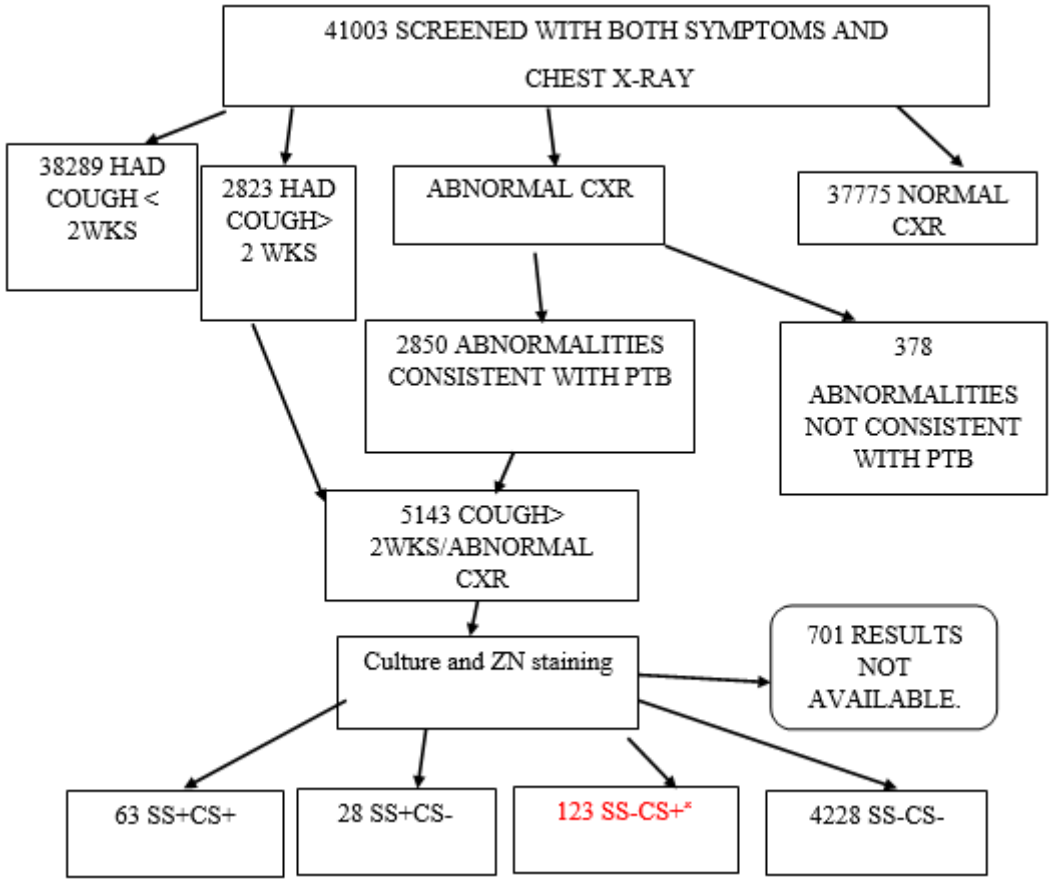

Figure 2. A flow diagram for the2013/2015 Uganda National TB prevalence survey.

3.5 Sampling criteria

The cases which were the 93 with smear negative culture positive PTB (SNPTB) were all consecutively sampled. Systematic random sampling was used to get 279 smear negative culture negative controls, in marching age brackets as the SNPTB cases, from the sample size of 4228. For each case, three controls were selected and matched with the cases.

3.6 Selection Criteria

3.6.1 Inclusion criteria

Chest radiographs, clinical and social demographic data of all persons aged 15 years and above who had SNPTB. Chest radiographs, clinical and social demographic data of the 279 selected controls aged 15 years and above with a smear negative culture negative result.

3.6.2 Exclusion criteria

Chest radiographs, clinical and social demographic data of all persons aged 15 years and above who had no bacteriological result or had smear positive PTB or had Mycobacteria other than Tuberculosis (MOT-

T).

3.7 Study instruments

A standardized study tool for diagnosis of PTB was used to extract data from the chest radiographs by the principal investigator. The data was entered into EPI data and transferred into STATA 13. The clinical and demographic data of the subjects was provided in STATA.

3.8 Study variables

3.8.1 Outcome variables

The outcome variables included clinical and demographic factors associated to SNPTB such as HIV status.

Radiographic variables included normal radiographs, consolidations, masses, nodules and their proportions.

3.8.2 Independent Variables

The independent variables included;

Clinical variables: HIV status, symptoms such as cough and their duration.

Social demographic variables: Sex, occupation and social habits such as smoking.

Radiographic variables: Quality of chest radiographs, artefacts due to poor storage.

3.9 Data collection and Analysis

3.9.1 Data collection

A research assistant sorted out all the 372 chest radiographs which belonged to the cases and controls. The radiographs were safely transported to the radiology department Mulago national referral.

While blinded to the bacteriological outcome, the social and demographic information of the subjects, the Principal investigator reviewed these chest radiographs while mounted on a viewer with white light in consultation with 3 different radiologists. The consensus findings were documented the findings in the study tool (Appendix 4).

3.9.2 Data management

After extraction, the data was cross checked for any omissions or errors by the Principal investigator. It was then entered into Epidata Version 3.1 and exported to Stata version 13 statistical software analysis. The clinical and demographic data was also received in Stata.

3.9.3 Data analysis

Descriptive statistics were used to summarize the categorical characteristics of the study participants in form of percentages. Continuous variables such as age were summarized into median and inter quartile range. Median and interquartile range were used because the data was not normally distributed.

Multiple logistic regression analysis was done using Stata 13 to find clinical, demographic and radiographic factors associated with SNPTB. Odds ratios (ORs)) were calculated to measure the effect of an independent variable on the outcome variable. Bivariate analysis, for independent variables was used and those which had p-values less than 0.2 at 95% confidence intervals were considered for multivariate analysis. Interaction and confounding were assessed in the regression model to determine the factors that are associated with SNTB. Variables with $p \leq 0.05$ were considered statistically significant.

3.10 Ethical consideration

Consent was obtained from the School of Public Health. Ethical clearance was obtained from the Institu-

tional Research and the Ethics Committee, of the School of Medicine**.**

A waiver of consent was obtained from IRB since subjects could not be accessed. Patient names were not used in this study since this was secondary data. The data and records were secured and only accessed by the research assistants, the principal investigator and the supervisory team. Once completed with the study, the raw data was returned to the School of Public Health.

3.11 Dissemination of results

The results were presented to the Department of Radiology. A copy of results will be delivered to the Institutional Research and Ethics Committee School of Medicine, the Library College of Health Sciences, National TB and Leprosy Program and to the School of Public Health, Makerere University.

CHAPTER FOUR: RESULTS.

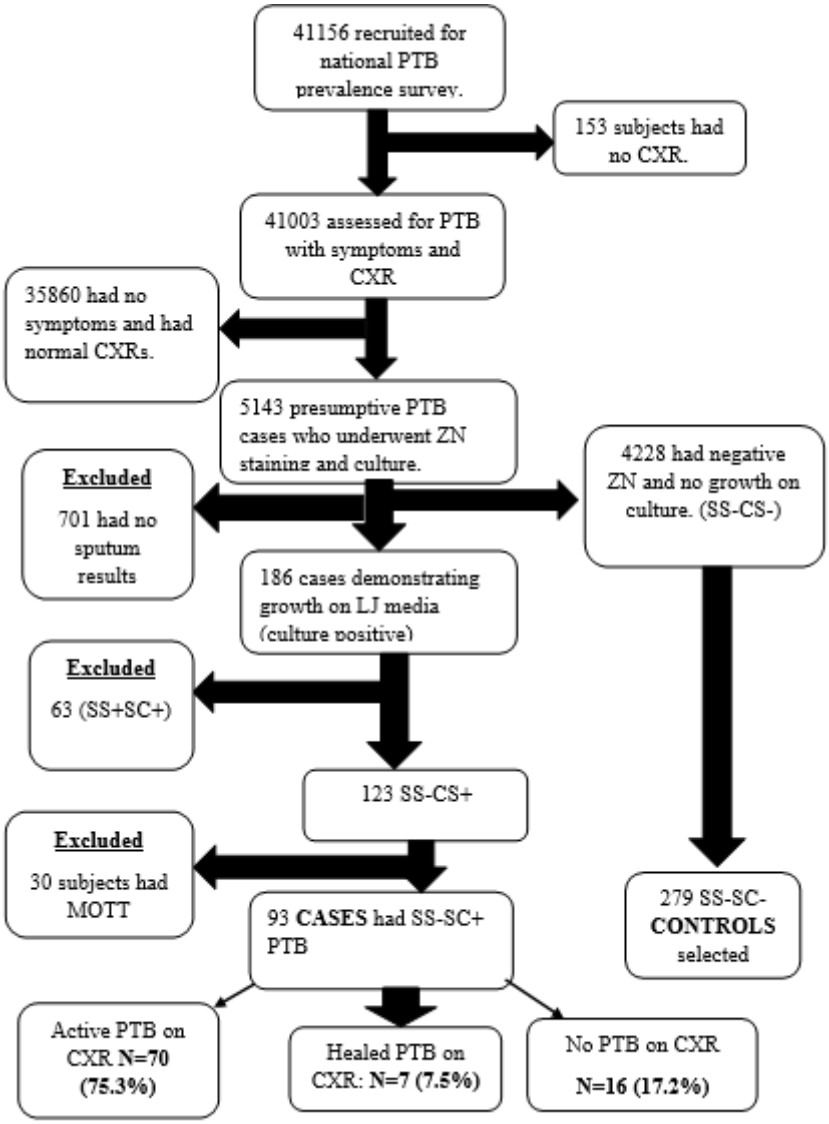

Figure 3: A profile of the study.

4.1 Socio-demographic characteristics of the study subjects.

Table 1: Social demographic characteristics of the cases (N=93) and the controls (N=279).

Characteristic	S-C+ N=93 (%)	S-C- N=272 (%)
Sex of subject		
Male	68 (73.12)	149 (53.41)
Female	25 (26.88)	130 (46.59)
Age group		
15- 24 years	13 (13.98)	39 (13.98)
25- 34 years	24 (25.81)	72 (25.81)
35- 44 years	20 (21.51)	60 (21.51)
45- 54 years	17 (18.28)	51 (18.28)
55- 64 years	7 (7.53)	21 (7.53)
65+ years	12 (12.90)	36 (12.90)
Occupation		
Business	11 (11.83)	28 (10.04)
Civil servant	7 (7.53)	13 (4.66)
Health worker	0 (0.00)	1 (0.36)
Student	10 (10.75)	41 (14.70)
Unemployed	6 (6.45)	8 (2.87)
Farmer	40 (43.01)	138 (49.46)
House wife/ husband	5 (5.38)	30 (10.75)
Skilled labor	14 (15.05)	20 (7.17)
Education		
None	23 (24.73)	67 (24.01)
Primary	39 (41.94)	134 (48.03)
Senior 1-4	20 (21.51)	50 (17.92)
Senior 5-6	4 (4.30)	13 (4.66)
Tertiary education	7 (7.53)	15 (5.38)
Marital status		
Single	24 (25.81)	44 (15.77)
Married	48 (51.61)	187 (67.03)
Separated	9 (9.68)	20 (7.17)
Divorced	1 (1.08)	3 (1.08)
Widowed	11 (11.83)	25 (8.96)
Smoking		
Yes	26 (27.96)	46 (16.49)
No	67 (72.04)	233 (83.51)
Setting		
Rural	43 (46.24)	178 (63.80)
Urban	50 (53.76)	101 (36.20)
Region		
Central	33 (35.48)	101 (36.20)

East	17 (18.28)	65 (23.30)
North	21 (22.58)	61 (21.86)
West	22 (23.66)	52 (18.64)

A total 372 subjects were studied with 93 cases and 279 controls. The male cases were more than twice the females. The most populous age bracket was between 25-34 for both the cases and the controls. Majority of the cases and the controls were married farmers with primary education. The smokers were less than half of the non-smokers for both the cases and the controls. More of the cases lived in an urban setting while more of the controls lived in a rural setting.

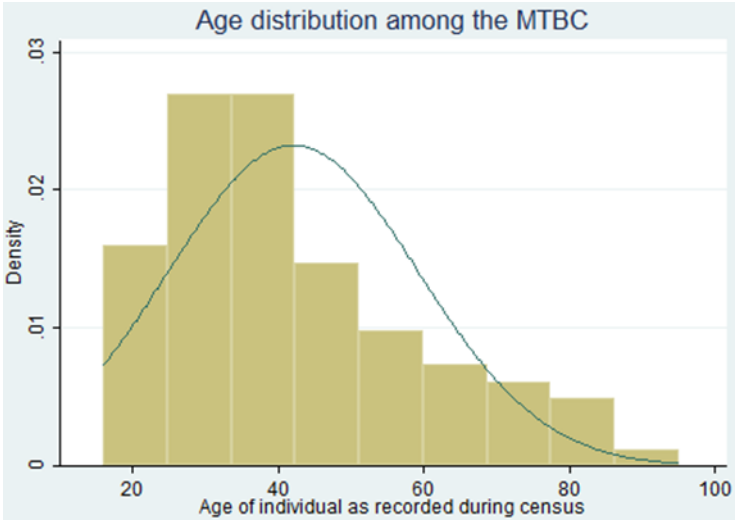

Figure 4: A bar graph showing the age distribution of the cases

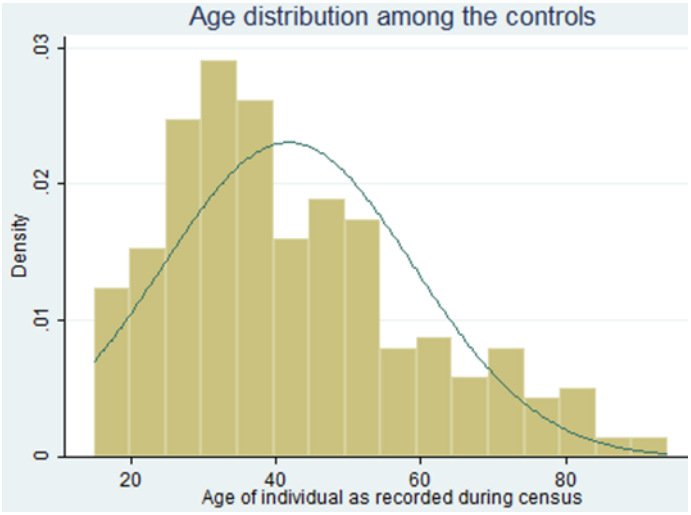

Figure 5: A bar graph showing the age distribution of the controls.

The age distribution was skewed to the right (Figure 4) for the cases, with a median of 36 years and an Interquartile range (IQR) of 22. The age distribution for subjects that did not have MTBC (controls) was also skewed to the right (Figure 5) with a median of 37 years and an IQR of 23.

4.2 Objective 1: The social demographic factors associated with SNPTB

Since the controls were selected while matching with the ages of the cases, the variables sex, occupation,

education, marital status, history of current and past smoking, setting and region were considered for bivariate analysis to determine how they individually associated with SNPTB. Those with a p-value less than 0.2 at 95 % confidence intervals would be considered for multivariate analysis after assessing for confounding and interaction.

Table 2: Bivariate analysis for social demographic factors associated with SNPTB in Ugandan communities in 2014. Significant p≤ 0.2 at 95% CI.

Characteristic	Cases (%)	Controls (%)	OR	95%CI	P-value
Sex of subject					
Male	68 (73.12)	149 (53.41)	2.37	1.417- 3.973	**0.001**
Female	25 (26.88)	130 (46.59)	Ref*		
Occupation					
Bus/civil servants*	18(19.35)	41(14.70)	Ref*		
Unemployed	21(22.58)	79(28.32)	0.61	0.291-1.261	**0.18**
Farmer	40(43.01)	138(49.46)	0.66	0.342-1.273	0.215
Skilled labour/ Health worker*	14(15.05)	21(7.53)	1.52	0.633-3.640	0.349
Education					
None	23 (24.73)	67 (24.01)	Ref*		
Primary	39 (41.94)	134 (48.03)	0.85	0.469- 1.537	0.585
Senior 1-4	20 (21.51)	50 (17.92)	1.17	0.577- 2.352	0.670
Senior 5-6	4 (4.30)	13 (4.66)	0.90	0.266- 3.026	0.860
Tertiary education	7 (7.53)	15 (5.38)	1.36	0.493- 3.749	0.553
Marital status					
Single	24 (25.81)	44 (15.77)	Ref*		
Married	48 (51.61)	187 (67.03)	0.47	0.261- .849	**0.012**
Separated	9 (9.68)	20 (7.17)	0.83	0.325- 2.093	0.685
Divorced	1 (1.08)	3 (1.08)	0.61	0.060- 6.200	0.677
Widowed	11 (11.83)	25 (8.96)	0.81	0.339- 1.918	0.627
Setting					
Rural	43 (46.24)	178 (63.80)	Ref*		
Urban	50 (53.76)	101 (36.20)	2.05	1.274- 3.296	**0.003**
Smoking now					
Yes	26 (27.96)	46 (16.49)	Ref*		
No	67 (72.04)	233 (83.51)	0.51	0.293- 0.884	**0.016**
Smoked in past					
Yes	13 (13.98)	31 (11.11)	Ref*		
No	54 (58.06)	202 (72.40)	0.64	0.312- 1.302	0.216
Not specified	26 (27.96)	46 (16.49)	1.35	0.602- 3.019	0.468

Skilled labour/ Health worker*- Combined due to small numbers.
Ref*- Reference category

The variables male sex, being married, setting Urban, not smoking now, and being un employed had a p-value less than 0.2 at 95 % confidence intervals and thus were considered for multivariate analysis. The regression model also assessed for interaction and confounding of the factors.

Table 3: Multivariate analysis for social demographic factors associated with SNPTB among Ugandans aged 15 ≥ Significant p≤ 0.05 at 95% CI.

Characteristic	aOR	95%CI	P-value
Male sex	2.48	1.458- 4.213	**0.001**
Single-Marital status	2.05	1.250- 3.371	**0.004**
Setting urban	1.92	1.177- 3.123	**0.009**
Smoking now	2.39	1.302- 4.391	**0.005**

Being male,being single, current smoking and, living in the urban setting were found to be positively associated with developing SNPTB.

4.3 Objective 2. Clinical factors associated with SNPTB

The variables cough for ≥2 weeks, fever, nightsweats, sputum production, bloody sputum production, chest pain, weight loss, previous history of PTB treatment and current PTB treatment were considered for bivariate analysis to determine how they are individually associated with SNPTB. Those with a p-value less than 0.2 at 95 % confidence intervals would be considered for multivariate analysis after assessing for confounding and interaction.

Table 4: Bivariate analysis for clinical factors associated with SNPTB among Ugandans aged 15≥ in 2014. Significant p ≤ 0.2 at 95% CI.

Characteristic	Cases (%)	Controls (%)	OR	95%CI	P-value
Cough ≤ 2 weeks					
No	16 (17.20)	125 (44.80)	Ref*		
Yes	77 (82.80)	154 (55.20)	3.91	2.170- 7.032	**<.001**
Abnormal cxr					
Yes	50 (53.76)	132 (47.31)	1.29	.809- 2.072	0.282
No	43 (46.24)	147 (52.69)	Ref*		
Abnormal cxr+ cough					
Yes	27 (29.03)	19 (6.81)	5.60	2.934- 10.682	**<.001**
No	66 (70.97)	260 (93.19)	Ref*		
History PTB treatment					
Yes	8 (8.60)	22 (7.89)	1.10	.472- 2.561	0.826
No	85 (91.40)	257 (92.11)	Ref*		
Current PTB treatment					
Yes	8 (8.60)	1 (0.36)	26.16	3.227- 212.175	**0.002**
No	85 (91.40)	278 (99.64)	Ref*		
HIV status					
Positive	24 (25.81)	18 (6.45)	5.29	2.691- 10.391	**<.001**
Negative	58 (62.37)	230 (82.44)	Ref*		

No result	11 (11.83)	31 (11.11)	1.41	.668- 2.966	0.369
Cough					
Yes	54 (58.06)	166 (59.50)	Ref*		
No	39 (41.94)	113 (40.50)	1.06	.659- 1.708	0.808
Sputum production					
Present	39 (41.94	119 (42.65)	Ref*		
Absent	54 (58.06)	160 (57.35)	1.03	.640- 1.656	0.904
Bloody sputum					
Present	1 (1.09)	7 (2.51)	Ref*		
Absent	91 (98.91)	272 (97.49)	2.34	.284- 19.291	0.429
Chest pain					
Yes	42 (45.16)	142 (50.90)	Ref*		
No	51 (54.84)	137 (49.10)	1.26	.786- 2.016	0.339
Weight loss					
Yes	18 (19.35)	41 (14.70)	1.39	.756- 2.569	0.288
No	75 (80.65)	238 (85.30)	Ref*		
Fever					
Yes	15 (16.13)	45 (16.13)	1.00	.528- 1.893	1.000
No	78 (83.87)	234 (83.87)	Ref*		
Night sweats					
Yes	12 (12.90)	21 (7.53)	1.82	.858- 3.861	**0.118**
No	81 (87.10)	258 (92.47)	Ref*		

Ref*- Reference category

The variables cough≤ 2 weeks, nightsweats, current PTB treatment,HIV test, having both cough and an abnormal CXR had a p-value less than 0.2 at 95 % confidence intervals. Thus they were considered for multivariate analysis. The regression model also assessed for interaction and confounding of the factors.

Table 5: Multivariate analysis for clinical factors associated with SNPTB among Ugandans aged 15 ≥ in 2014.

Characteristic	AOR	95%CI	P-value
Cough ≤ 2 Weeks.	2.92	1.548- 5.535	**0.001**
Cough +abnormal cxr	3.19	1.550- 6.548	**0.002**
Current PTB rx	14.67	1.675- 128.517	**0.015**
HIV Positive	2.54	1.437- 4.496	**0.001**

The variable nightweats was found to be confounding and thus was dropped.

After multivariate analysis, the factors the variables cough ≤ 2 weeks, current PTB treatment and having both cough and abnormal xray as well as being HIV positive had a p-value less than 0.05 at 95 % confidence intervals and thus were considered statistically significant.

4.4 Objective 3. The chest radiographic features of the cases and the controls.

12(12.9%) of the cases and majority of (63.4%) of the controls had normal chest radiographs.

The rest of the radiographic findings are tabulated in table 6 below in proportions.

Table 6: Table showing the chest radiographic features suggestive of PTB among the cases (N=93) and the controls.(N=272)

PTB CXR FINDINGS		Cases n (%)	Controls n (%)
Cavities	Absent	74(79.6)	100(35.8)
	Present	7(7.5)	2(0.7)
	Normal	12(12.9)	177(63.4)
Consolidation*			
Upper lung zone	Absent	54(58.1)	97(34.8)
	Present	**27(29.0)**	**5(1.8)**
	Normal	12(12.9)	177(63.4)
Middle lung zone	Absent	53(57.0)	98(35.1)
	Present	**28(30.1)**	**4(1.4)**
	Normal	12(12.9)	177(63.4)
Lower lung zone	Absent	69(79.2)	99(35.5)
	Present	**12(12.9)**	**3(1.1)**
	Normal	12(12.9)	177(63.4)
Atelectasis	Absent	61(65.6)	85(30.5)
	Present	**20(21.5)**	**17(6.1)**
	Normal	12(12.9)	177(63.4)
Nodules	Absent	45(48.4)	88(31.5)
	Present	**36(38.7)**	**14(5.0)**
	Normal	12(12.9)	177(63.4)
Miliary	Absent	78(83.9)	102(36.6)
	Present	2(2.2)	0(0.0)
	Normal	13(14.0)	177(63.4)
Pleural effusion	Absent	72(77.4)	99(35.5)
	Present	**9(9.7)**	**3(1.1)**
	Normal	12(12.9)	177(63.4)
Adenopathy	Absent	75(80.6)	101(36.2)
	Present	**6(6.4)**	**0(0.0)**
	Normal	12(12.9)	178(63.8)
Calcifications	Absent	76(81.7)	96(34.4)
	Present	**5(5.4)**	**5(1.8)**
	Normal	12(12.9)	178(63.8)
Masses	Absent	78(83.9)	101(36.2)
	Present	**3(3.2)**	**1(0.4)**
	Normal	12(12.9)	177(63.4)

* Variable split into zones due to radiological implications.

Table 7. Table showing a summary of the radiographic diagnoses for the cases and the controls.

Radiographic Presentation*	Number of cases. N=93	Number of controls. N=279
Typical of Post primary PTB	**N=60(64.5%)**	**N=26 (9.32%)**
Cavitation	7	2
Consolidation in upper zones	27	5
Nodular infiltrates	36	14
Bronchiectatic changes	20	17
Miliary	2	0
Typical of Primary PTB	**N=10 (10.7%)**	**N=0**
Pleural effusion +Mid. Zone consolidation	3	0
Pleural effusion +Low. Zone consolidation	4	0
Middle/ lower zone consolidation +adenopathy	3	0
Typical of healed(Inactive)PTB	**N=7 (7.5%)**	**N=53(19%)**
Pleural fibrosis only	5	49
Calcified nodules	2	4
Atypical of any phase of PTB	**N=11(11.8%)**	**N=23 (8.2%)**
Others	4	23
Isolated middle zone/lower zone consolidation	4	0
Solitary mass	3	1
Normal	**N=12 (13%)**	**N=177(63.4%)**

* some radiographic features were overlapping

Table 7 shows that 60.4% of the cases and 9.32% of the controls had radiographic features suggestive of PTB. And whereas 10.7% of the cases had features suggestive of Primary PTB, non of the controls had the same.

Both the cases and controls had modest proportions with features suggestive of healed disease at 7.5% and 19% respectively. There were no cases of only pleural effusion with ipsilateral hilar adenopathy.

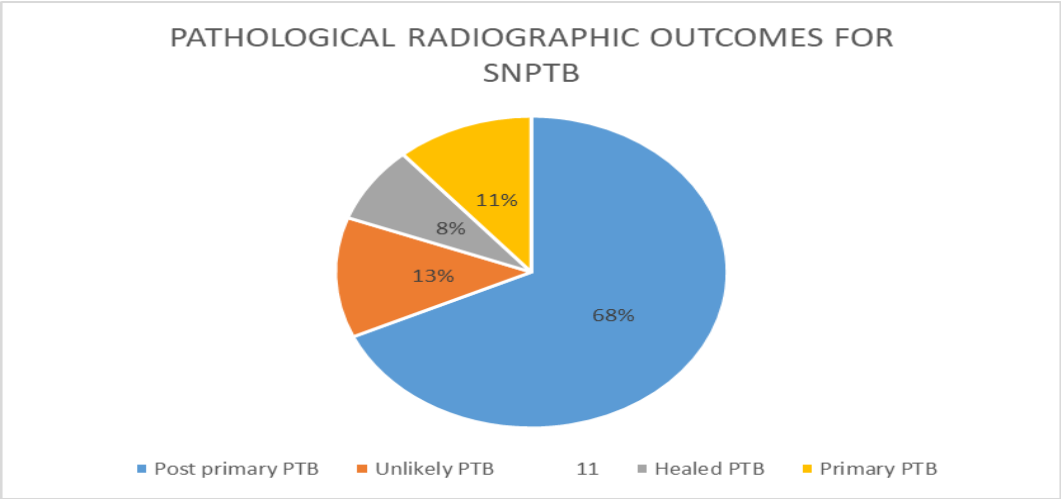

Figure 6. A pie chart demonstrating the proportions of the pathological outcomes on the CXR

The most predominant features were suggestive of post-primary tuberculosis.

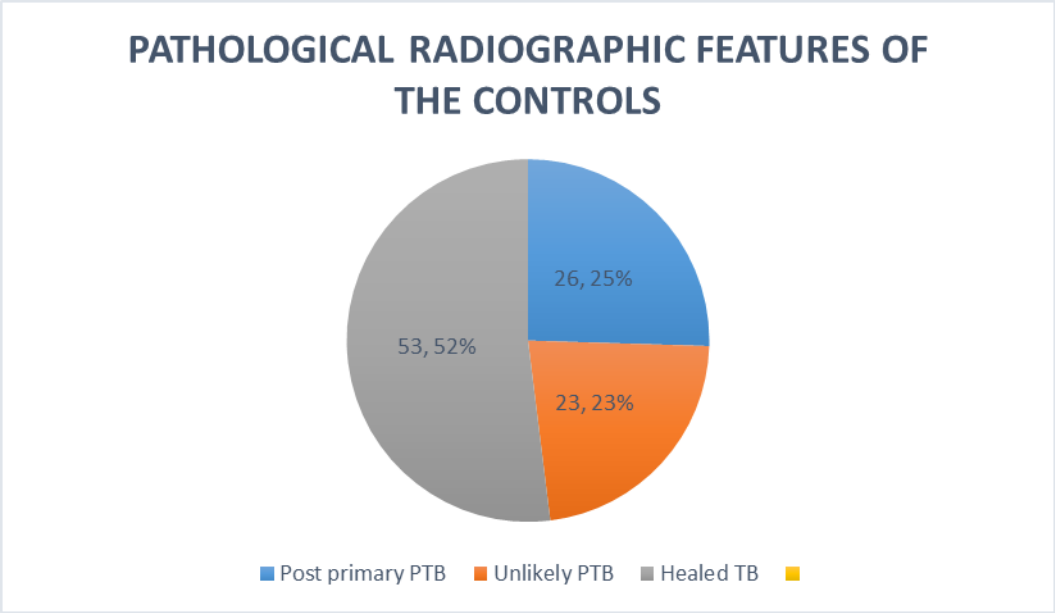

Figure 7. A pie chart demonstrating the proportions of the pathological outcomes on the CXR

The most predominant abnormalities were suggestive of healed pulmonary disease.

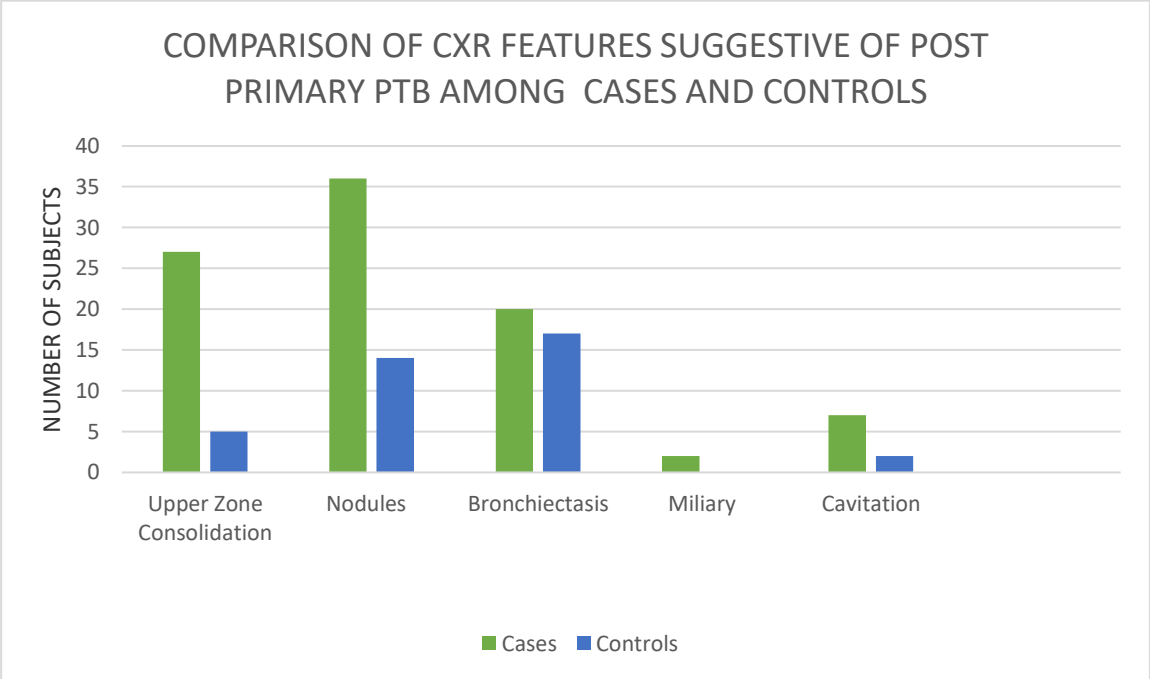

Figure 8. A bar chart comparing the radiographic features suggestive of post primary PTB in both the cases and the controls.

Majority of the cases with features suggestive of post primary PTB had nodules followed by consolidations and bronchiectasis. On the other hand, majority of the controls with features suggestive of post primary PTB and bronchiectatic changes followed by nodular opacities.

4.4.1 Radiographic factors associated with SNPTB

The variables cavity, consolidation, pleural effusion, atelectasis, nodules, adenopathy, miliary masses, and calcification were considered for bivariate analysis to determine how they individually associated with SNPTB. Those with a p-value less than 0.2 at 95 % confidence intervals were considered for multivariate analysis after assessing for confounding and interaction.

Table 8: Bivariate analysis for radiographic factors associated with SNPTB among Ugandans aged 15 ≥ in 2014. Significant p ≤ 0.2 at 95% CI.

Radiographic findings	Cases (%)	Controls (%)	OR	95%CI	P-value
Cavity					
Absent	86(92.5)	277(99.3)			
Present	7(7.5)	2(0.7)	11.27	2.299-55.280	**0.003**
Consolidation					
Upper lung zones					
Absent	66(71.0)	274(98.2)			
Present	27(29.0)	5(1.8)	22.42	8.319-60.415	**<0.000**
Lower& mid lung zones					
Absent	63(67.7)	272(97.5)			
Present	30(32.3)	7(2.5)	18.50	7.774-44.040	**<0.000**
Pleural effusion					
Absent	84(90.3)	276(98.9)			
Present	9(9.7)	3(1.1)	9.86	2.609-37.243	**0.001**
Atelectasis					
Absent	73(78.5)	262(93.9)			
Present	20(21.5)	17(6.1)	4.22	2.103-8.474	**<0.000**
Nodules					
Absent	57(61.3)	260(93.2)			
Present	36(38.7)	19(6.8)	8.64	4.624-16.152	**<0.000**
Miliary*					
Absent	91(97.9)	279(100.0)			
Present	2(2.2)	0(0.0)			
Adenopathy*					
Absent	87(93.6)	279(100.0)			
Present	6(6.5)	0(0.0)			
Calcification					
Absent	89(95.7)	272(97.5)			
Present	4(4.3)	7(2.5)	1.75	0.500-6.105	0.383
Masses					
Absent	90(96.8)	278(99.6)			
Present	3(3.2)	1(0.4)	9.27	0.952-90.201	0.055

* Number of cases and controls in these categories were too few to be analysed.

The variables cavity, upper zone consolidation,lower and middle zone consolidation, pleural effusion, atelectasis, and nodules had a p value of ≤ 0.2 at 95%CI and thus were considered for multivariate analysis. The model also assessed for interaction and confounding.

Table 9: Multivariate analysis for radiographic factors associated with SNPTB among Ugandans aged 15 ≥ in 2014 at 95%CI. p≤ 0.05.

Variables	AOR	95% CI	p-value
Upper lung consolidation	10.01	3.086-32.442	**<0.001**
Middle/ lower lung zones consolidation	3.97	1.267-12.488	**0.018**
Nodules	7.65	3.330-17.569	**<0.000**
Pleural effusion	10.65	2.042-55.598	**0.005**

The variables upper zone consolidation, middle/ lower lung zones consolidation nodules and pleural effusion all had p ≤ 0.05 at 95 % CI. However of note are the big confidence intervals.

4.5 The power of the study.

The power of the study was determined by calculating the value of Zβ from the sample size, using the formula recommended by Charan and Biswas for obtaining minimum sample size for cases in case control(48).

Sample size for cases $= \frac{r+1 \times (P^{\times})(1-P^{\times})(Z\beta+Z\alpha/2)2}{1 \quad (P1-P2)2}$

In this study the exposure was considered to be having cough of equal or less than two weeks and abnormal chest radiographs.

Where

r = Ratio of control to cases (which is 3 in this study)

$P^{\times}$ = Average proportion exposed= [(proportion of exposed cases (27/93) + proportion of exposed controls (19/279)]/2. =0.179

Zα/2 = standard normal variate for level of significance = 1.96

(P1-P2)2 = (proportion in cases- proportion in controls) 2. = [(27/93)-(19/279)] 2 = 0.0494

Since the number of cases is known

$93= \frac{4 \times (0.179) \times (0.821) \times (Z\beta +1.96)}{0.0494}$

$93= 17.56 \times (Z +1.96)2$

Zβ = 0.835 which corresponds to a power of 41%.

ILLUSTRATIONS

Illustration 1.

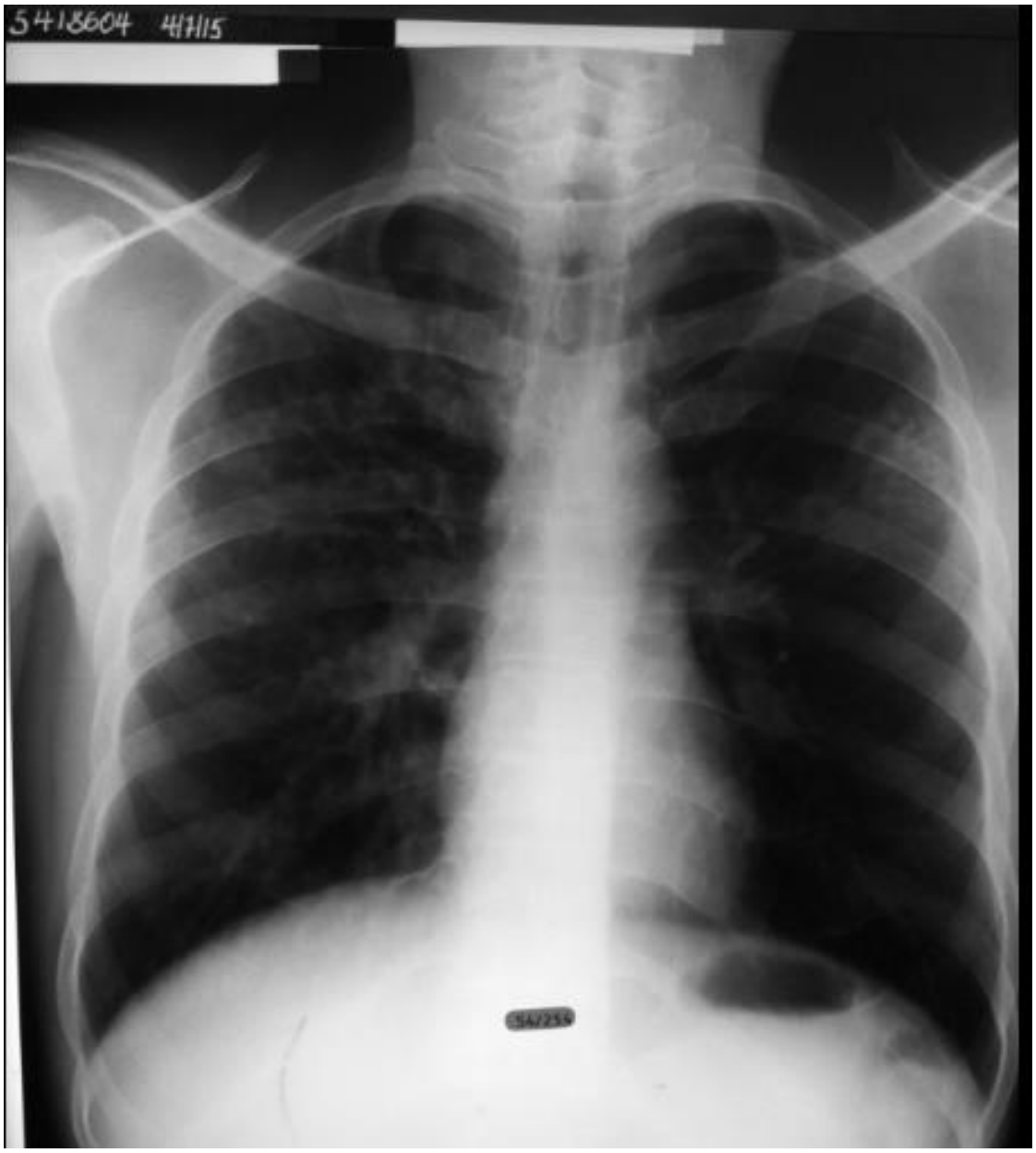

Figure 9 is a chest radiograph (CXR) of a 49 year old HIV negative male who presented with one week history of productive cough and chest pain. The radiograph shows right sided diffuse reticulo-nodular opacities predominantly in the right middle and upper zones. There are in addition left sided peripheral middle zone reticular linear disease with tram lines. Culture confirmed presence of SNPTB.

Illustration 2

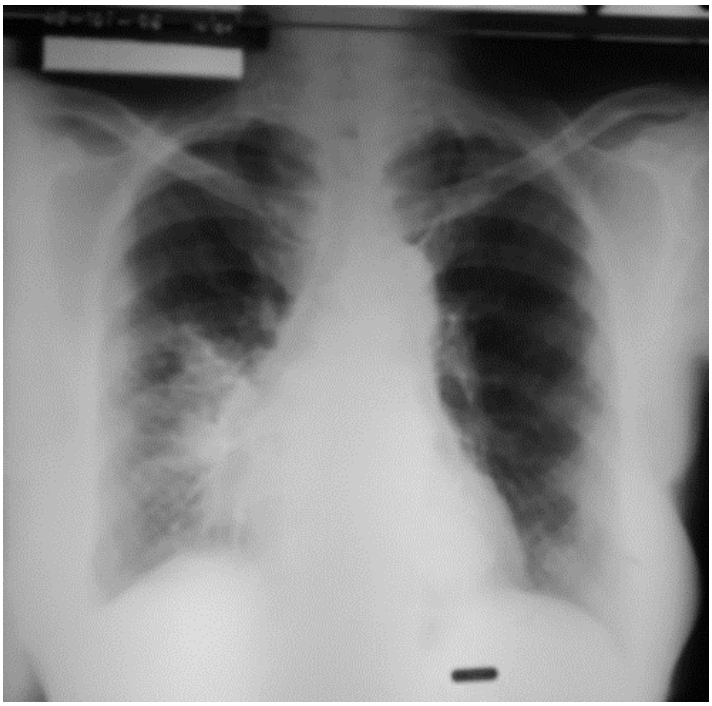

Figure 10. A P.A CXR of a 79/female unknown HIV serology who had productive cough for 90 days associated with weight loss. CXR revealed right middle and lower zone reticular linear opacities confluencing in the right paracardiac region. She was found to have SNPTB on culture.

Illustration 3

Figure 11. A P.A CXR of a 30 HIV positive asymptomatic male. The radiograph shows reticular nodular infiltrates with a tendency to confluence in the right middle zone as well as the paracardiac areas. The left hilar region is prominent. The apices are clear. This patient was diagnosed with SNPTB on culture.

Illustration 4

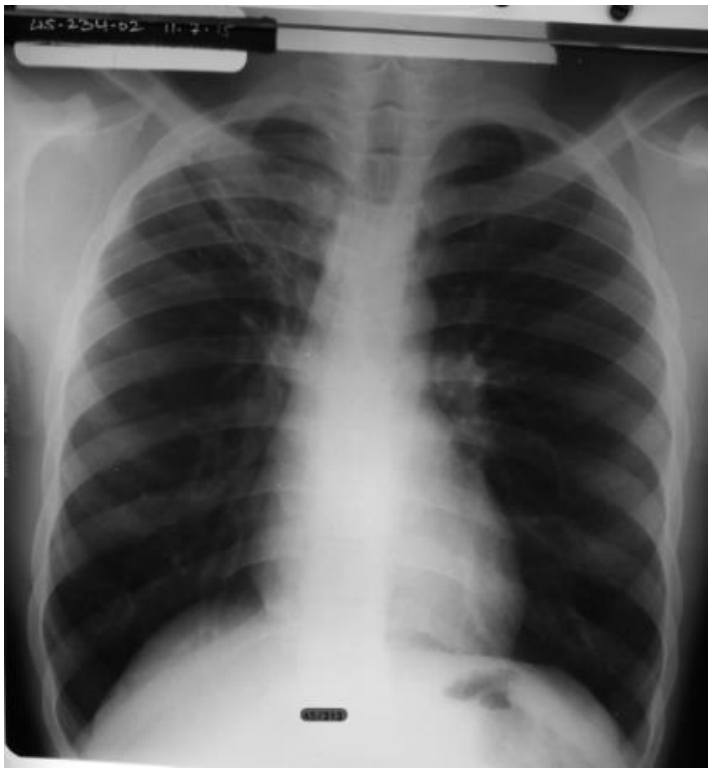

Figure 12. A P.A CXR of a 20 HIV negative asymptomatic male showing right reticular nodular opacities with cystic spaces and tram lines in the right upper zone. This patient was confirmed to have SNPTB on culture.

Illustration 5

Figure 13. A P.A CXR of a 33 HIV positive asymptomatic male showing reticular nodular opacities with cystic spaces and tram lines in right upper and middle zones. PTB was ruled out on culture.

Illustration 6

Figure 14. A P.A CXR of a 49 years old male of unknown HIV status who had an un-productive cough for one week which was associated with chest pain.
The radiograph shows bilateral blunting of costal phrenic angles with flattened hemi-diaphragms translucent lung fields.
He was found to have SNPTB on culture.

Illustration 7

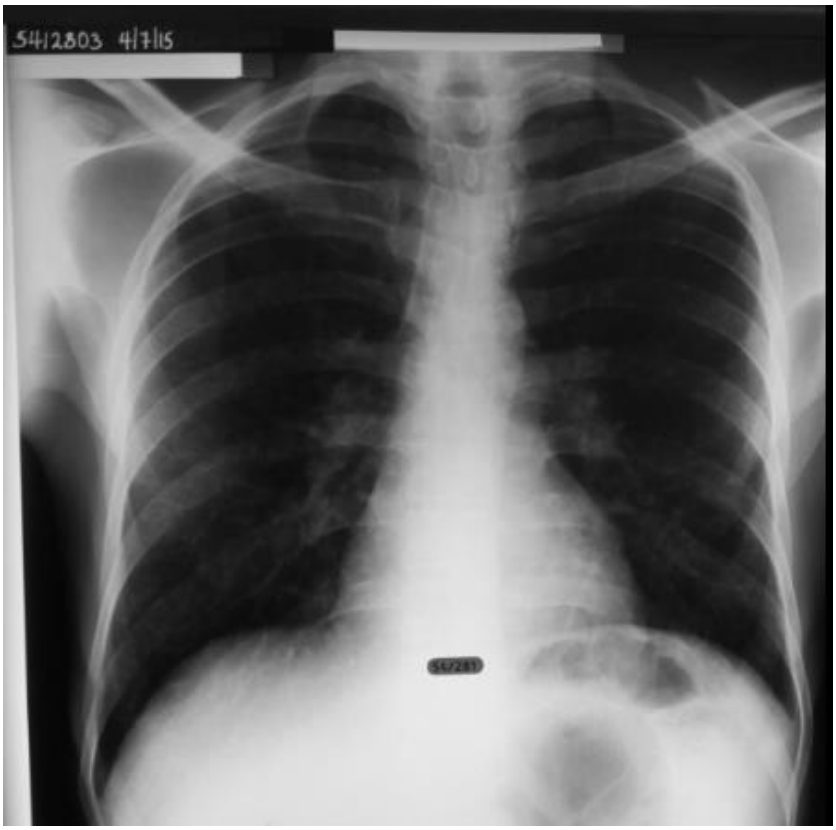

Figure 15. A P.A CXR of a 33 years old HIV positive male who had fevers and weight loss for two weeks. The radiograph shows bilateral diffuse soft nodules. He was confirmed to have SNPTB on culture.

Illustration 8

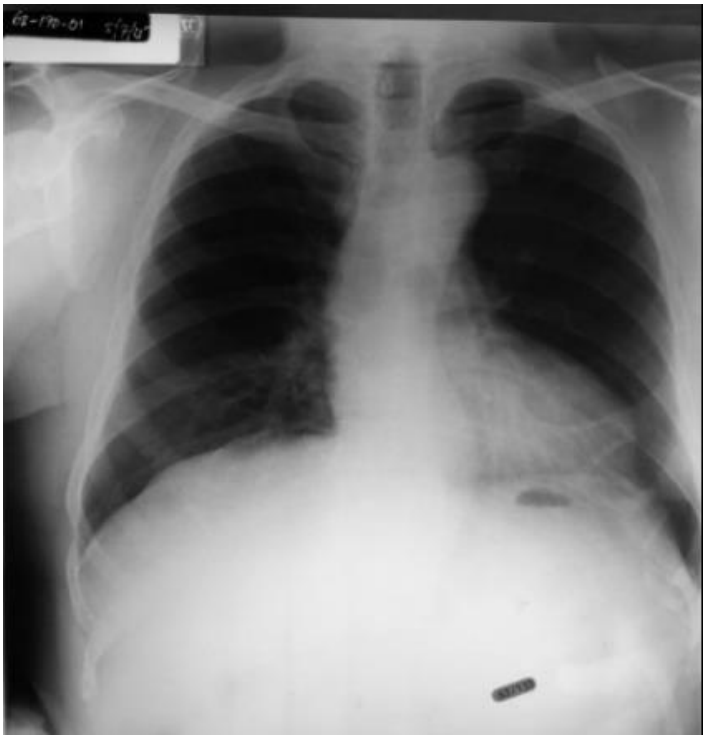

Figure 16. A P.A CXR of a 62 years old HIV negative male who had a productive cough for two weeks. The radiograph shows cardiomegaly (CTR 0.56) with a dilated tortuous aorta. He was confirmed to have SNPTB on culture.

CHAPTER FIVE: DISCUSSION.

5.0 Summary of the results.

The social demographic factors namely: male sex, current smoking, living in an urban setting, as well as being single had a positive association with developing SNPTB.

The clinical factors namely: having no cough or a cough of less than 2weeks, being HIV positive, being on current treatment for PTB as well as having both cough and an abnormal CXR were positively associated with SNPTB.

The radiographic variables namely: upper zone consolidation, middle/ lower lung zones consolidation, nodules and pleural effusion all had positive association with developing SNPTB.

Radiographic features of active PTB were seen in both cases and controls but in different proportions.

5.1 Social demographic factors associated with SNPTB

5.1.1 Gender

This study found that there was a positive association between male sex (AOR=2.48, 95% CI=1.458-4.213 p=0.001) and SNPTB. This meant that the male sex is almost 2.5 times more likely to develop SNPTB than the females. These findings were in agreement with another study also conducted in South western Uganda, which found that males were twice as likely to have culture confirmed PTB than females (AOR= 2.2, 95% CI =1.56-3.18, P < 0.001)(49). Another study which was carried out in South India also found that the male to female ratio in patients of pulmonary tuberculosis was 2:1, which was also maintained when smear positive and smear negative were studied separately(50). Regardless of the smear status, many countries are finding sexual inequality among PTB cases with males having higher incidence than females(51). There is speculation that biological differences may explain this difference in susceptibility(51), however no study has confirmed this as yet. In addition social factors could play a role. For example in Uganda more men than women smoke cigarettes and smoking has been positively associated to developing SNPTB(52). Furthermore, males are more likely to migrate to urban areas while in such for work and thus have increased exposure.

5.1.2 Marital status

The study found that the single were 2.04 times more likely to develop SNPTB compared to the married. (AOR=2.04 95%CI=1.250-3.271, P=0.004).Although this has not been collaborated by other known research, a study conducted in Ethiopia by Begna et al, found that the unmarried respondents were about eight times (AOR = 8.40, 95% CI = 3.02-23.20) more likely to develop smear positive PTB than married ones(53). It is been postulated that psychosocial stress resulting from isolation and absence of close social support is the reason.

5.1.3 Demographic setting

The study found urban setting to be positively associated with SNPTB (AOR=1.92, 95%CI=1.177-3.123, p=0.009). This finding was not unusual since PTB is generally more prevalent in urban settings than rural settings, owing predominantly to the overcrowding which is an important risk for any respiratory disease including tuberculosis(53).

5.1.4 Current Smoking

Current smoking was found to be 2.4 times more associated with developing SNPTB (AOR= 2.39, 95%CI=1.302- 4.391, p=0.005). These findings were comparable to findings in a study conducted in Mwanza Tanzania, by Nyagosya et al in 2008, where men who were currently smoking were 2.5 times more likely to have SNPTB than men who were not smoking, while the smoking women were 17.75 times more likely to develop SNPTB than their non-smoking counterparts (men AOR =2.50, 95%CI= 1.38 - 4.5, p=1 0.002, women AOR = 17.75 95%CI=3.04 -103.47, p= 0.001)(54). Not many studies have demonstrated this relationship, however smoking generally has been previously reported to be associated with an increased risk of developing TB disease(55).

5.1.5 Other social demographics

The variables occupation, education level, region of residence and previous history of smoking were independently assessed on bivariate analysis, and all had p- values of greater than 0.2 at 95%CI. Thus they were not considered to be associated with SNPTB.

Previous studies conducted within the region have not found an association between SNPTB and these variables(56).

5.2 Clinical factors associated with SNPTB

The study found that being HIV positive is 2.5 more times associated with developing SNPTB than being HIV negative (AOR=2.54, 95%CI= 1.437-4.496 p=0.001). This finding was alike to findings in other previously conducted studies both in Africa(57, 58), and abroad(59).

HIV suppresses the body's cell mediated immunity which in turn reduces both the detectable mycobacterial load in sputum as well as the clinical and radiographic presentations. Furthermore, a study done in Cambodia found association between concomitant respiratory tract infection and negative sputum AFB(60). This was attributable to the antibiotics used to treat the respiratory tract infection which reduce the sputum mycobacterial load.

This study found a strong positive association between being on current PTB treatment and SNPTB (AOR=14.67, 95%CI=1.675- 128.517, p=0.015). For a smear to be positive, there must be at least 5000-10 000 acid-fast bacilli per mL sputum. However, the anti-tuberculous drugs can reduce these quantities to levels which may be hard for the microscopy to detect.

Having a cough ≤ 2 weeks was found statistically significant (AOR=2.92, 95% CI=1.548-5.535, p=0.001). This meant that persons with a cough of less than 2 weeks were 2.9 times more likely to have SNPTB than those with a longer duration of cough. This finding is consistent with findings in other studies (39, 61). For example a study conducted in Dakar Senegal by Toure et al, found that SNPTB was associated with no or minor cough(59).

Other clinical features namely fever, sputum production, bloody sputum production, chest pain, weight loss, were not found to be statistically significant on bivariate analysis, and thus were found not to be associated with development of SNPTB. This was not unusual because similar findings have been obtained before (39, 59). SNPTB does not arouse an aggressive systematic response possibly due to the low microbial load among other factors. As a result the clinical presentation is often mild, and this is one of reasons for delayed diagnosis of SNPTB.

5.3 The chest radiographic features

70 (75.2%) of the SNPTB cases and 26 (9.32%) of the controls had radiographs that had features which were highly suggestive of active PTB. Of these, 59 (63.4%) of the cases had features that were indicative

of post-primary Tuberculosis, while 11(11.8%) of the cases had features which were more in keeping with primary infection. None of the controls had features suggestive of primary PTB. The finding of chest radiographs belonging to the controls with features that are highly suggestive of active PTB is not surprising. Previous studies have found CXR to have low specificity in diagnosis of PTB, more so SNPTB (62-64). This means that although CXR can be used as supportive investigation for diagnosis of SNPTB, culture should be encouraged as much as possible.

The most predominant presentation of post-primary disease was nodular infiltrates which 38.7% of the cases had, followed closely by upper lung zone consolidations which 29% of the cases had. Also present were bronchiectatic changes found in 21.5% of all the cases along with cavitating disease in 7.5% of the cases and miliary disease in 2.1%. In majority of the cases, multiple features would be seen on the same radiograph. The finding of typical features of post primary PTB on a majority of SNPTB chest radiographs is rather uncommon because previous studies have shown that in SNPTB the radiologic picture is often that of primary PTB (40, 65). However since Uganda has a relatively high burden of PTB, most people have been exposed to the primary infection by adolescence and thus are more likely to have a post-primary picture. Unfortunately this study could not accurately depict the relationship between HIV and the radiographic features due to some missing HIV results, however 81% of the cases with features of primary PTB were HIV positive. It has been previously reported that SNPTB often develops in persons with impaired immune systems or persons with a low microbial burden (40, 65). Both of these factors result in an often milder form of disease both clinically and radiologically(39). The cases in this study which had features suggestive of primary disease mostly had middle or lower zone consolidations with either ipsilateral hilar adenopathy or ipsilateral pleural effusions.

Also present, albeit a rare occurrence were solitary, round or oval homogenous masses with no air bronchograms. The masses had smooth margins. The surrounding lung did not show architectural distortion. This benign appearance alluded to possibility of tuberculomas however differentials such as lung tumors and round pneumonias could not be excluded. Tuberculomas have also been known to occur in primary Tuberculosis.

Another un-surprising find was 13% of the cases having normal chest radiographs of which 5% were HIV positive. This is a known radiographic presentation of SNPTB (66), which unfortunately also happens to be a sinister finding, in the setting of HIV-TB co infection(67). These patients have been reported to have increased mortality compared to those with abnormal radiographs (67). Therefore presumptive PTB cases who present with symptoms of PTB and normal chest radiographs should be closely followed up and evaluated further.

7(7.5%) of the SNPTB cases had features suggestive of healed disease. These included calcified nodules as well as isolated pleural fibrosis. Chest radiography was unable to detect radiological features indicative of active PTB in these cases. A previous study has shown that the sensitivity of chest radiography for early diagnosis of recurrent pulmonary tuberculosis, in asymptomatic cases is not very high at 60%(68). Thus bacteriological examinations should be done irrespective of chest X-ray finding in a previously treated SNPTB patient presenting with new symptoms of PTB.

4(4.3%) of the cases and had radiographic features that were atypical for any of the known stages of PTB infection. Majority these features included cardiovascular conditions but they were not suggestive of TB pericarditis.

After multivariate analysis, the radiographic features upper lung zone consolidation (AOR=10.01, 95%CI=3.086-32.442, p=<0.001), middle/ lower lung zones consolidations (AOR=3.97, 95%CI=1.267-

12.488, p=0.018), nodules (AOR=7.65, 95%CI=3.330-17.569, p=<0.000) and pleural effusion (AOR=10.65, 95%CI=2.042-55.598,p=0.005) were positively associated with developing SNPTB, however the wide confidence intervals means that the association is not very specific for SNPTB.

A study done to evaluate the validity and reliability of chest radiography in the diagnosis of PTB among SNPTB patients in Ethiopia found that, similar to this study, the most common CXR finding was consolidation (40.3%) followed by cavitation's (23.9%) and nodular lesions (17.0%). The sensitivity and specificity of CXR findings were 77.1% (37/48) and 36.9% (41/111), respectively. The positive and negative predictive values were 34.6% (3 7/107) and 78.8% (41/52), respectively(64). The low specificity of CXR makes it difficult to accurately identify the radiographic factors associated with SNPTB.

5.6 Limitations to the study

The study being retrospective was limited by insufficient numbers as well as the missing data. This greatly reduced the power of the study, which was found to be 41%.

Furthermore a number of the radiographs had artefacts caused by poor storage conditions, and this greatly reduced their quality.

5.7 Conflict of interest

There was no conflict of interest in carrying out this study

CHAPTER SIX: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

- The results from this study confirm that the male gender, current smoking, living in urban settings and being single are positively associated with developing SNPTB.
- The study also confirms that having no cough or a cough of less than 2 weeks, along with being HIV Positive are positively associated with developing SNPTB.
- Furthermore, this study affirms that chest radiography has a high catch rate for smear negative PTB. However a normal chest radiograph does not exclude SNPTB infection in a patient with symptoms and a negative smear. And also one must keep in mind the low specificity of CXR in diagnosing PTB.
- Due to the wide confidence intervals and the low power of the study, it is not possible to correctly identify the radiographic factors associated with SNPTB from this study.
- In addition, chest radiography is not sufficient when evaluating new symptoms in a patient with previous PTB since new radiological features can be masked by the pre-existing lung fibrosis and calcifications.

6.2 Recommendations

- From this study it is recommended that chest radiography should continue to be part of the early diagnostic work up for SNPTB however bacteriological confirmation is encouraged as much as possible.
- Moreover, patients with previously healed PTB should be evaluated radiologically as well as bacteriologically should they present with new symptoms of PTB disease.
- High resolution Computed Tomography scan should be done in cases with radiological features suggestive of PTB who do not respond to treatment.
- Future studies need to further explore the reasons behind the increased susceptibility of the male sex to SNPTB, and also confirm and assess the positive association between being single and develop-

pment of SNPTB.

- Additionally, prospective studies with sufficient numbers need to further explore the current radiologic features of SNPTB in HIV infection in Uganda.

REFERENCES

1. WHO. Global Tuberculosis Report 2016. Global Tuberculosis Report. 2016.
2. Maher D CP, Spinaci S, Harries AD. Treatment of tuberculosis: guidelines for national programmes. WHO 1997.
3. WHO. Global Tuberculosis Report 2015. 2015.
4. Organisation WHO. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents. Recommendations for HIV prevalent and resource-constrained settings. World Health Organisation. 2007.
5. Kulpati D. Diagnosis of smear negative pulmonary tuberculosis by flexible fibreoptic bronchoscopy. The Indian journal of tuberculosis. 1986;33:179-82.
6. Getahun H, Harrington M, O'Brien R, Nunn P. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. Lancet. 2007 Jun 16;369(9578):2042-9.
7. Alma Tostmann S. Tuberculosis Transmission by Patients with Smear-Negative Pulmonary Tuberculosis in a Large Cohort in The Netherlands. Clinical Infectious Diseases. 2008;47(9):1135-42.
8. Leandro Cruz Campos MVVR, Denise Maria Cunha Willers, Denise Rossato Silva. Characteristics of Patients with Smear-Negative Pulmonary Tuberculosis (TB) in a Region with High TB and HIV Prevalence. PloS one. 2016;10.
9. Shaw JB, Wynn-Williams N. Infectivity of pulmonary tuberculosis in relation to sputum status. American review of tuberculosis. 1954 May;69(5):724-32.
10. Behr MA WS, Salamon H, Hopewell PC, Ponce de LA, Daley CL, et al. Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacilli. The Lancet Global health. 1999 (353):444-9.
11. Chongguang Yang XS, Ying Peng, Rushu Lan, Yuling Zhao, Bo Long, Tao Luo, Guomei Sun, Xia Li, Ke Qiao, Xiaohong Gui, Jie Wu, Jiying Xu,Fabin Li, Dingyue Li,Feiying Liu, Mei Shen, Jianjun Hong, Jian Mei,a Kathryn DeRiemer,a and Qian Gao. Transmission of Mycobacterium tuberculosis in China: A Population-Based Molecular Epidemiologic Study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;61(2):219-27.
12. Oludiran Kehinde HD-A. Epidemiology of Smear - Negative Tuberculosis in Ibadan, Nigeria. African journal of infectious diseases. 2013;7(1):14-7.
13. WHO. Implementing the WHO Stop TB Strategy: a handbook for national tuberculosis control programmes. World Health Organization;. 2008.
14. WHO. Tuberculosis prevalence surveys: a handbook. World Health Organization;. 2011.
15. Jarlier V, Nikaido H. Mycobacterial cell wall: structure and role in natural resistance to antibiotics. FEMS microbiology letters. 1994 Oct 15;123(1-2):11-8.
16. WHO. Global tuberculosis control 2011. World Health Organization;. 2012.
17. Getahun Hea. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings. PLoS Medicine. 2011;8(1).

18. WHO. Global Tuberculosis Report. World Health Organisation. 2013.
19. Suslov VA. [Etiopathogenesis, clinical picture and treatment of progressive forms of pulmonary tuberculosis]. Voenno-meditsinskii zhurnal. 1996 Jul;317(7):29-34, 80.
20. Abebe DS, Bjune G, Ameni G, Biffa D, Abebe F. Prevalence of pulmonary tuberculosis and associated risk factors in Eastern Ethiopian prisons. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2011 May;15(5):668-73.
21. Ebonyi AO, Oguche S, Ejeliogu EU, Agbaji OO, Shehu NY, Abah IO, et al. Prevalence of and risk factors for pulmonary tuberculosis among newly diagnosed HIV-1 infected Nigerian children. Germs. 2016 Mar;6(1):21-8.
22. Werner E. [Pathogenesis of pulmonary tuberculosis from the current viewpoint]. Zeitschrift fur die gesamte innere Medizin und ihre Grenzgebiete. 1983 Aug 15;38(16):445-7. 23. Jevric S, Pavlovic M, Radojcic M. [Development of Primary and Postprimary Pulmonary Tuberculosis in the Yugoslav Army]. Vojnosanitetski pregled. 1963 Sep;20:555-8.
23. Karam Bechara J, Escorcha Rambal HR. [Primary pulmonary tuberculosis in children under 2 years of age (22 cases)]. Boletin medico del Hospital Infantil de Mexico. 1978 Jan-Feb;35(1):115-21.
24. Dannenberg AM, Jr. Pathogenesis of pulmonary tuberculosis: basic principles. The Indian journal of chest diseases & allied sciences. 1982 Apr-Sep;24(2-3):68-77.
25. Roy M, Ellis S. Radiological diagnosis and follow-up of pulmonary tuberculosis. Postgraduate medical journal. 2010 Nov;86(1021):663-74.
26. Pakasi TA, Karyadi E, Dolmans WM, van der Meer JW, van der Velden K. Malnutrition and socio-demographic factors associated with pulmonary tuberculosis in Timor and Rote Islands, Indonesia. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2009 Jun;13(6):755-9.
27. Davis SD, Yankelevitz DF, Williams T, Henschke CI. Pulmonary tuberculosis in immunocompromised hosts: epidemiological, clinical, and radiological assessment. Seminars in roentgenology. 1993 Apr;28(2):119-30.
28. Curley CA. Rule out pulmonary tuberculosis: clinical and radiographic clues for the internist. Cleveland Clinic journal of medicine. 2015 Jan;82(1):32-8.
29. Frigati L, Maskew M, Workman L, Munro J, Andronikou S, Nicol MP, et al. Clinical Predictors of Culture-confirmed Pulmonary Tuberculosis in Children in a High Tuberculosis and HIV Prevalence Area. The Pediatric infectious disease journal. 2015 Sep;34(9):e206-10.
30. Alvarez Martin T, Merino Arribas JM, Anso Olivan S, Montero Alonso R, Gil Rivas MT, Aldea Martinez J, et al. [Clinical and radiological characteristics of primary pulmonary tuberculosis in adolescents]. Anales espanoles de pediatria. 2000 Jan;52(1):15-9.
31. Ismail Y. Pulmonary tuberculosis--a review of clinical features and diagnosis in 232 cases. The Medical journal of Malaysia. 2004 Mar;59(1):56-64.
32. Organisation WH. Proposed reduction of number of smears for the diagnosis of Pulmonary TB. World Health Organisation. 2007.
33. Organization WH. Implementing the WHO Stop TB Strategy: a handbook for national tuberculosis control programmes. World Health Organization. 2008.

34. Ramos JM, Perez-Butragueno M, Tisiano G, Yohannes T, Reyes F, Gorgolas M. Evaluation of Ziehl-Neelsen smear for diagnosis of pulmonary tuberculosis in childhood in a rural hospital in Ethiopia. International journal of mycobacteriology. 2013 Sep;2(3):171-3.
35. Lawn SD, Evans AJ, Sedgwick PM, Acheampong JW. Pulmonary tuberculosis: radiological features in west Africans coinfected with HIV. The British journal of radiology. 1999 Apr;72(856):339-44.
36. Samb B, Sow PS, Kony S, Maynart-Badiane M, Diouf G, Cissokho S, et al. Risk factors for negative sputum acid-fast bacilli smears in pulmonary tuberculosis: results from Dakar, Senegal, a city with low HIV seroprevalence. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 1999 Apr;3(4):330-6.
37. Elliott AM NK, Allen BW, Luo N. Negative sputum smear results in hiv-positive patients with pulmonary tuberculosis in Lusaka, zambia. Tuber Lung Dis, . 1993 (74):191-4.
38. Campos LC, Rocha MV, Willers DM, Silva DR. Characteristics of Patients with Smear-Negative Pulmonary Tuberculosis (TB) in a Region with High TB and HIV Prevalence. PloS one. 2016;11(1):e0147933.
39. Alka M. Kanaya DVG, Henry f. Chambers. Identifying Pulmonary Tuberculosis in Patients With Negative Sputum Smear Results. Chest journal. August 2001;Volume 120(Issue 2): Pages 349–55.
40. Affusim C, Abah V, Kesieme EB, Anyanwu K, Salami TA, Eifediyi R. The Effect of Low CD4+ Lymphocyte Count on the Radiographic Patterns of HIV Patients with Pulmonary Tuberculosis among Nigerians. Tuberculosis research and treatment. 2013;2013:535769.
41. Akhtar S, Mohammad HG. Time series cross-correlation analysis of HIV seropositivity and pulmonary tuberculosis among migrants entering Kuwait. International journal of mycobacteriology. 2012 Mar;1(1):29-33.
42. Busi Rizzi E, Schinina V, Palmieri F, Girardi E, Bibbolino C. Radiological patterns in HIV-associated pulmonary tuberculosis: comparison between HAART-treated and non-HAART-treated patients. Clinical radiology. 2003 Jun;58(6):469-73.
43. Tauro CK, Gawde NC. Diagnosis and Treatment of Childhood Pulmonary Tuberculosis: A Cross-Sectional Study of Practices among Paediatricians in Private Sector, Mumbai. Interdisciplinary perspectives on infectious diseases. 2015;2015:960131.
44. WHO. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource constrained settings. WHO. 2011.
45. Ceccon RF, Maffacciolli R, Burille A, Meneghel SN, Oliveira D, Gerhardt TE. Tuberculosis mortality in Brazilian capitals, 2008-2010. Epidemiologia e servicos de saude : revista do Sistema Unico de Saude do Brasil. 2017 Apr-Jun;26(2):349-58.
46. Zwang J, Garenne M, Kahn K, Collinson M, Tollman SM. Trends in mortality from pulmonary tuberculosis and HIV/AIDS co-infection in rural South Africa (Agincourt). Transactions of the Royal Society of Tropical Medicine and Hygiene. 2007 Sep;101(9):893-8.
47. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian journal of psychological medicine. 2013 Apr;35(2):121-6.
48. Boum Y, 2nd, Atwine D, Orikiriza P, Assimwe J, Page AL, Mwanga-Amumpaire J, et al. Male Gender is independently associated with pulmonary tuberculosis among sputum and non-sputum producers people with presumptive tuberculosis in Southwestern Uganda. BMC infectious diseases. 2014 Dec 10;14:638.

49. Rao S. Tuberculosis and patient gender: An analysis and its implications in tuberculosis control. Lung India : official organ of Indian Chest Society. 2009 Apr;26(2):46-7.
50. Neyrolles O, Quintana-Murci L. Sexual inequality in tuberculosis. PLoS medicine. 2009 Dec;6(12):e1000199.
51. Kabwama SN, Ndyanabangi S, Mutungi G, Wesonga R, Bahendeka SK, Guwatudde D. Tobacco use and associated factors among Adults in Uganda: Findings from a nationwide survey. Tobacco induced diseases. 2016;14:27.
52. Begna T ND, Yibeltal Kassa and Biruhalem Taye. Smear positive pulmonary tuberculosis and its risk factors among tuberculosis suspect in South East Ethiopia; a hospital based cross-sectional study. BMC research notes. 2014 (7):285.
53. Range Nyagosya1, Åse B. Andersen2, Frank van Leth3,7, Pascal Magnussen4 , Mugomela Apolinary5 and Henrik Friis. Risk Factors for Smear Negative And Culture Positive Results Among Pulmonary Tuberculosis Patients in Mwanza, Tanzania. The Open Tropical Medicine Journal. 2008;1:68-73.
54. Gupta KP GR. Association between smoking and tuberculosis. The Indian journal of tuberculosis. 2003;50:5-7.
55. Jimmy O. Prevalence and factors associated with sputum smear negative Tuberculosis among adult TB patients in Kawempe Division-Kampala: A nested case control. 2013.
56. Hargreaves NJ, Kadzakumanja O, Whitty CJ, Salaniponi FM, Harries AD, Squire SB. 'Smear-negative' pulmonary tuberculosis in a DOTS programme: poor outcomes in an area of high HIV seroprevalence. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2001 Sep;5(9):847-54.
57. Elliott AM, Namaambo K, Allen BW, Luo N, Hayes RJ, Pobee JO, et al. Negative sputum smear results in HIV-positive patients with pulmonary tuberculosis in Lusaka, Zambia. Tubercle and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 1993 Jun;74(3):191-4.
58. Toure NO, Diatta A, Dia Y, Niang A, Ndiaye EH, Thiam K, et al. [Determination of risk factors of smear-negative pulmonary tuberculosis]. Dakar medical. 2005;50(3):98-103.
59. Loïc Chartier CL, Jean-Marie Sire, Odile Le Minor, Manil Saman, Raymond Bercion, Lila Rahalison, Arnaud Fontanet, Yves Germany, Pierre L'Her, Charles Mayaud, Muriel Vray. Factors Associated with Negative Direct Sputum Examination in Asian and African HIV-Infected Patients with Tuberculosis PloS one. 2011.
60. Linguissi LS, Vouvoungui CJ, Poulain P, Essassa GB, Kwedi S, Ntoumi F. Diagnosis of smear-negative pulmonary tuberculosis based on clinical signs in the Republic of Congo. BMC research notes. 2015 Dec 18;8:804.
61. van Cleeff MR, Kivihya-Ndugga LE, Meme H, Odhiambo JA, Klatser PR. The role and performance of chest X-ray for the diagnosis of tuberculosis: a cost-effectiveness analysis in Nairobi, Kenya. BMC infectious diseases. 2005 Dec 12;5:111.
62. Kumar N, Bhargava SK, Agrawal CS, George K, Karki P, Baral D. Chest radiographs and their reliability in the diagnosis of tuberculosis. JNMA; journal of the Nepal Medical Association. 2005 Oct-Dec;44(160):138-42.
63. Tewolde E, Atnafu A, Kebede T, Tedla Y, Assefa G, Bedane A, et al. Evaluating the Validity and Reliability of Chest Radiography in the Diagnosis of Tuberculosis among Smear Negative

Pulmonary Tuberculosis Patients. Ethiopian medical journal. 2015 Apr;53(2):83-9.
64. Shah NS, Cavanaugh JS, Pratt R, Cain KP, Wells C, Laserson K, et al. Epidemiology of smear-negative pulmonary tuberculosis in the United States, 1993-2008. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2012 Sep;16(9):1234-40.
65. Pepper T. Normal chest radiography in pulmonary tuberculosis: Implications for obtaining respiratory specimen cultures. The international journal of tuberculosis and lung disease. 2008;12(4):397-403.
66. Yoo SD, Cattamanchi A, Den Boon S, Worodria W, Kisembo H, Huang L, et al. Clinical significance of normal chest radiographs among HIV-seropositive patients with suspected tuberculosis in Uganda. Respirology. 2011 Jul;16(5):836-41.
67. Ito K. [Limits of chest X-ray investigation in the diagnosis of recurrent pulmonary tuberculosis]. Kekkaku : [Tuberculosis]. 2005 Jul;80(7):521-6.