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**Pathways to tuberculosis diagnosis and treatment in Ghana:
identifying the gaps and seeking solutions**

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**Thesis submitted in accordance with the requirements for the
degree of**

**Doctor of Philosophy
of the
University of London**

March 2021

Department of Clinical Research

Faculty of Infectious and Tropical Diseases

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**Funded by Commonwealth Scholarship Commission,
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Abstract

Background

Ghana's national tuberculosis (TB) prevalence survey in 2013 showed higher than expected prevalence, indicating people with TB are being missed.

Aim

To identify barriers in the pathway to TB diagnosis and treatment initiation for people presenting to health facilities and make recommendations for improvement.

Methods

In Volta region, Ghana, a cross-sectional study was conducted among symptomatic patients exiting the health facility to determine TB screening practices of healthcare workers (HCWs); a prospective cohort study among presumptive TB patients to determine if sputum was submitted; and in-depth interviews with HCWs and clinic observations to explore barriers to TB case finding.

Results

In the cross-sectional study, 386/581 (66.4%) reported their TB-related symptoms to a HCW; 157/386 (40.6%) were eligible for a sputum test but only 31 (19.7%) were asked to submit a sputum. Prior TB treatment was the strongest predictor of being asked to submit a sputum (adjusted odds ratio [aOR]: 6.25, 95% CI: 2.24-17.46). In the prospective cohort study, among rural facility attendees, only 45/143 (31.5%) submitted a sputum for testing. Travel distance >10 km to the diagnostic laboratory was the strongest predictor of sputum not submitted (aOR 0.12, 95%CI 0.05-0.33). Barriers identified in the qualitative study were either health system- related such as no diagnostic laboratories in rural facilities and HCWs' non-adherence to diagnostic guidelines; or HCW-related such as lack of training on guidelines, fear of infection leading to low motivation for TB work.

Conclusions

There are gaps in the pre-diagnostic cascade in the steps before a sputum is submitted for a TB test. Factors causing these gaps are multifaceted and there is no single solution for these barriers. Collaborations between health facilities and the national TB control programme to implement patient-centred strategies for improved case finding are needed.

Acknowledgements

I praise God for how far He has brought me in this PhD journey. Lord, the essence of my praise is centred on your Grace.

There are numerous people who have supported me during my PhD study. Firstly, I am very grateful to my primary supervisor, Professor Alison Grant for her untiring support and guidance throughout the process of this PhD study. Her patience and encouragement made this possible. I am fortunate to have worked and learnt from you. I thank my secondary supervisor, Dr Daniel Grint for providing all the statistical support and guidance I needed for the study. You committed time to this, and I am grateful. I am also thankful to Dr Virginia Bond for all the advice and support on the qualitative component of my study and for always being nice and encouraging me. I thank Dr Chrissy Robert for providing support on ODK during my data collection. A special thanks to the Commonwealth Scholarship Commission, UK for giving me a scholarship for this PhD, without it, I would not have been able to do a PhD in the UK.

I am grateful to my former Vice Chancellor of the University of Health and Allied Sciences - Ho, Ghana, Professor Fred Binka for his encouragement, mentorship and motivation. I thank Dr Frank Bonsu, former Programme Manager, Ghana National Tuberculosis Control Programme (NTP) for his guidance and logistical support for this study. I also thank Madam Francisca Dzata of the NTP who has always encouraged me to do research in the area of tuberculosis. My friends and colleagues who encouraged me and gave me moral support, I say thank you: Clement T. Narh, Samuel Otu-Nyarko, Faith Agbozo, Jerry John Kponyo, Amos Kotey and Cynthia Fatchu. To all the Nudidi study team members, I appreciate your support.

Lastly to my wonderful family who believed in me and supported me throughout this

journey. To my loving mum, Clare who took up caring responsibilities for my children so I could do this PhD, I say am indebted to you. To my children; Tiffany, Kayla and Owen who endured my absence and prayed for me every time, I say thank you. Magnus (brother), Gloria (sister), Rainer (niece) and Uncle Simon, I am grateful for your support. Many thanks to Uncle Francis Saayeng for accommodating me during my stay in London. To my late husband, Bonny, may you continue to rest in peace. To everyone who made this possible, I say thank you and God bless you all.

~

For Tiffany, Kayla and Owen

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Abbreviations

AFB	Acid-fast bacilli
CRF	Case report forms
DOTS	Directly observed treatment short course
EPTB	Extra-pulmonary TB
HCW	Healthcare worker
HF	Health facility
HIV	Human immunodeficiency virus
ISTC	International Standards for TB Care
IQR	Interquartile range
LMIC	Lower- and-Middle Income Countries
LSHTM	London School of Hygiene & Tropical Medicine
LTFU	Loss to follow-up
MTB	Mycobacterium tuberculosis
NTP	National tuberculosis control programme
ODK	Open data kit
OPD	Outpatient department
PPE	Personal protective equipment
PQE	Programme quality and efficiency
RIF	Rifampicin
SOP	Standard operating procedure
TB	Tuberculosis
TSO	Task-shifting officer
USAID	United States Agency for International Development
WHO	World Health Organization
XTEND	Xpert for TB: Evaluating a New Diagnostic

Chapter 1: Introduction

1.1 Public health importance of tuberculosis

Tuberculosis (TB) is a highly infectious disease that is a major public health threat. It is the leading cause of death from a single infectious agent ranked above the human immunodeficiency virus (HIV) [1]. It is estimated that about a quarter of the world's population is infected with *Mycobacterium tuberculosis* (the bacterium that causes TB) and thus at risk of developing TB disease [1]. In 1993, the World Health Organization (WHO) declared TB as a global public health emergency and initiated a management strategy called directly observed treatment short course (DOTS) [2, 3]. The DOTS strategy was aimed at controlling the TB epidemic and had five key elements: political commitment with increased and sustained financing; case detection through quality-assured bacteriology; standardized treatment, with supervision and patient support; an effective drug supply and management system; monitoring and evaluation system, and impact measurement [2, 4]. There has been some progress towards TB control; between the years 2000 and 2014, 43 million lives have been saved through effective TB diagnosis and treatment [5]. Also, there was a 42% reduction in TB deaths among HIV-negative people between the period 2000 and 2017 [6].

Despite this progress, TB remains a disease of major public health importance. In 2018, it was estimated that 10 million people had TB globally with an estimated 1.2 million deaths among HIV-negative people and an additional 251,000 deaths among HIV-positive people [1]. Africa bore 24% of the global TB burden in 2018 and also had the highest burden of HIV-associated TB accounting for 84% of all TB/HIV deaths [1, 6]. TB is more common in men accounting for 57% of people with TB, and 89% of TB is in adults (aged over 15 years). Drug-resistant TB is also a continuing public health

threat and in 2018, about half a million people had a new episode of rifampicin-resistant TB, 78% of them were multidrug-resistant (i.e. resistant to two of the most important TB drugs, isoniazid and rifampicin) [1].

1.2 Biology of TB

TB is caused by a bacterium called *Mycobacterium tuberculosis* and it is transmitted via the airborne route when individuals with active respiratory tract infections expel bacilli into the environment. Humans are both the obligate host and vector of this organism [7]. TB has many manifestations, affecting bone, the central nervous system, and many other organ systems, but it is primarily a pulmonary disease that is initiated by the deposition of the bacilli, contained in aerosol droplets, onto lung alveolar surfaces [8]. It is not everyone infected with *Mycobacterium tuberculosis* that becomes sick, therefore, there are two TB-related conditions: latent TB infection and TB disease. However, recent research has clearly demonstrated that human TB infection, from latent infection to active disease, exists within a continuous spectrum of metabolic bacterial activity and antagonistic immunological responses. This revised understanding has led to the proposition of two additional clinical states: incipient and subclinical TB [9]. The progression of the disease can have several outcomes, determined largely by the response of the host immune system. The efficacy of this response is affected by intrinsic factors such as the genetics of the immune system and extrinsic factors such as the nutritional and physiological state of the host. In addition, the pathogen may play a role in disease progression since some *Mycobacterium tuberculosis* strains are reportedly more virulent than others, as defined by increased transmissibility as well as being associated with higher morbidity and mortality in infected individuals [8]. Some people develop TB disease soon (within

weeks) after becoming infected before their immune system can fight the bacteria. Other people may develop the disease years later, when their immune system becomes weak for other reasons. Many people with TB infection never develop TB disease [10].

1.3 Finding the missing TB cases and ending the epidemic

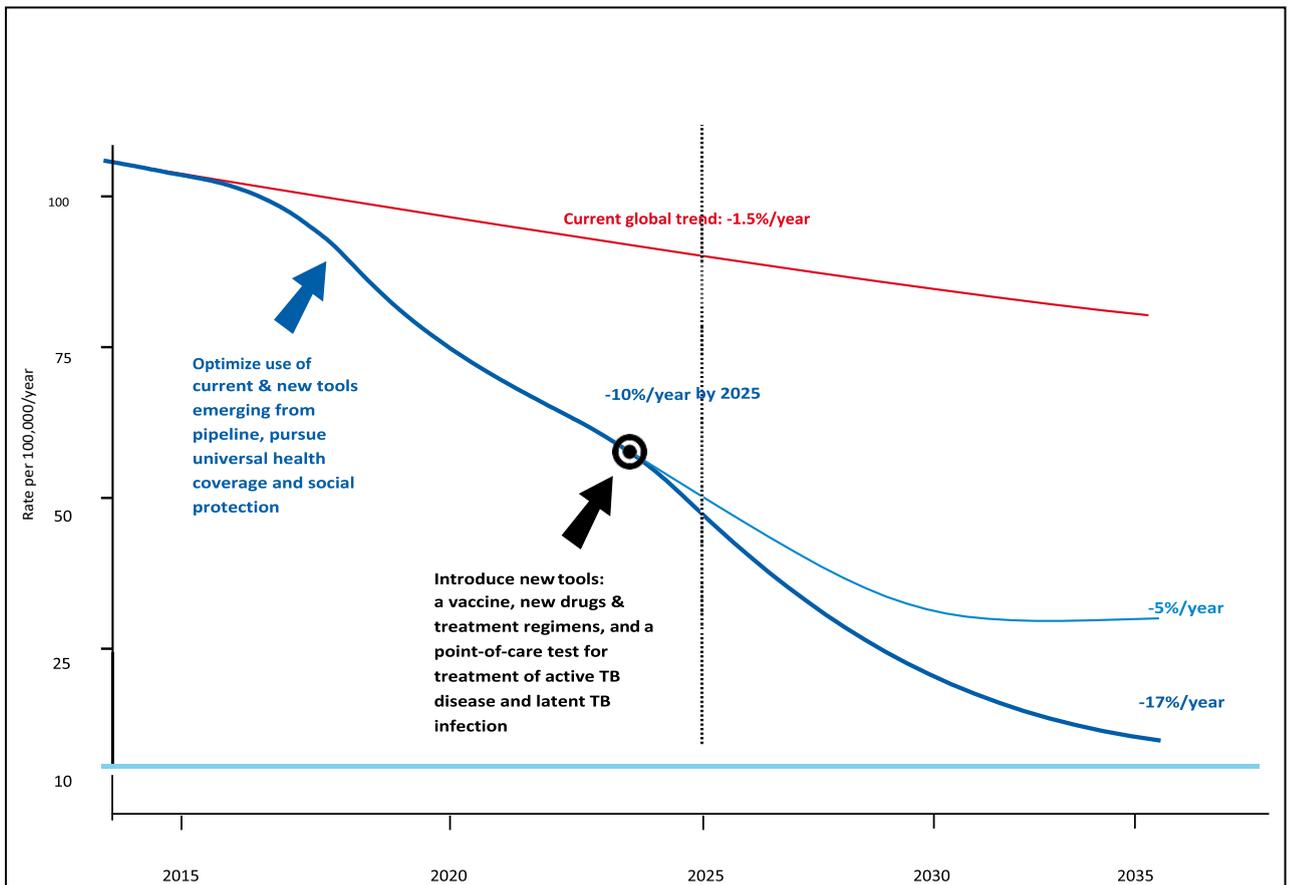
One of the main challenges in TB control is finding the missed TB cases. The term “missed” is the gap between the estimated number of people who became ill with TB (incident episodes) in a year and the number of people who were notified to national TB programmes [11]. The estimated incidence of TB is calculated by WHO using four methods: (i) results from TB prevalence surveys and estimates of the duration of disease derived from a model that accounts for the impact of TB/HIV disease and antiretroviral therapy (ART) on the distribution of disease duration, (ii) notifications adjusted by a standard factor to account for underreporting, overdiagnosis and underdiagnosis, (iii) results from national inventory studies that measured the level of underreporting of detected TB cases and (iv) case notification data combined with expert opinion about case detection gaps [1].

According to the WHO, every year three million people with TB are missed globally. There are several reasons for which people with TB are missed: they may not access care at all due to limited awareness of TB, inaccessibility to health services or financial barriers; others may access health services but are not diagnosed due to inaccurate or inappropriate diagnostic tests or overburdened and undertrained healthcare workers (HCW). Also, others may get diagnosed but they are not documented because of weaknesses in recording and reporting within public health systems or poor linkage

between private and public health systems [11]. The high burden of undiagnosed TB causes much suffering and economic hardship, and sustains transmission [12].

There are several global strategies and targets for TB prevention, care and control. The United Nation's sustainable development goals (SDGs) and the WHO's End TB strategy all seek to end the TB epidemic by reducing the global TB incidence rate by 90% and 95% by 2030 and 2035 respectively compared to the 2015 rate [3, 5]. However, progress towards these targets is slow. The global average rate of decline of TB incidence was 1.6% per year between 2000-2018 and 2.0% between 2017 and 2018 [1]. The decline in global TB incidence must increase to 10% per year by the year 2025 to achieve these goals [3]. Figure 1.1 below shows how the decline in global TB incidence can be accelerated by optimization of current tools combined with pursuing universal health coverage and social protection from 2015, and the additional impact of new tools by 2025. To meet these global targets, it is imperative that people with TB are identified promptly and put on treatment to reduce adverse health outcomes, social and economic consequences of TB, as well as to interrupt transmission.

Figure 1. 1: Projected acceleration in the decline of global TB incidence rates to target levels



Source: WHO: The End TB Strategy – Global Strategy for tuberculosis prevention, care and control after 2015 ^[3]. (Reproduced with permission from WHO)

1.4 TB control in Ghana

Ghana is among the 30 TB/HIV high burden countries according to the WHO’s classification [13]. TB control in Ghana is managed by the national TB control programme (NTP) with regional, district and institutional focal persons. TB case finding is the responsibility of all health facilities in the country.

A national TB prevalence survey conducted in 2013 showed the prevalence of TB in Ghana was 253/100,000, almost four times higher than the WHO estimates of 72/100,000 for that same year [14]. In 2018, the estimated incidence of TB was

148/100,000 (translating to 44,000 TB patients) with estimated deaths of 15,800, however, the notification rate was 48/100,000 (translating to 14,289 TB patients) [15] indicating a case detection rate of 32%. This implied lots of people with TB in 2018 were not identified which could lead to sustained TB transmission in the country and some of these people may die.

There are 10 regions in Ghana and in 2019, six regions (Western, Brong Ahafo, Upper East, Greater Accra, Eastern and Volta) had case notification rates higher than the national average of 48.8/100,000 population [16]. The majority of people notified to have TB in Ghana are classified as new and in 2019, 2.5% of TB cases were previously treated TB patients. The proportion of bacteriologically-confirmed TB increased from 51% in 2013 to 64% in 2019. This increasing trend is likely due to the introduction of Xpert MTB/RIF (Cepheid, Sunnyvale CA, USA) as the first line diagnostic test for all presumed TB. Among total incident cases notified in Ghana from 2013 to 2019, the proportion of extra pulmonary TB (EPTB) ranged between 8-9% and the proportion of childhood TB remained below 6% which is low compared to the expected global average of 10%. Also, in 2019, the prevalence of HIV among TB patients tested for HIV was 21.2% of which 74.9% were enrolled on antiretroviral therapy [16]. Since 2013, TB treatment success rates (percentage of notified TB patients who were successfully treated) have been above 80% but death rates are high ranging from 9-10%. Most of the deaths are among HIV coinfecting patients [16].

In Ghana, TB diagnosis and treatment is mainly done at government health facilities. Smear microscopy was the main diagnostic method until the last quarter of 2017 when Xpert MTB/RIF (Cepheid, Sunnyvale CA, USA) was introduced as the first-line

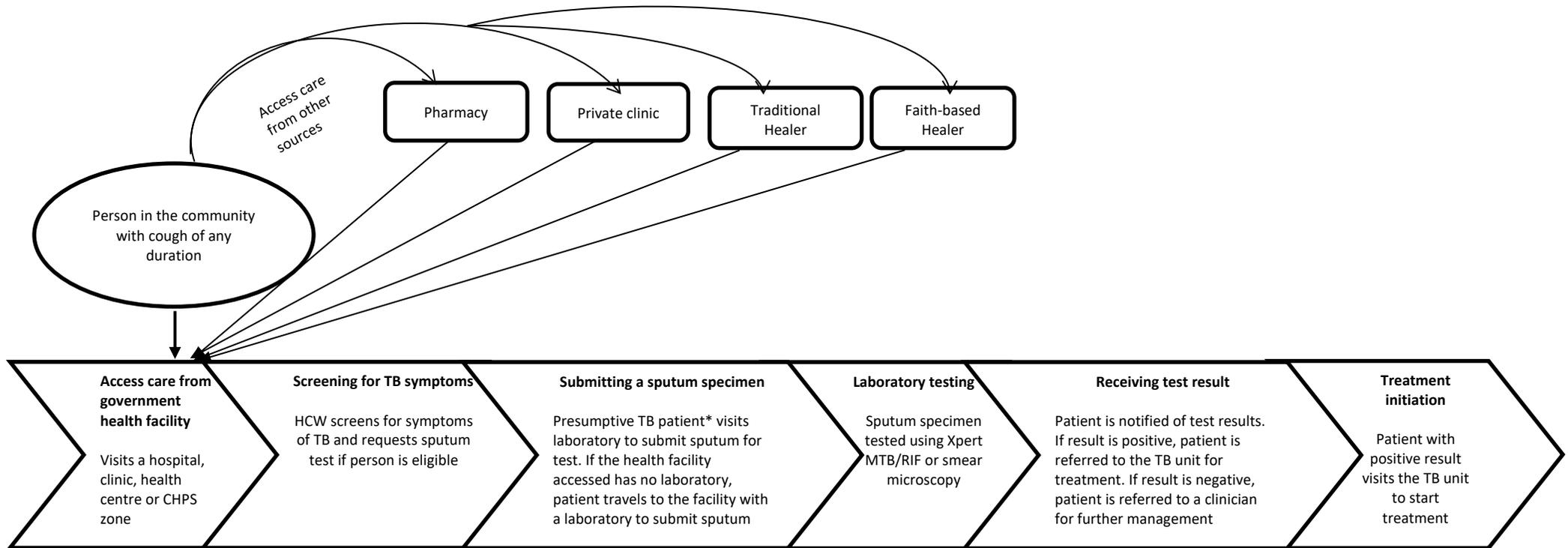
diagnostic method. Xpert MTB/RIF is an automated polymerase chain reaction platform, developed for rapid diagnosis of TB [17]. In 2011, WHO recommended the use of Xpert MTB/RIF for diagnosis of TB in HIV positive patients and suspected drug-resistant TB [18] with a policy update in 2013 [19]. In 2017, WHO recommended Xpert Ultra (Cepheid, Sunnyvale, USA) (Ultra) the next generation of Xpert MTB/RIF, as the initial TB diagnostic test for adults and children, regardless of HIV status [20]. In Ghana, there are about 370 TB diagnostic laboratories nationwide with 126 GeneXpert machines installed at selected health facilities by the NTP [16]. Also, most diagnostic laboratories are located at teaching, regional and district hospitals but not at the lower levels of care such as health centres and clinics which are more easily accessible. Therefore, a person with symptoms of TB might be identified at a health centre but will have to travel to the district hospital for a sputum test to confirm the diagnosis. Community health workers are supposed to transport sputum samples to the diagnostic centres but most often they lack the means of transportation to do this. Patients with symptoms suggestive of TB are thus required to visit the diagnostic centres themselves for sputum testing. This can lead to loss to follow-up and patients with TB might be missed by the health system.

There is a national standard operating procedure (SOP) for TB case finding that outlines activities to be carried out in health facilities to improve case detection [21]. The SOP requires that all adult patients presenting to health facilities should be asked about cough by HCWs regardless of presenting symptoms and those reporting a cough should be screened with a symptom questionnaire. Eligible persons, that is, those reporting cough longer than two weeks or cough of any duration with at least two other TB-related symptoms (chest pain, weight loss, night sweats and fever), should be asked to submit

a sputum for a TB test [22]. Patients who are HIV-positive with cough of any duration, fever, weight loss or night sweats should also be asked to submit sputum for a TB test.

Figure 1.2 shows the pathway to TB diagnosis and treatment in health facilities in Ghana where a person with cough may seek care from different providers (pharmacy, private clinic, traditional healer or faith-based healer) where they might not be screened for TB. Others too might visit a government health facility and must go through several steps in the care cascade to get a TB diagnosis and initiated on treatment. Those who first visit other providers may end up at some point in time in a government health facility to get a TB diagnosis.

Figure 1. 2: Pathway to TB diagnosis and treatment in Ghana



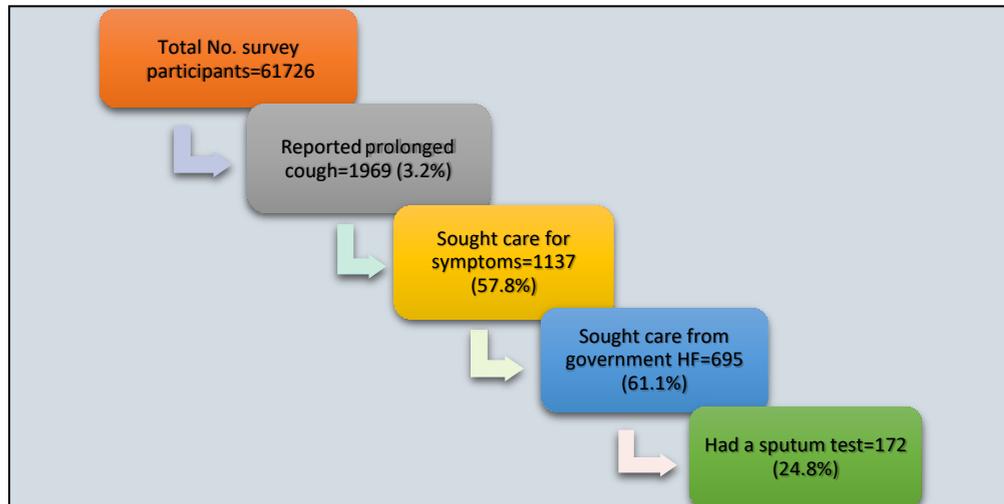
CHPS (community-based service delivery point) = community health planning services, HCW= healthcare worker, TB= tuberculosis. *Presumptive TB patient= a patient who presents with symptoms or signs suggestive of TB

1.5 Rationale for the study

The national TB prevalence survey conducted in 2013 showed that the burden of TB in Ghana was higher than previously assumed. In 2014 when programme data were combined with revised prevalence data, it showed that TB case detection rates were low with only 33% of people with TB detected, implying ongoing transmission of infection [23]. Improving case finding is a priority of the NTP. This will ensure that persons with TB are identified early and put on treatment to reduce the duration of infectiousness and reduce transmission. This in the long term will also enable the NTP to meet global targets of reduced incidence of TB.

Also, findings from the prevalence survey showed that among persons with prolonged cough who visited a health facility, only 25% did a sputum test [14]. This is illustrated in figure 1.3 which shows the cascade of care among survey participants who sought care from a government health facility. Survey participants were adults aged 15 years and above selected from 98 clusters across the ten regions of Ghana and screened with a TB symptom questionnaire. They were eligible for the survey based on being a resident or visitor who had lived in a household within a cluster for the most of the last two weeks preceding the census, conducted two months prior to the prevalence survey. The findings from the prevalence survey indicate weaknesses in the diagnostic pathway and implies people with TB go undetected through the health system.

Figure 1. 3: Cascade of prevalence survey participants who did a sputum test



Source: Ghana national population-based TB Prevalence survey report ^[14] (data used with permission from Ghana's national TB control programme). No=Number, HF=health facility

Many studies have described the health facility contribution to delayed or missed diagnosis of TB; however, the methodologies used are mainly cross-sectional in design [24, 25]. These mainly involve interviews with TB patients on treatment about when they developed symptoms and when they were diagnosed in a health facility [26-28]. Most often data related to individual level characteristics of these patients are used to determine associations with health system delay (normally dichotomized based on a mean or median time interval from the time a patient accessed care at the health facility until they get a TB diagnosis or start treatment) [26]. These studies have several limitations, including relying on the recall of TB patients already on treatment, which might introduce recall bias in remembering when they developed symptoms and the steps they went through to get a final diagnosis. Moreover, if a study recruits TB patients already on treatment, this implies that persons with symptoms suggestive of TB who attended a health facility but did not get diagnosed by the health system are not studied. Therefore, the factors associated with their inability to get diagnosed are

not determined but such factors are rather relevant for health system improvement.

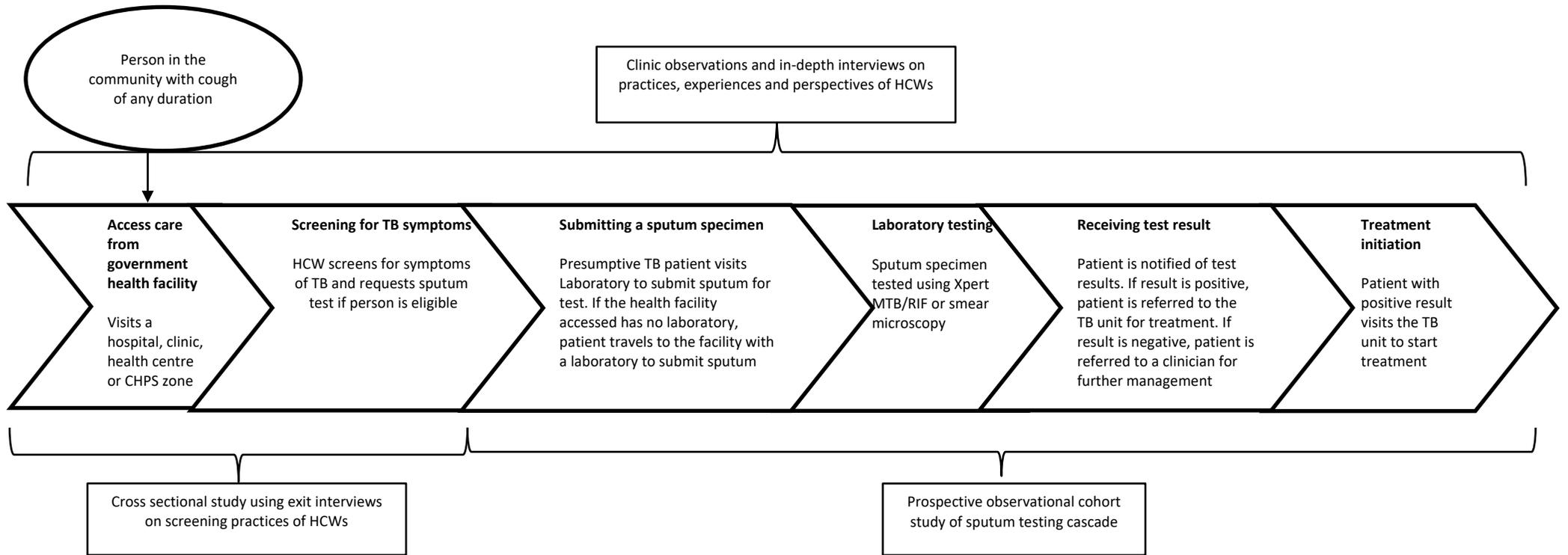
Although several studies have shown that only small proportions of people with symptoms suggestive of TB do a sputum test, none of these studies have been able to differentiate between if a patient was asked to do a sputum test or actually did a sputum test [29-33]. Few studies have focused on persons with cough who have been asked to do a sputum test by a HCW or patients exiting the health facility after seeking care to investigate the TB care cascade to find out at which points patients are missed or delayed in being diagnosed. In addition, most studies on pre- treatment or treatment delays have either a quantitative or qualitative design with limited studies employing both quantitative and qualitative designs to understand better the delays in the TB care cascade and the barriers and practices within health facilities that facilitate these delays or missed diagnosis.

The steps in the pre-diagnostic cascade prior to a sputum specimen being submitted at the laboratory are much less studied compared to the post-diagnostic cascade but are very important. This is because if a person with symptomatic TB who accesses care from a health facility never gets diagnosed, then they will not be treated. This is evidenced by findings from Ghana's national TB prevalence survey as illustrated in figure 1.3 above. A person with symptomatic TB who never gets diagnosed may die from the disease or remains a source of infection to others. Therefore, the steps in the pre-diagnostic cascade were the focus of our study. To better understand the gaps, we designed a set of studies to examine the steps in the cascade prior to submission of a sputum sample, namely (i) whether people who seek care from health facilities are screened for symptoms of TB by a HCW and if eligible, whether a sputum test is

requested; (ii) whether patients who have been asked to submit a sputum by a HCW, do actually submit a sputum and (iii) identify barriers within the health system that hinder early diagnosis and treatment of TB (Figure 1.4). The TB care cascade encompasses patient health-seeking behaviour and access to care as well as activities and practices within the health system. Factors associated with delayed/missed diagnosis or treatment can either be patient-related or health system-related.

Every unidentified person with pulmonary TB, as well as every delayed diagnosis, is a missed opportunity to stop the spread of the disease and improve health outcomes [34]. It is important to look holistically at TB case finding activities at health facility level. This includes cough screening practices of HCWs, requesting a sputum test, submitting a sputum sample, the testing pathway, treatment initiation and barriers to TB case finding from the perspective and practices of HCWs to identify the gaps and recommend appropriate interventions. This PhD study focused on health system-related factors especially on the steps before a sputum is submitted in order to identify modifiable factors that contribute to delayed or missed TB diagnosis in health facilities and suggest interventions to reduce diagnostic and treatment delay for people with TB. We focused on health system-related factors because we believed they may be more important (e.g. system in place for submission of sputum for a TB test in facilities without a TB diagnostic laboratory) and are more rarely studied. Also, some health system factors (e.g. adherence to guidelines) may be easier to modify than patient behaviours and attitudes.

Figure 1. 4: Pathway to TB diagnosis and treatment in Ghana and components of study



CHPS (community-based service delivery point) = community health planning services, HCW= healthcare worker, TB= tuberculosis

1.6 Thesis aim and objectives

1.6.1 Aim

The aim of the thesis was to identify barriers in the pathway to TB diagnosis and treatment initiation for people presenting to health facilities with symptoms suggesting TB in Ghana, and make recommendations for strengthening of health systems to improve TB case finding in health facilities.

1.6.2 Specific objectives

The specific objectives to address the aim were:

1. To determine the proportion of health facility attendees eligible for sputum test according to national guidelines who were asked to do a sputum test by a HCW and the prevalence of having sputum positive on Xpert MTB/RIF among health facility attendees who met the criteria for sputum test according to study criteria.
2. To determine the proportion of patients with a request for sputum test who submitted a sputum for testing, the time from test request to submitting sputum, and factors contributing to non-submission of sputum for testing.
3. To compare the time from test request to submitting sputum among patients attending a health facility with vs. without a co-located laboratory.
4. To explore HCWs' perspectives concerning barriers to TB case finding in health facilities, their experiences, practices and suggested solutions for improvement.

1.7 Thesis structure

This thesis follows the research paper style format. A review of the literature is presented in chapter 2 and focuses on health systems' delay or missed diagnosis of TB. A general overview of the study setting as well as the quantitative and qualitative methods employed are presented in chapter 3. In chapter 4, results of an initial situation assessment at the study health facilities are presented. Chapters 5, 6 and 7 are presented as research papers.

Chapter 5 addresses objective 1 which was to determine the proportion of health facility attendees who are eligible for a sputum test according to the national standard operating procedures for case detection who were asked to give a sputum by a HCW in outpatient clinics of a municipal hospital, and to determine the prevalence of having a sputum positive result on Xpert MTB/RIF in this study population. This used a cross sectional study design with exit interviews of persons who sought care from the health facility for their own health and had at least one TB-related symptom. This was to determine TB symptom screening and requesting for sputum testing practices within the health facility. The use of exit interviews was a more robust way to determine if symptomatic patients were asked to do a sputum test compared to using a retrospective approach. It helped reduce the recall bias since patients were interviewed immediately after consultation with a HCW rather than after an interval.

Chapter 6 addresses objectives 2 and 3 which aimed to determine the proportion of patients with a request for sputum test who actually submitted a sputum for the test and the time from test request to submitting a sputum comparing between health facilities with vs without co-located laboratory. This was to enable us to identify steps in the testing cascade where presumptive TB patients (a patient who presents with

symptoms or signs suggestive of TB [35]) might be missed or delayed in getting a diagnosis, and factors associated with missed or delayed diagnosis. We used a prospective cohort study design to follow up on persons who had been asked to do a sputum test to find out if they got the test done. This was to investigate what happens after the sputum test has been requested. The prospective cohort design was to ensure that the sequence of events in doing a sputum test could be followed, to determine factors that might hinder people from doing the test.

Chapter 7 addresses objective 4 which was to explore the barriers to TB case finding in health facilities from the perspective, experiences and practices of HCWs. This was a qualitative study where we used clinic observations and in-depth interviews with HCWs. Since we were focusing on the health system, we needed to find out the perspective of HCWs on TB case finding and observe their activities within the health facility to determine if there were any barriers to TB case finding especially during the pre-diagnostic phase. We used clinic observations and in- depth interviews to help us understand and confirm the barriers to TB case finding in health facilities.

Finally, chapter 8 presents the summary of the findings and reflections on these findings in relation to existing literature. It also presents the implications of this work for TB case finding in health facilities, the conclusions drawn and recommendations made.

The PhD study was thus designed to have three components: a cross sectional study using exit interviews; a prospective observational cohort study; and a qualitative study using clinic observations and in-depth interviews. The different components of the study are illustrated in figure 1.4 above.

1.8 Contributions to the work presented in this thesis

1.8.1 Conception, study design, protocol development, and regulatory approvals

The conception of the idea for this research study started at the beginning of my PhD journey from discussions with Prof Alison Grant on issues bordering around improving TB case finding in Ghana. This was after I had read the national TB health sector strategic plan for Ghana, 2015-2020 to identify areas in TB control that were of priority to the national TB control programme (NTP) to improve TB case finding. Once we decided what was relevant and feasible to do in the context of a PhD study, I developed the study protocol with support from Dr Daniel Grint who provided statistical advice and Dr Virginia Bond who advised on the qualitative component of the study. I contacted the NTP and had discussions with the programme manager, Dr Frank Bonsu, who made inputs to the study protocol and agreed to be the local supervisor for the data collection in Ghana. Once all my supervisors approved the study protocol, I applied for ethical clearance from the Ghana Health Service Ethics Review Committee and the London School of Hygiene & Tropical Medicine Ethics Committee. I also contacted the regional and district health directorates of the study area as well as the management of all health facilities the study was to be conducted to seek permission. I visited the two health facilities where the study was to be conducted and based on preliminary findings relating to TB case finding activities in these facilities, I had to apply for an amendment to the study protocol to include three more health facilities which was approved by the ethics committees.

1.8.2 Study management and data collection

It was my primary responsibility to manage all the three components (cross-sectional study using exit interviews, prospective observational cohort study and qualitative

study using clinic observations and in-depth interviews) of the study. Open data Kit (ODK) which is an electronic platform for data collection was used for data collection in this study and since I had no knowledge of ODK at the beginning, Dr Chrissy Roberts was very supportive in explaining how it works and provided resources to enable me develop the case report forms (CRFs) in ODK format.

I designed and coordinated the piloting of all CRFs as well as writing standard operating procedures (SOPs) for all activities to be carried out in the field and developed a training manual. I recruited research assistants and trained them on the study protocol, CRFs and SOPs. I was involved in the day-to-day activities of data collection: coordinated and supervised data collection, conducted some participant interviews for the cross-sectional and prospective cohort studies, conducted all in-dept interviews for the qualitative study and conducted all clinic observations with support from a colleague, Dr Clement Narh from the School of Public Health, University of Health and Allied Sciences, Hohoe, Ghana.

1.8.3 Data management & analysis

I reviewed all CRFs for consistency and missing data daily after data were collected before uploading onto a secure server. I managed all the data for the different components of the study and generated dashboards in Excel spreadsheets to monitor data collection. All analyses presented in this thesis were done by me with advice from Dr Daniel Grint. I developed the do- files for the different data sets in STATA version 15 (Stata Corp, College Station TX, USA) and was assisted in developing some of the codes by Dr Daniel Grint and Dr Clement Narh.

1.8.4 Multi-authored papers

Three papers are presented in this thesis. Each paper represents a component of the study. I carried out all the analyses, wrote the drafts for all the papers and maintained overall control of the content of the papers. Dr Daniel Grint made important suggestions to statistical methods, presentation of results, table structure and figures for papers 1 and 2 while Dr Virginia Bond made important suggestions to the content of paper 3. Prof Alison Grant offered guidance and made important suggestions to the overall content of all three papers. All authors reviewed and approved the final manuscripts prior to submission.

Prof Alison Grant was involved at every stage of the development of this thesis and critically reviewed and provided input on all the material presented here.

Chapter 2: Literature review

2.1 Introduction

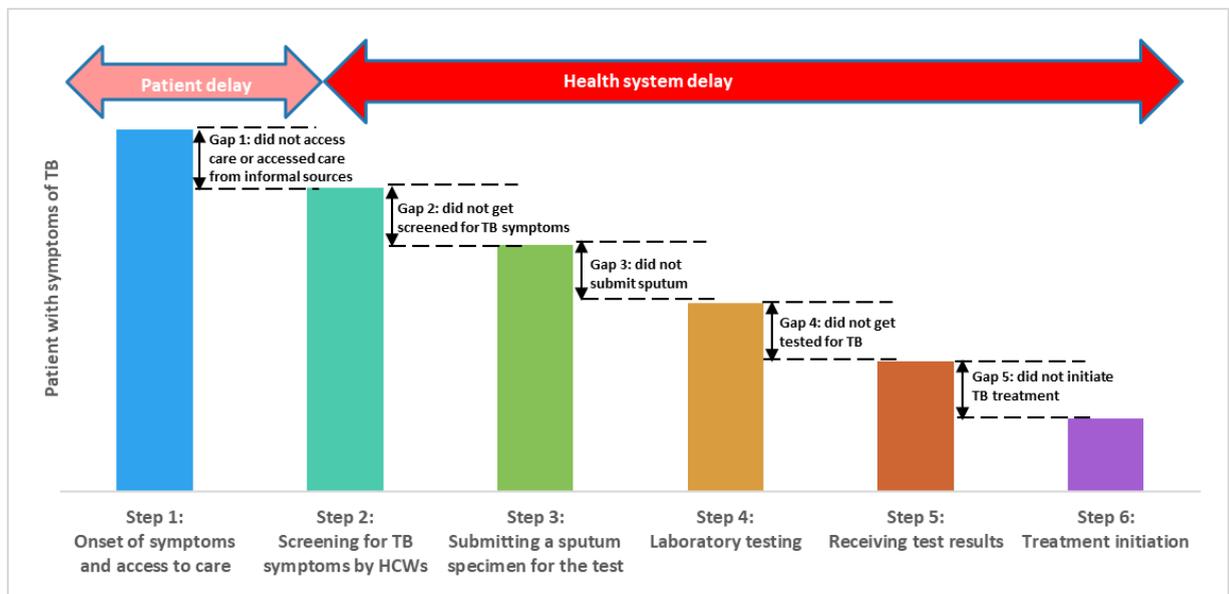
This chapter reviews the literature on delayed or missed diagnosis of TB.

Early diagnosis of TB disease and prompt initiation of treatment are key elements for an effective TB control programme. It was estimated historically that a patient with untreated smear positive pulmonary TB may infect on average more than 10 persons per year [36], however, this number has been found to be lower (2.6-5.8) in surveys conducted in China, Philippines and Republic of Korea in the era of established TB control and efficacious TB treatment regimens [37]. It beholds on people in the community with symptoms of TB to seek appropriate health care, and it is the responsibility of health facilities to diagnose people with TB, initiate them on treatment and ensure they are cured. However, the ability of people to recognize their TB symptoms and their health seeking behaviour can often lead to missed or delayed diagnosis of the disease. Likewise, strategies such as passive case finding (identifying TB among people who are actively seeking care in a health facility [38]) employed by TB control programmes to identify people with TB can also lead to missed or delayed diagnosis of the disease. Passive case finding has been the main strategy employed by most TB control programmes to identify persons with TB in health facilities. Unfortunately, passive case finding has not been very effective especially in lower-and middle- income countries (LMICs) [39]. The effectiveness of this strategy is dependent on the health seeking behaviour of patients, the efficiency and ability of HCWs to identify symptoms, and the quality of laboratory facilities [40]. Health facilities thus play a vital role in TB diagnosis and treatment and ultimately reducing TB incidence. There is enormous literature that has documented factors which lead to health system diagnostic and treatment delays for TB patients. Delays can occur at different points in

the diagnostic pathway shown in figure 2.1 below.

This literature review is focussed on factors within health facilities that lead to missed or delayed diagnosis at the various steps in the pathway especially the steps in the pathway prior to diagnosis. It also provides a brief overview of factors that affect what happens prior to a patient visiting a health facility. The reasons for the focus being on health systems are explained in Chapter 1.

Figure 2. 1: TB care cascade and gaps where patients are missed or delayed in health facilities



Source: modified from model of Subbaraman *et al*, 2019 ^[41]. TB=tuberculosis, HCW=healthcare workers

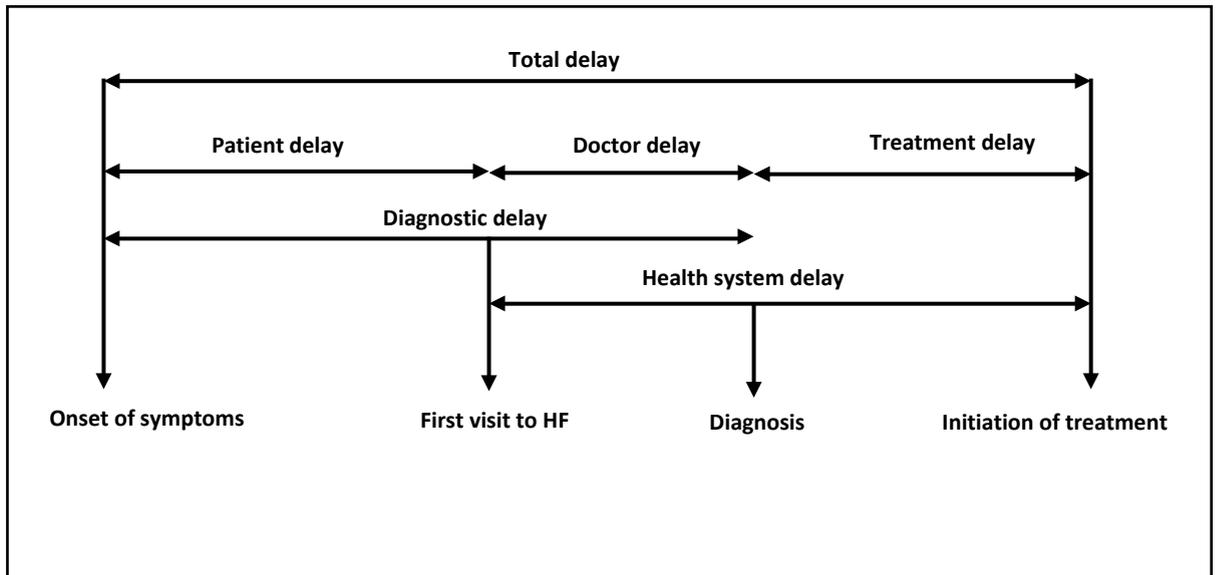
2.2 Types of delay in diagnosis and treatment of TB

Studies reporting on delays in TB diagnosis and treatment use different terms to classify delay as shown in figure 2.2. Most studies classify delay into three main categories: patient delay (time interval between the onset of patient symptom(s) and the patient's first consultation to a healthcare provider), health system delay (time

interval between the patient's first consultation with a healthcare provider and initiation of treatment) and total delay (the sum of patient delay and health system delay or time interval from onset of symptoms to initiation of treatment) [32, 42-44]. Other studies include categories such as diagnostic delay (time interval between onset of symptoms and diagnosis of TB), doctor's delay (time interval between first visit to healthcare provider and diagnosis of TB). TB diagnosis is normally the day a patient is confirmed to have TB by the laboratory or a clinician's judgement and treatment delay is time interval between diagnosis of TB to initiation of treatment [34] (Figure 2.2).

These delays are mostly measured in days [32, 42, 43, 45] or weeks [33] and there is a lack of consensus in literature about what duration between onset of TB symptoms and diagnosis is considered as delay [46]. Some studies use the median duration of their findings as a cut-off point and dichotomize it into delay or no delay. Others put a specific time limit such as 2 weeks (15 days), 3 weeks (21 days) or 1 month (30 days) [39]. However, the WHO recommends that a TB diagnosis within 2-3 weeks of onset of symptoms is acceptable delay [47]. Notwithstanding the type of categorization used, both patients and health systems can contribute to delayed diagnosis of TB by patients deferring their presentation to health care and health systems missing the opportunity to diagnose TB at the right time [46].

Figure 2. 2: Conceptual framework of delays in diagnosis and treatment of tuberculosis



Source: Bello *et al*, 2019 ^[34]. HF= Health facility

2.3 Method of literature review

The aim of the literature review was to describe the factors that contribute to delayed or missed diagnosis of TB focusing on the different steps and gaps in the pre-treatment TB care cascade: onset of symptoms and health seeking behaviour of patients; TB screening practices of HCWs and adherence to guidelines; laboratory diagnosis; receiving of test results, and treatment initiation as shown in figure 2.1.

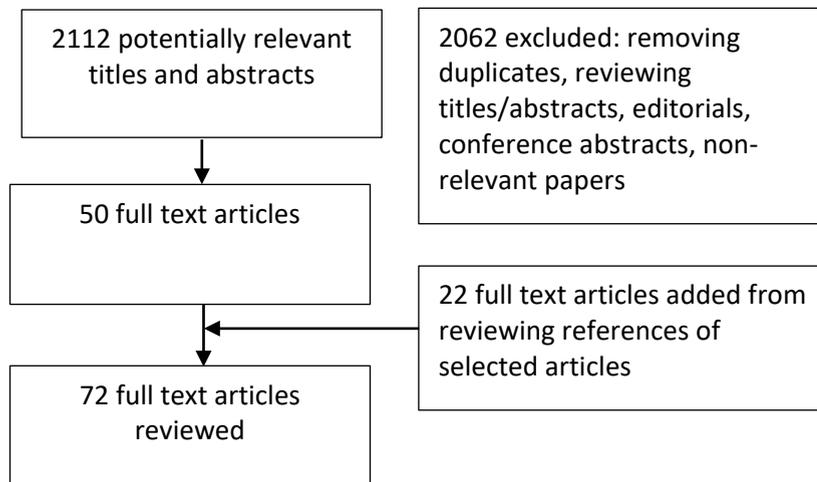
This literature review was based on a search strategy using relevant search terms on health system delay or missed diagnosis of TB conducted in two databases namely Medline and Embase for the period 2000-2020. The search terms and strategy used in Medline database are shown in table 2.1.

Table 2. 1: Medline database search terms and strategy

	Search terms
1	Tuberculosis
2	delayed diagnosis
3	missed diagnosis
4	2 OR 3
5	case detection
6	case finding
7	5 OR 6
8	testing pathway or diagnostic pathway
9	testing cascade or diagnostic cascade
10	8 OR 9
11	healthcare system
12	Hospital
13	Clinic
14	health facility
15	health cent*
16	11 OR 12 OR 13 OR 14 OR 15
17	1 AND 4 AND 7 AND 10 AND 16

The search retrieved 2112 potentially relevant titles and abstracts for health system delay and missed diagnosis of TB. After removing duplicates, reviewing titles/abstracts and excluding all other papers that were not relevant, 50 full text articles were reviewed. A search of references of the selected articles and other sources added 22 other full text articles. The literature review was thus based on 72 full text articles as shown in figure 2.3. At the end of the literature review, 18 out of the 72 full text articles reviewed are summarized in table 2.2. These 18 articles were selected based on their definition of health systems delay being the time between first contact with a public or private health facility and diagnosis of TB or initiation of TB treatment. Studies that included pharmacies, drug stores and traditional healers as part of health systems delay are not included in the table.

Figure 2. 3: Flow chart describing the selection of studies included in the literature review



Factors contributing to patient and health system delays are presented below, organised according to steps in the TB care cascade:

2.4 Health-seeking behaviour of patients (onset of symptoms and access to care)

Health care seeking behaviour is how people in the community seek help from formal or informal sources for their symptoms to attain or regain good health and to prevent illness [48, 49]. People in the community who develop symptoms of TB will either access care or ignore their symptoms. Several studies have shown TB patients delay in seeking care for their symptoms (patient delay). Studies conducted in Ethiopia, Peru and Ghana have reported median patient delays of 20, 57 and 59 days respectively [26, 42, 50] which were all said to be unacceptable delays according to the definition of patient delay used in these studies. A systematic review and meta-analysis on evidence of delay in diagnosis and treatment of TB from 78 countries globally found, among 79 studies (524,462 patients) enrolling a median of 234 patients, patient delay ranged from 5 to 1097 days. The pooled mean patient delay was 81 (95% CI: 70–92) days [34]. For as long as people in the community with symptoms of TB do not seek care, those with

pulmonary TB will continue to be a source of infection to others. There are several reasons for which people do not seek care for their TB symptoms and these are outlined below:

2.4.1 Poor knowledge/awareness of TB symptoms

Studies have found that poor knowledge or awareness of TB symptoms is a main reason for which people do not seek care. A systematic review and meta-analysis conducted in China found 17 out of 29 studies reporting lack of knowledge or awareness as a factor for which TB patients delayed in seeking care [51] and a similar one conducted in LMICs found seven out of 40 studies reported similar findings [39]. TB symptoms are very non-specific, and many diseases present with cough or weight loss or both. Therefore, most people do not recognize them as symptoms of TB and this often led people to think their symptoms were symptoms of an upper respiratory tract infection which will self-resolve [33, 52-55]. Mostly, because people do not recognise their symptoms as TB-related, they self-medicate or seek care from different sources such as traditional healers, faith-based healers, pharmacies/drug stores, drug peddlers or private clinics which do not provide TB services (non-formal providers) instead of government health facilities that provide these services (formal providers) [26, 33, 42, 45, 50, 54, 56-60]. Seeking care from non-formal providers often leads to patient delay. In Northwest Ethiopia, Asres *et al* found in East Gojjam zone that due to lack of awareness of TB symptoms, more than half (53.4%) of TB patients in their study delayed seeking care but rather resorted to traditional medicines [61]. Also, Gebreegziabher *et al* found in West Gojjam zone that TB patients who first consulted non-formal providers had a median patient delay of 60 days compared to 14 days for those who first consulted formal providers [50]. Other studies have reported that first seeking care from non-formal providers led to patient delay [42, 50, 54]. However,

when patients felt their symptoms were severe, they visited a health facility because they thought their illness was at its terminal stage [59].

2.4.2 Access to health facilities

One of the reasons for which patients with symptoms of TB delay in seeking health care from formal sources is the availability of health facilities and this is mostly a challenge for people who live in rural areas. Community members and TB patients in a qualitative study conducted in Nepal said most health centres were in areas that were not easily accessible [62]. This was particularly because politicians who lobby for these health facilities especially in rural areas ask that the facilities are built in their village or close to their residence making it difficult for the majority of people to access them [62]. They also complained that the geographical nature of the area where most villages are located in mountainous areas and where settlements are sparse with uphill routes, forested paths towards health centres coupled with the long distance mostly discouraged patients from accessing health services. The difficult terrain was further complicated by the lack of roads for vehicles and means of public transportation. Similarly, a study among pulmonary TB patients in rural Nigeria reported there was poor availability of public health facilities and this caused patients to walk more than one hour to the nearest public health facility to access care [60]. This caused patients in rural areas to resort to non-formal provider [42]. Again, the systematic review on delay in diagnosis of pulmonary TB in LMICs also revealed five studies reported long travel distance to public health facilities and three studies reported rural residence as determinants of patient delay. The reason for this could be that mostly in rural areas they have a health post which is the lowest level of care and these facilities do not offer TB services so patients have to travel a longer distance to access care from health centres or hospital [39]. Several studies also reported long travel distance to the

nearest health facility and rural dwelling as risk factors for patient delay in seeking care [24, 33, 43, 63, 64].

Also, as distance to the health facility can result in patient delay, it can also lead to unfavourable outcomes for people with the disease. Robsky *et al* in their retrospective cohort study in Uganda among all patients initiating TB treatment in six health facilities reported that unfavourable treatment outcomes occurred in 20% of TB patients and those living ≥ 2 km from the facility had increased risk of death compared to those who lived < 2 km from the facility [65]. Long distance to the health facility could have led to delayed diagnosis causing severity of illness and invariably leading to increased risk of death as explained in the Ugandan study [65].

2.4.3 Financial constraints and opportunity cost

TB is considered as a disease of poverty because it mainly affects poor and socially disadvantaged people [39]. In a qualitative study in Peru on social determinants underlying TB diagnostic delay among TB patients, it was universally agreed that indirect and direct costs associated with healthcare visits often contributed to patients' delay in seeking professional care [58]. Even though TB services in Peru were free, the anticipated cost of a visit to a hospital often deterred people from seeking care from the hospital. Also, most participants admitted they will prioritize working over seeking professional medical attention when sick. This is because they needed the income to take care of their families. Often because most people in resource-constrained settings struggled to maintain sufficient household income, they fear seeking care from health facilities because that could lead to repeated visits to the hospital which could cause them to lose their job so they prefer to self-medicate [58]. This study however excluded extrapulmonary TB (EPTB) patients who were even more

likely to incur more cost, due to longer delay in diagnosis resulting in repeated visits, than pulmonary TB patients. Similarly, in Nepal, a qualitative study found that although attending and accessing health care services was free, indirect costs associated with travelling, and opportunity costs relating to household chores or employment, led to patient delay [62].

In Ghana, Osei *et al* found that patients who were not medically insured were at risk of patient delay. People who were poor were those who could not afford medical insurance and this mostly discouraged them from seeking prompt medical care for their TB symptoms [26]. A lack of medical insurance as a risk factor for patient delay was found in Arkhangelsk, Russia where they also reported that out of pocket payment for TB services such as liver protection drugs and computerized tomography (CT) scan was a reason for which patients did not seek medical care [53]. A systematic review in Ethiopia on health-seeking behaviour among presumptive TB patients found lack of money as one of the main reasons why patients delay in seeking care from formal health providers [66]. Severe socioeconomic hardships and low-income levels have all been reported as determinants of patient delay in TB care [24, 64, 67]. Bogale *et al* in their study in Ethiopia found that increased household income was associated with a shorter patient delay [25].

2.4.4 Stigma

Stigma has been reported to be an important factor in delaying healthcare seeking despite decades of public health efforts. In Malawi, a qualitative study found perceived TB stigma to be linked with HIV in two forms. Firstly, there was the general community belief of TB and HIV coexistence where it is assumed that a person with TB is HIV positive leading to stigmatization of TB patients. Secondly, the management for a

person diagnosed with TB includes having an HIV test but this caused fear in patients. Most patients were afraid of having a positive HIV test result because of the stigma associated with it, so they feared to seek care from the hospital for a cough [68]. In the systematic review on delayed diagnosis of TB in LMICs, three studies reported stigma relating to HIV being associated with TB, and two studies reported on perceived social stigma of TB [39]. In Peru, Bonadonna *et al* reported that TB patients faced discrimination within their communities, causing fear among people with cough of a possible diagnosis of TB [58] and in North Ethiopia, more than half (59.7%) of TB patients who delayed in seeking care had high perceived stigma [59]. Other studies in Nepal, Ghana and Ethiopia all reported high TB- associated stigma and for fear of being diagnosed with TB, patients with TB- related symptoms did not seek care until their symptoms became worse [26, 32, 62]. Stigma, therefore, could cause delay in care seeking for patients with symptoms of TB because of the associated stigma relating to HIV. This stigma could be individual level stigma or stigma from the community.

2.5 Health system related factors contributing to delayed or missed diagnosis of TB

The health system plays a crucial role in the identification of people with TB and initiating them on treatment. However, the organization and quality of health care can lead to delayed or missed diagnosis of TB [69].

2.5.1 Practices of healthcare workers

2.5.1.1 Index of suspicion of TB among healthcare workers

Some studies have shown that the reason why there is delayed or missed diagnosis of TB in health facilities is because of the low index of suspicion of the disease among HCWs. Several factors account for this and they include:

2.5.1.1.1 Clinical presentation of disease

Persons with TB can present with non-specific symptoms thus making it difficult for the disease to be easily identified by HCWs. The coexistence of cough with other chronic diseases [54, 70], EPTB presenting with a wide range of clinical symptoms [42, 43], smear negative TB [50, 71, 72], fever and short duration of cough [73] makes it difficult for HCWs to recognize these less common presentations of TB and patients are often misdiagnosed. These clinical presentations are non-specific since very many diseases can result in cough and / or weight loss and therefore might not trigger suspicion of TB by HCWs. Such patients are likely to suffer diagnostic delay and may need to make repeated visits to the health facility before they finally get diagnosed with TB. The non-specific symptoms are one challenge faced by clinicians in high income, low TB incidence countries where the absence of respiratory symptoms might not trigger a suspicion for TB. Even when patients have respiratory symptoms or classical TB symptoms like prolonged cough, they are often not recognized because TB is a rare disease in low incidence countries. Therefore, even in low TB incidence countries, not all patients with TB get a prompt and rapid diagnosis [46].

2.5.1.1.2 Type of health facility visited by a patient

Literature has shown that persons with symptoms suggestive of TB who first visit lower level public health facilities (primary health centres, clinics or health post) or private providers (private clinics, pharmacies/drug stores and traditional healers) might experience diagnostic delay compared to those who visit secondary and tertiary level health facilities [25, 27, 33, 42, 43, 50]. These studies claim that HCWs at lower levels of care are mostly less qualified clinical staff with a low index of suspicion of TB among persons presenting with symptoms [25, 27, 33, 42, 43, 50]. Also, clinical staff in private health facilities lack adequate knowledge in TB diagnosis and management [56, 60].

Since TB is not suspected in these lower-level facilities and private providers, they resort to treatment with antibiotics for upper respiratory tract infections [45, 74, 75]. At times, inappropriate antibiotic treatment like the use of fluoroquinolones can modify the clinical picture and give patients temporary relief; however fluoroquinolones monotherapy in a person with TB may result in acquisition of fluoroquinolone-resistant TB [26, 45].

The low index of suspicion leads to a cycle of repeated visits to different care providers or at times to the same care provider. This has been demonstrated by a number of cross-sectional studies: in India, Ghana, Ethiopia and Mozambique, 50%, 59%, 70% and 74% respectively of patients taking TB treatment reported that they were diagnosed after two or more health visits to a health care provider [26, 42, 54, 74]. Because these studies recruited TB patients on treatment, presumptive TB patients who accessed care but did not start TB treatment were not studied. Such patients may have made more repeated visits to health facilities without being tested. There is a need for prospective cohort studies enrolling presumptive TB patients that can directly measure the health system delays and factors associated with these delays. The cross-sectional designs prevented the investigators from measuring directly the delays caused by these multiple visits to different or same health providers. Evidence from Uganda showed the median number of visits before a TB diagnosis was 4 (range:1-30) and 97% of study respondents consulted on average two providers before a diagnosis was made [76]. Some patients even make as many as five visits to a health facility before being diagnosed with TB. This is evidenced by a study conducted in Ethiopia in 2016 among 296 adults visiting health facilities for TB treatment where they found more than half of patients sought care from more than five health care providers prior to TB diagnosis, however, delay in diagnosis was shorter among people who were HIV positive [25]. A

study in Iran on diagnostic error found among 158 hospitalized TB patients, 42.3% were referred to four or more physicians before a diagnosis of TB was made [77]. These multiple visits or referrals may result in high expenditure for patients and cause them to drop out of the diagnostic pathway [78]. Therefore, the type of health facility a presumptive TB patient accesses care may determine whether they get a TB diagnosis and how soon they get the diagnosis.

2.6 Screening for TB symptoms and requesting for sputum test by HCWs

The International Standards for TB Care (ISTC), 3rd Edition developed by TB Care 1 and endorsed by almost all TB programmes worldwide aims to describe a broadly accepted level of care that all public and private sector providers should employ in managing patients with symptoms of TB, those who have TB or at increased risk of developing TB [79]. The standards that focus on TB diagnosis recommend that all patients with unexplained cough lasting two weeks or more should have at least two sputum specimens submitted for smear microscopy and be treated if the test result is positive for acid-fast bacilli (AFB). This was before the advent of Xpert MTB/RIF because now in most places, only one sputum is requested for a TB test. However, several studies have shown that HCWs do not adhere to these guidelines. In Zambia, a national TB prevalence survey showed only 12.1% of persons with cough of more than two weeks reported being asked to do a sputum microscopy test [29]. Other studies including prevalence surveys and cross-sectional studies in Uganda, Ghana and Ethiopia showed 15%, 25% and 44% respectively of persons reporting symptoms of TB did a sputum test [32, 33, 80]. The Ghana study was a national TB prevalence survey and comparable with the Zambian study in that they both recruited representative sample of the general population while the Ugandan and Ethiopian studies were cross-sectional

studies that recruited TB patients already on treatment. A limitation with all these studies is that they did not differentiate between a patient being asked to do a sputum test by a HCW and a patient actually going ahead to do a sputum test. This is because a patient could be asked to do a sputum test but due to several factors, they might not do the test. It is important to determine if it is the HCWs who are not requesting the sputum test or whether patients encounter challenges that prevent them from doing the test. These findings will help inform appropriate intervention to reduce diagnostic delay.

In South Africa, a pragmatic cluster-randomised trial (the XTEND trial) aimed to determine whether replacing microscopy with Xpert as first line test for TB reduced six-month mortality among people being investigated for TB. An ancillary study of this XTEND trial was designed using exit interviews among patients to determine if the new diagnostic method influenced HCWs practice in requesting a sputum test, but findings showed only slightly more than a quarter (28.2%) out of 3604 participants self-reported being asked to do a sputum test after they reported their TB symptoms to a HCW [81]. In a second study in South Africa that sought to determine if HCWs asked about respiratory symptoms related to TB, among 423 adults exiting health facilities with respiratory symptoms, the authors found 21 (5%) were culture-positive for TB. Of this 5%, none had sought care at the facility for their respiratory symptoms, none were asked about respiratory symptoms during their visit and none were asked to produce a sputum sample [82]. The limitation of this study was that there was a high non-response rate of 62%, possibly introducing selection bias. If the non-responders differed significantly from the responders, then that could affect the outcome. Even though the non-response rate was high, the study still showed that HCWs screening practices of TB-related symptoms was sub-optimal. Yet another study conducted in

South Africa in 2015 investigating the number of pulmonary TB patients missed by primary health care clinics estimated that the health system missed 62.9– 78.5% of TB patients attending primary health clinics for TB-related symptoms and 89.5–100% of those attending a clinic for other reasons. This was attributed to low rates of TB screening and testing by the health system [83]. However, this study was not able to report a response rate because the investigators could not fully account for the number of persons eligible for the study and the number of persons who declined to be part of the study making it difficult to judge if there were any biases. Several cross-sectional and qualitative studies have reported patients with TB not appropriately screened and a sputum test not requested for those who are eligible [24, 52, 63, 68, 84, 85].

The reasons for which HCWs might not screen for symptoms of TB or request a sputum test are varied and include:

2.6.1 Lack of diagnostic facilities

Some health facilities especially at the lower levels of care do not have diagnostic facilities for sputum testing and are not able to confirm if a person has TB [33, 42, 71]. In addition, in most LMICs, the referral systems for referring symptomatic patients to facilities that have diagnostic capacity may not work effectively [51, 86-88] and this leads to diagnostic delay. Moreover, the location of most TB diagnostic facilities is mostly far from the patient's residence or community making it difficult for a patient to travel to these facilities for a TB diagnosis or to complete follow up diagnostic procedures since a TB diagnosis requires more than one visit to the health facility. A number of studies have reported distance to the diagnostic facility as a significant factor for health system delay [26, 27, 32, 39, 62, 64, 67, 75, 88, 89].

2.6.2 Inadequate human resources

Qualitative studies among HCWs on barriers they encounter in TB diagnosis have shown shortage of human resources can lead to not requesting a sputum test. This is because few staff result in high workload especially at outpatient department (OPD) of health facilities [53, 68, 90]. This prevents them from properly evaluating patients with symptoms suggesting TB and requesting a sputum test [53, 68, 90]. Also, shortage of experienced staff and constant turnover of staff might lead to the use of less experienced staff who might not screen for cough or request a sputum test [51, 87, 91-93]. Other studies have shown that the shortage of staff and high workload coupled with various activities competing for HCWs attention are some of the reasons for not requesting a sputum test [87, 90, 94]. In some instances, inadequate staff leading to high workload resulted in poor patient-provider interaction causing underassessment of patients for symptoms of TB [95].

2.6.3 Fear of infection

In some settings, fear of infection with TB caused some HCWs to neglect presumptive TB patients leading to inadequate screening of patients and requesting sputum tests. In Malawi, HCWs in a qualitative study said fear of infection at times made some HCWs not very approachable, so patients were not comfortable telling them their symptoms leading to them not being fully assessed [68]. In Uganda, Ghana and Mozambique, qualitative studies found HCWs fear of infection to affect TB diagnosis [93, 96-98]. In Mozambique, fear of infection caused HCWs not to want to contact or manage TB patients. They neglected TB patients because of stockouts of N95 respirators [93]. In Ghana, fear of infection caused HCWs to shun, avoid or maltreat TB or presumptive TB patients. There were times when TB patients were wrongly accused of spreading infection. HCWs claimed TB patients spat around indiscriminately and started to

cough as soon as they got closer to a HCW with the intention of infecting the staff [98]. Cattamanchi *et al* in Uganda reported that laboratory staff did not want to process sputum specimen for testing for fear of getting infected with TB, and that other HCWs were deeply concerned about the risk of contracting the disease from their patients causing fear of working in the TB wards [97]. In all these studies, HCWs felt it was not worth it to risk their lives doing TB-related work since no incentive packages or compensation would be given to them if they got infected with TB.

2.7 Laboratory testing for TB

Delays or missed diagnosis of TB can occur at the point of doing the sputum test. Literature from both quantitative and qualitative studies have shown factors relating to laboratory testing that can cause delay. Some of these factors are:

2.7.1 Multi-day sputum smear microscopy testing

Per the design of the testing pathway for TB, a patient with symptoms suggestive of TB may be required to make at least two visits to the laboratory to have a sputum test done. In some health facilities, a patient needs to visit the laboratory to produce a spot sputum specimen and return the following day with an early morning specimen before they can receive a test result. In some instances, they might need to make a third visit for their test result. The need for multiple visits can lead to loss to follow-up [97, 99]. Patients might be too weak or may not have money for transportation to return to complete this testing pathway and initiate treatment for those with a positive test result. Chandra *et al* in their study in India suggested the use of two spot sputum specimen for smear microscopy on the same day to reduce patients failing to return to complete the diagnostic procedure or even being lost to follow-up [100].

2.7.2 Sensitivity of the diagnostic method

In most LMICs, sputum smear microscopy is still the main diagnostic method for TB. This technique is known to have a low sensitivity and can lead to false negative results especially in patients with HIV [91, 101]. The inability of this technique to confirm TB in patients with symptoms can lead to delayed or missed diagnosis. In view of the low sensitivity of sputum smear microscopy, Xpert MTB/RIF was introduced and it has a higher sensitivity [102] and a shorter turn-around-time [103] compared to smear microscopy. The use of Xpert MTB/RIF is intended to reduce missed diagnosis and improve TB case detection. Several studies have shown that Xpert MTB/RIF is a robust, sensitive and specific test for accurate diagnosis of TB as compared to conventional tests like sputum smear microscopy [104-108]. A systematic review conducted in 2014 on Xpert MTB/RIF assay for pulmonary TB and rifampicin resistance in adults had among other objectives to assess the diagnostic accuracy of Xpert MTB/RIF for pulmonary TB detection, where Xpert MTB/RIF was used as both an initial test replacing microscopy and an add-on test following a negative sputum smear microscopy result [109]. The review included 27 studies involving 9557 participants. Sixteen studies (59%) were conducted in LMICs. The authors found that as an initial test replacing sputum smear microscopy, Xpert MTB/RIF pooled sensitivity was 89% [95% credible interval (CrI) 85% to 92%] and pooled specificity 99% (95% CrI 98% to 99%). As an add-on test following a negative smear microscopy result, Xpert MTB/RIF pooled sensitivity was 67% (95% CrI 60% to 74%) and pooled specificity 99% (95% CrI 98% to 99%). They also found that in comparison with sputum smear microscopy, Xpert MTB/RIF increased TB detection among culture-confirmed cases by 23% (95% CrI 15% to 32%). In addition, the authors reported that if pooled sensitivity estimates for Xpert MTB/RIF and smear microscopy were applied to a hypothetical cohort of 1000 patients where 10% of those with symptoms had TB, Xpert MTB/RIF would diagnose 88 cases and miss 12 cases,

whereas sputum smear microscopy would diagnose 65 cases and miss 35 cases [109].

Studies have also evaluated the effect of using Xpert MTB/RIF on time to TB treatment initiation compared to smear microscopy. Auld *et al* conducted a narrative review of Xpert impact trials to summarize which patient-relevant outcomes Xpert had improved and explore reasons for no observed morbidity or mortality reductions [110]. Eight trials were included in the review, of which six were from sub-Saharan Africa, one from Brazil, and one from Indonesia. All eight trials were conducted in routine healthcare settings, with the potential for existing programmatic weaknesses to impact trial outcomes. The authors reported that in six of the eight trials, Xpert achieved higher diagnostic yield than microscopy and in these six trials, compared with microscopy, Xpert increased TB diagnostic yield by a factor of about 1.2-3.0. Four of the eight trials reported time from sample collection to result availability among drug-sensitive TB positive patients, and they found Xpert reduced this time in three trials (0-2 days for Xpert compared to 0-12 days for smear microscopy). Also, six trials reported median time from enrollment or sputum collection to TB treatment initiation among all patients who started TB treatment, regardless of reason for starting TB treatment; in four of the six trials there was either strong or weak evidence that the median time to treatment was shorter in the Xpert than microscopy arms. In these four trials, Xpert reduced median time to TB treatment by about 1 day in two of the trials, 3.3 days in one trial and 4 days in the other trial. However, reduction in time to treatment initiation might not necessarily influence treatment outcome as factors such as adherence to treatment also play a role. In addition, of two trials reporting the percentage of bacteriologically confirmed TB patients lost to follow-up before TB treatment initiation, one trial reported lower loss to follow-up in the Xpert arm (15 vs 8%, $p=0.03$). However, among five trials that reported incidence of unfavourable

outcomes following TB treatment initiation, the percentage with unfavourable TB treatment outcomes was similar between microscopy and Xpert arms [110].

The literature has shown that Xpert MTB/RIF has advanced TB diagnostic capability compared to smear microscopy. In some settings it has reduced time to treatment initiation, and it has also reduced pre-treatment loss to follow-up. However, Xpert has not yet demonstrated impact on reductions in patient morbidity and mortality as evidenced in recent trials.

2.7.3 Laboratory turnaround times

Several factors affect laboratory turnaround times and these include irregular supply of reagents and availability of technical staff to perform the test. The irregular supply of laboratory reagents in some health facilities for sputum testing can lead to delay in diagnosis [90, 91, 97, 103]. This is because patients might send their sputum sample to the laboratory but due to lack of reagents, the test cannot be performed. The patient might need to wait till reagents are supplied then they can return to the laboratory for the test to be done. Also, in some health facilities there are few trained technical staff who can perform smear microscopy test [62, 87, 91]. Therefore, when these staff are not around, then the test cannot be done and patients with a request for sputum testing will have to wait till staff are available to perform the test. These factors may result in loss to follow-up since some patients might not return to have the test done. If such patients turn out to have TB, then they will continue transmitting the disease in the community.

2.8 Receiving test results

In the TB testing pathway, usually patients are required to visit the health facility for a second or third time to receive a test result after submitting sputum for the test [85]. In Uganda, a cross sectional study among 392 patients showed a quarter (25.5%) of patients received test results after 3-5 working days while the national standard operating procedure states results should be reported within 24 hours [96].

When a test result is positive for TB, the patient is referred to the TB treatment centre to commence treatment but if the result is negative, there should be some follow up tests. According to the International standards for tuberculosis care, a patient with smear negative result should be treated with broad spectrum antimicrobials and if there is no improvement, the sputum microscopy test should be repeated. If the result is still negative, then a chest radiograph should be taken and a physician should make a judgement to either treat for TB or not [79]. In South Africa, a study evaluating adherence to TB diagnostic algorithms in primary health clinics for people with a negative test result as part of the XTEND trial showed that of 4,037 patients with a negative test result, 2,155 (53%) were HIV positive and 540 (13%) had unknown HIV status. Among HIV-positive patients, after 6 months of the index negative result, only 507 (24%) had evidence of further investigation, while among those with unknown HIV status, there was no evidence of further investigation found in clinic records. This proved a lack of adherence to diagnostic algorithms which could lead to high mortality [111]. Other studies have shown that smear negative result was a determinant of health system delay for TB diagnosis [39, 50, 72, 73, 112].

2.9 Initiating TB treatment

The final steps in the TB care cascade are initiating persons confirmed to have TB on treatment and ensuring they complete treatment. Delays or pre-treatment loss to follow-up do occur at this point just like the other steps in the care cascade. TB patients may be 'lost' after diagnosis and before treatment initiation. This is called initial or pre-treatment loss to follow-up [113]. A systematic review and meta-analysis of pre-treatment loss to follow-up in TB patients in LMICs and high-burden countries, that included 23 studies from 14 countries, reported a pre-treatment loss to follow-up range of 4 to 38% [114]. This was common in studies from Africa and Asia. One study that reported minimal delays in treatment initiation was a retrospective, descriptive cohort study using routinely collected programmatic data from TB registers in Pakistan, where the authors reported that among 152 diagnosed TB patients, 66% initiated TB treatment on the day of TB diagnosis or the next day and a further 34% initiated TB treatment within a mean time of 7 days [115].

However, other retrospective cohort studies have reported high pre-treatment loss to follow-up proportions [116, 117]. A cohort study using secondary programme data was conducted in Zimbabwe to quantify and assess trends and risk factors for loss to follow-up and delays before treatment initiation among bacteriologically-confirmed pulmonary TB patients in 2012–16 [118]. The study reported that, of 2443 TB patients, 508 (20.8%) were lost to follow-up after being diagnosed with TB and this included 252 (10.3%) deaths. The mean delay from sputum receipt at the laboratory to testing was 2.7 days and from testing to result dispatch was 8.8 days. Among 1935 patients registered for TB treatment, the mean delay was 29.1 days. This study revealed a high frequency of loss to follow-up, death and delay before TB treatment initiation [118].

In qualitative studies, HCWs have suggested some reasons for delays or pre-treatment loss to follow-up. They mentioned that, at times, results being transferred from the laboratory to the TB clinic go missing in transit [99]. When this happens, nurses at the TB clinic are not able to initiate treatment and patients might need to go back to the laboratory for a copy of the results before they initiate treatment. This was reported by Bulage *et al* in a qualitative study among 20 HCWs conducted in a rural district in Uganda [96]. Some HCWs also said the inability of patients to keep clinic appointments is a cause for delay in initiating treatment [96]. Though the staff at the TB clinic might have received a positive test result from the laboratory, the affected patient might not turn up on their appointment date and treatment cannot be initiated. At times too, delays are due to shortage of anti-TB drugs at the health facility [25, 73, 95] so patients are forced to wait till the drugs are available before they start treatment. In peripheral health facilities where they lack HCWs, irregular attendance of HCWs from other facilities from time to time to support, often led to inadequate counselling and poor adherence to treatment [62]. Delays or pre-treatment loss to follow-up leads to unfavourable outcomes for patients [119, 120].

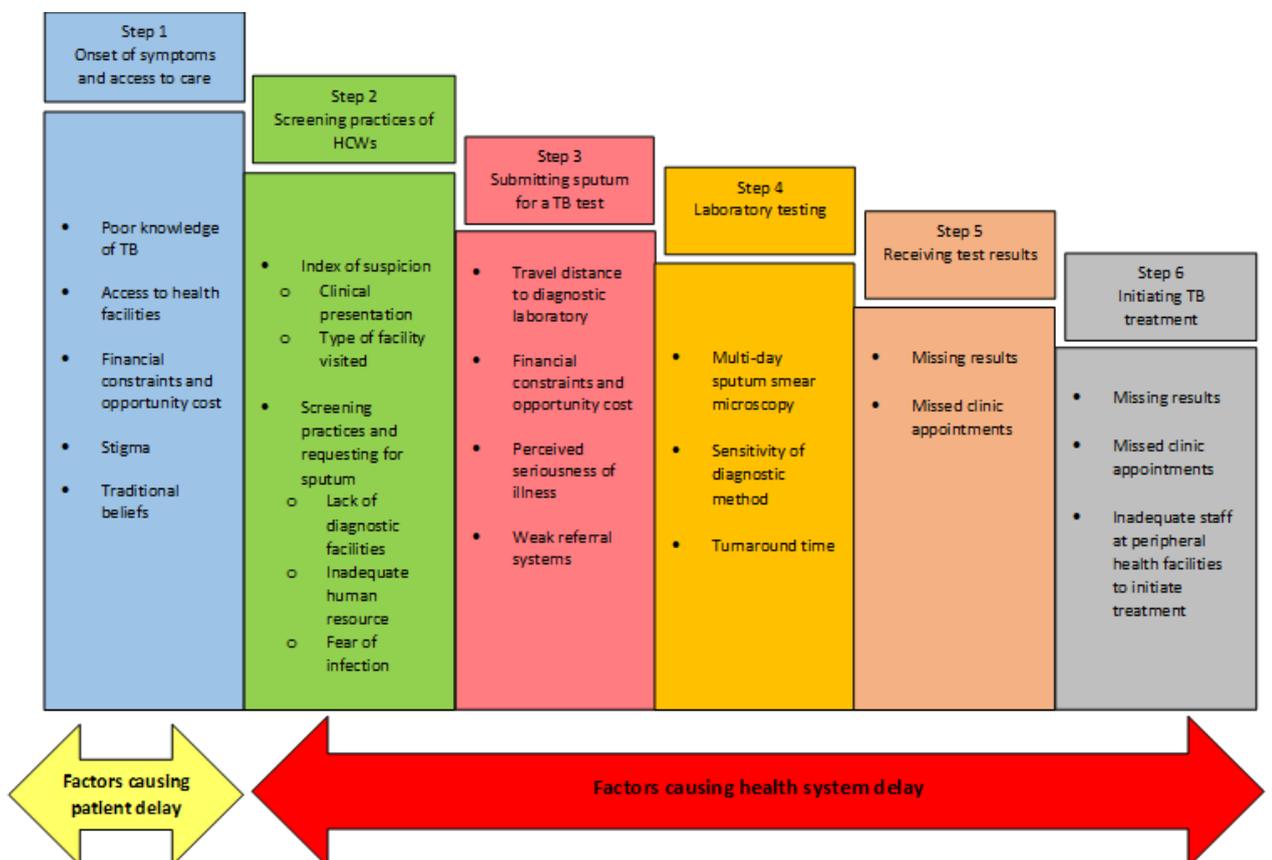
2.10 Summary

Review of literature has shown that delayed or missed diagnosis of TB occurs at different points in the diagnostic pathway. Figure 2.3 provides a summary of factors that are associated with delayed or missed diagnosis of TB. A combination of patient and health system related factors are associated with delay in the pre-diagnostic stage of the pathway. The low sensitivity of the diagnostic method and inadequate laboratory staff are causes of delay in the diagnostic stage of the pathway while inadequate staff at peripheral health facilities to initiate TB treatment is a cause of delay in the treatment

stage of the pathway.

Few studies have looked at the entire diagnostic pathway to identify points at which these delays occur and why they occur. Of studies that look at the care cascade, many of these studies enrolled only people on TB treatment thus not exploring the experiences of people with TB symptoms who never started treatment. Also, many of these studies were cross-sectional rather than cohort so again not allowing any opportunity to trace people who were lost from the system. Thus, this PhD attempted to address these gaps by looking at various steps in the TB care pathway with focus on the steps in the health facility prior to a sputum being submitted to the laboratory for testing to identify points at which diagnosis can be delayed or missed using more robust study methods.

Figure 2. 4: Summary of factors that can cause delayed or missed diagnosis of TB at the different steps in the diagnostic pathway



TB=tuberculosis, HCW=healthcare worker

Table 2.2 is a summary of 18 studies on health systems delay in TB diagnosis selected from the 72 papers reviewed based on their definition of health systems delay being first contact with a public or private health facility to diagnosis of TB or initiation of TB treatment.

Table 2. 2: Summary of studies on health system delay in TB diagnosis

Author/country/year	Study population	Study design/sample size	Type of facility	Important findings	Comments
Adejumo et al, Nigeria, 2016 [56]	TB patients aged >14 years	Cross-sectional study, 470	DOTS facilities	Median HSD in public DOTS facilities was 14 days and 12.5 days in private DOTS facilities. TB patients who first visited a non-hospital facility were over four times more likely (odds ratio 4.12; 95% confidence interval 2.25–7.54) to have prolonged HSD than those who first visited the government hospital.	Use of cross-sectional design and recruiting TB patients already on treatment implies those who never started treatment were not studied. Participants from private DOTS facilities could differ in characteristics from those in public DOTS facilities and could introduce bias
Adenager et al, Ethiopia, 2017 [32]	PTB patients aged ≥15 years	Cross-sectional study, 425	10 Public and 10 private health facilities that provide TB treatment.	Median HSD was 9 days and 54.8% experienced HSD. Hemoptysis and being unemployed were less likely to experience HSD	Use of cross-sectional design and recruiting TB patients implies those who never started treatment were not studied. Participants from private DOTS facilities could differ in characteristics from those in public DOTS facilities and could introduce bias
Belay et al, Ethiopia, 2012 [42]	TB patients aged ≥18 years	Cross-sectional study, 216	1 hospital and 1 health centre	Median HSD was 33.5 days. Extra-pulmonary TB (aOR. 2.08, CI 1.08- 4.04), and first visit to health posts/clinics (aOR. 19.70, CI 6.18-62.79), health centres (aOR. 4.83, CI 2.23-10.43) and private health facilities (aOR. 2.49, CI 1.07-5.84) were found to be independent predictors of HSD	The authors did not report on the number of health facilities in the study area out of which they chose two for the study but mentioned security threats in the area as the reason for not including more health facilities. This may affect the representativeness of the study findings
Belkina et al, Uzbekistan, 2014 [45]	PTB patients aged ≥15 years	Cross-sectional study, 538	1 specialized hospital for Phthisiology and Pulmonology, 2 hospitals and 1 dispensary	Median HSD was 7 days. Prescribed with OR: 2.19 (95% CI: 1.18 to 4.09) and visiting a private clinic OR: 2.87 (95% CI: 1.83 to 4.54) were predictors of HSD	Use of cross-sectional design and recruiting TB patients already on treatment implies those who never started treatment were not studied
Bogale et al, Ethiopia, 2017 [25]	TB patients aged ≥18 years	Cross-sectional study, 296	Public health facilities	Median HSD was 5 days (IQR = 4–7). Seeking care from >1 health care provider (β : 0.28, 95% CI: 0.23, 0.34) and seeking initial care from primary level health care facilities (β : 0.10, 95% CI: 0.07, 0.13) were positively associated with HSD.	The use of cross-sectional design and patients already on treatment could have introduced recall bias since patients might not remember the exact date of symptoms onset and first visit to a public health facility
Chimbatata et al, Malawi, 2017 [86]	Malawi: smear positive PTB patients aged ≥ 16 years. China: smear positive PTB patients ≥ 18 years	Cross-sectional study, 450	Hospitals, health centres and designated TB clinic	Median HSD were 12 and 11.5 days ($p>0.05$) in Malawi and China, respectively. Initial healthcare visits at village level led to longer HSD in both Malawi (aOR=2.055, 1.211–3.487) and China (aOR=5.627, 2.218–14.276).	Conducting the study in a LMIC and a HIC both with high TB burdens to share experience and lessons on TB case detection was relevant

Ebrahimi et al, Iran, 2018 [52]	TB patients aged ≥18 years	Cross-sectional study, 173	Tuberculosis and Lung Diseases Research Centre	Median HSD was 53 days. Factors associated with HSD were: ≥ 3 vs. < 3 visits to health facilities before correct diagnosis (OR = 9.44, 95% CI: 4.50 to 19.82), without vs. with access to TB diagnostic services (OR = 3.56, 95% CI: 1.85 to 6.83), and misdiagnosis as cold or viral infection vs. not (OR = 2.62, 95% CI: 1.40 to 4.91).	The presence of only one dedicated Tuberculosis and Lung Diseases Research Centre could have contributed to long HSD because all other facilities had to refer presumptive TB patients there for diagnosis and treatment
Ekinci et al, Turkey, 2014 [63]	PTB patients aged ≥15 years (Group 1: smear negative and group 2: smear positive)	Cross-sectional study, 136	1 Hospital	The median HSD was 41 days in group 1 and 16 days in group 2 (P < 0.0001). A low index of suspicion for TB by physicians and underutilized or delayed sputum examinations for acid-fast smears were the most common reason for doctor's delay.	Separating smear positives and smear negatives patients was a good way to measure delay since the experiences might not be the same
Gebreegziabher et al, Ethiopia, 2016 [50]	PTB patients aged ≥15 years	Cross-sectional study, 706	30 Public health facilities	Median HSD was 22 days (IQR: 4–88 days). Smear-negative TB (aOR, 1.88; 95 % CI, 1.32–2.68) and first visit to public health centres (aOR, 2.22; 95 % CI, 1.52–3.25) and health posts (aOR, 5.86; 95 % CI, 1.40–24.39) were found to be independent predictors of HSD.	The inclusion of both smear negative and smear positive patients was useful in determining delay and factors associated with delay, but the use of a cross-sectional study design could have introduced some recall bias
Jurcev-Savicevic et al, Croatia, 2013 [72]	Cultured confirmed PTB patients aged ≥15 years	Cross-sectional study, 241	Hospital and community	Median HSD was 15 days. Almost 30% of TB patients remained undiagnosed for more than 30 days after the initial health care visit. Female patients (p = 0.008), patients with a negative sputum smear (p = 0.003) and patients having symptoms other than the usual ones (0.037) were associated with HSD.	Use of cross-sectional design and recruiting TB patients already on treatment implies those who never started treatment were not studied
Kansiime et al, Uganda, 2013 [73]	PTB patients aged ≥18 years	Cross-sectional study, 266	1 Referral hospital	Median HSD was 9 days (IQR=8-19). 65.4% experienced HSD. Factors associated with HSD were: 1n-patient (OR= 4.68, 95% CI: 1.91-11.45), secondary as highest level of education attained (OR= 3.56, 95% CI: 1.18-10.74), primary as highest level of education attained (OR= 6.70, 95% CI: 2.13-21.02), presence of fever (OR= 3.28, 95% CI: 1.05-10.79), and patient delay at health facility (OR= 5.01, 95% CI: 1.33-18.9).	The inclusion of only one referral hospital in the study could possibly affect the generalizability of the study findings
Osei et al, Ghana, 2015 [26]	TB patients aged ≥15 years	Cross-sectional study, 73	1 Hospital	Median HSD was 45 days (IQR: 38–128). Multiple healthcare contact following signs and symptoms (aOR = 10.26; 95 %CI: 2.95–35.72; P < 0.0001) was associated with prolonged HSD.	The relatively small sample size makes it difficult to draw conclusions from the findings
Peri et al, Italy, 2018 [46]	TB patients aged >18 years	Cross-sectional study, 137	7 Referral hospitals	Median HSD was 31 days (IQR: 7.25–85) Extra-pulmonary TB (OR 4.3; 95% CI 1.4–13.8) and first contact with general practitioner (OR 5.1; 95% CI 1.8–14.5) were independently associated with higher risk of HSD > 10 weeks.	The exclusion from enrolment of patients due to language barriers and inability to sign informed consent could imply selection bias

Saifodine et al, Mozambique, 2013 [54]	PTB patients aged ≥ 18 years	Cross-sectional study, 622	5 TB clinics	Median HSD was 62 days (37–120). More than two visits to a health facility, farming and coexistence of a chronic disease were associated with increased HSD.	Use of cross-sectional design and recruiting TB patients already on treatment implies those who never started treatment were not studied but the inclusion of both smear positive and smear negative patients made it relevant to measure delay and associated factors for these different groups
Seid et al, Ethiopia, 2018 [64]	TB patients aged >18 years	Cross-sectional study, 382	Public health facilities	Median HSD was 6 (IQR: 4, 8) days. Initial visit to general practitioners (aOR: 2.57; 95% CI: 1.43–4.63) and >1 health care visit (aOR: 2.12; 95% CI: 1.30–3.46) were independent predictors of HSD.	The use of the median value as cut-off for delay may limit comparability of study findings with national and international expected delay periods of TB control programme
Shiferaw et al, Ethiopia, 2019 [24]	All TB patients	Cross-sectional study, 170	Public health facilities	Mean HSD was 33.3 days (range: 1-51weeks). Average repeated visits to health facility was 3 times (SD+1.9). 56% of patients asked about TB-related symptoms at first health facility visit. 47% of patients not asked to submit sputum at first health facility visit	The aim of the study was to assess delay in TB diagnosis among patients taking TB treatment and the delay included both patient and health system delay and factors associated with these delays. Apart from descriptive findings on some health system factors, no associated factors for HSD were shown except for patient delay
Yang et al, China, 2019 [27]	All TB patients	Cross-sectional study, 1342	TB clinics	23.6% TB patients experienced delay in diagnosis. The time to reach a township hospital or the facility of a patient's first consultation was significantly associated with delays in diagnosis.	No mean or median HSD was reported and the use of cross-sectional design and recruiting TB patients already on treatment implies those who never started treatment were not studied
Yimer et al, Ethiopia, 2014 [43]	TB patients aged >15 years	Cross-sectional study, 201	1 Referral hospital	Median HSD was 27 days (IQR 8-60). Patients who first visited health centres [(aOR) 5.1; 95% (CI 2.1, 12.5)], private facilities [(aOR) 3.5; 95% (CI 1.3, 9.7)] and health posts [(aOR) 109; 95% (CI 12, 958)], were more likely to experience an increase in HSD compared to those who visited hospitals.	The use of only referral hospital may affect the representativeness of the findings

HSD= health system delay, DOTS= directly observed treatment short course, TB= tuberculosis, OR= odds ratio, aOR= adjusted odds ratio, CI= confidence interval,

IQR= interquartile range, SD= standard deviation

Chapter 3: Methods

This chapter provides an overview of the different methodologies used in this thesis. It gives details of the study area, study designs, data collection, data handling, data analysis and ethics. Further details of each methodology used to answer each of the objectives are described in the research papers (chapters 5, 6 and 7 of this thesis).

3.1 Overview of methods

The thesis applied a mixed-method research commonly defined as research that focuses on collecting, analysing, and mixing both quantitative and qualitative data in a single study or a series of studies [121]. The reason for employing this type of research was that it could address the study research questions more comprehensively than using either quantitative or qualitative methods alone [121]. The use of both quantitative and qualitative methods provided a more complete analysis, and they complement each other where the quantitative results were explained in more detail through the qualitative data [122]. Even though some researchers argue that it is neither possible nor desirable to combine quantitative and qualitative methods in a study as they represent essentially different and conflicting ways of viewing the world and how we collect information about it, others too believe that concerns about the incommensurability of world views can be set aside if the combination of quantitative and qualitative methods addresses the research question effectively [123]. In health systems research, many of the areas explored are complex and multifaceted, therefore, combining quantitative and qualitative methods to address a research question is a useful way of addressing these complexities [124].

The mixed-methods design employed was a convergent parallel design where data were collected parallelly from quantitative and qualitative components in a single

phase and the results from both components were considered together in the discussion for the purpose of corroboration and validation [121]. In this design, quantitative data were collected using a prospective cohort study and a cross-sectional study among patients; the qualitative data were collected using clinic observations and in-depth interviews with HCWs. The data collected from the different components were analysed separately and independently from each other using quantitative and qualitative analytic procedures. The results were then combined in the discussion and interpreted to provide a more complete understanding of gaps in the pathway to TB diagnosis in health facilities [121]. The rationale for this approach was to obtain different but complementary data on steps in the diagnostic pathway where presumptive TB patients are missed and the barriers within the health system that could account for this, in order to create a better understanding of gaps in the pathway [125].

3.2 Study setting

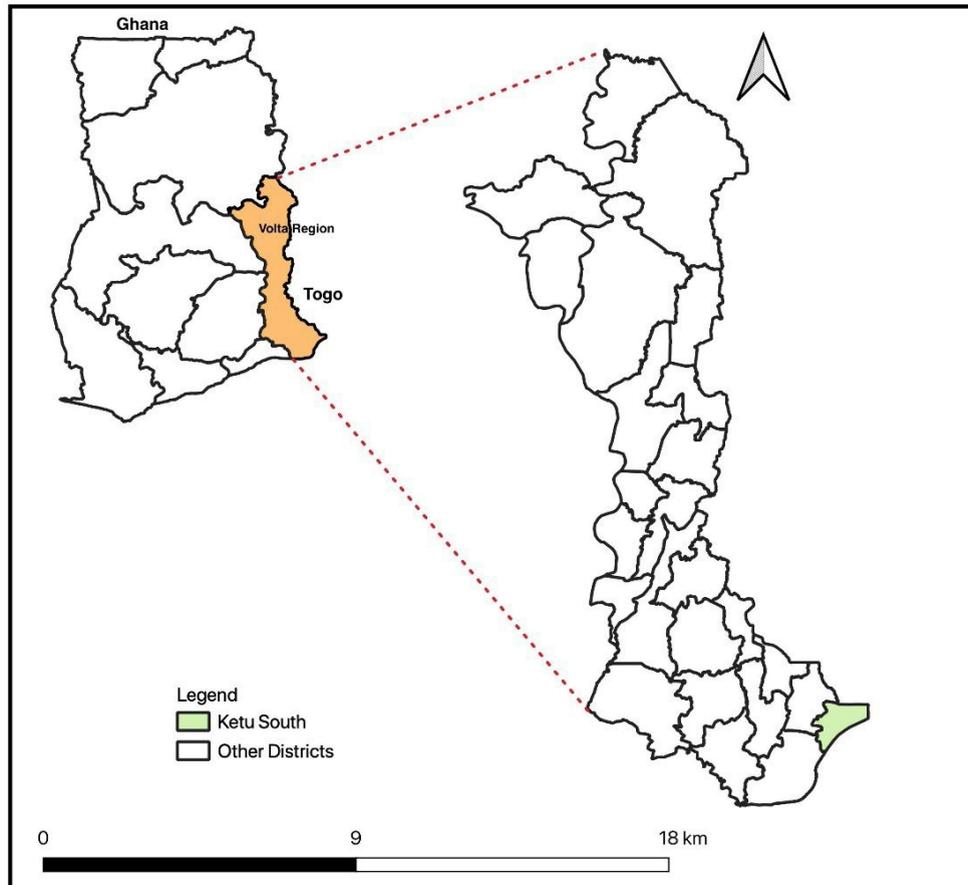
The study was conducted in Ketu South Municipality of the Volta region of Ghana. It is one of the 25 administrative districts/municipalities in the Volta region with a population of 202,406 based on extrapolation from the 2010 population census. It is located in the south-eastern part of Ghana and shares boundaries with the Republic of Togo to the east, Ketu North district to the north, Keta municipal to the south-west and the Gulf of Guinea to the south. The main occupations are fishing and trading with majority of the inhabitants being traditional worshippers and Christians. The municipality has six health demarcated sub-municipalities with one government hospital, four private hospitals, two private clinics, eight health centres and 14 Community Health Planning Services (CHPS) compounds which are the lowest level of care [126]. Community Health Planning Services compounds are community-based

health service delivery points. The primary focus is communities in deprived sub-districts and bringing health services close to the communities [127].

With reference to TB diagnosis and treatment, there is only one TB diagnostic laboratory at the municipal hospital. At the time of planning the study in 2017, the main diagnostic method for TB was sputum smear microscopy but by the time we started the study in 2018, the main diagnostic method was Xpert MTB/RIF (Cepheid, Sunnyvale CA, USA). There is also one TB treatment centre (chest clinic) located at the municipal hospital. All other health facilities in the municipality refer patients with symptoms of TB to the municipal hospital for testing. Also, all patients diagnosed as having TB receive their treatment from the hospital and they make monthly visits to the hospital to collect their drugs. Supervision of treatment is by a treatment supporter (a person chosen by the patient whom they trust) at the community level.

The research was conducted in the municipal hospital, which has a co-located laboratory, in an urban area, and four health centres without a laboratory, in rural areas. The health centres were located about 10-20 km from the municipal hospital and the mode of transportation between the health centres and the hospital was mainly by public buses, taxis or commercial motorbikes. Figure 3.1 shows the municipality where the study was conducted.

Figure 3. 1: Map of the Volta region showing Ketu South Municipality



3.3 Initial health facility assessment

Initially, the study was planned to be conducted in the municipal hospital and one rural health facility. In order to familiarize myself with the study facilities and to find out the type of TB services offered; an initial site visit to the municipal hospital and selected health centre was made before the commencement of the study. This initial site visit led to a protocol amendment to include three additional rural health centres for the study. After the approval by the ethics committees for the inclusion of the three additional rural health centres, site visits were made to these additional facilities before the commencement of the study. The findings of this assessment are described in chapter 4 of this thesis.

3.4 Study components

The study comprised of three components using different methods to investigate the various aspects of the diagnostic pathway. Two of the components used quantitative methods while the third component used qualitative methods. As stated earlier, details of methods used in the different components are described in result chapters 5, 6 and 7 of this thesis.

The first component was a cross-sectional study using exit interviews and addressed objective 1 which was to determine the proportion of health facility attendees eligible for sputum test according to national guidelines who were asked to do a sputum test by HCW, and the prevalence of having sputum positive on Xpert MTB/RIF among health facility attendees who met study criteria for having a sputum test. This was conducted among patients exiting the health facility after seeking care for their own health and reported at least one TB-related symptom to the study team. A standardized questionnaire was used to collect information from patients who consented to take part in the study.

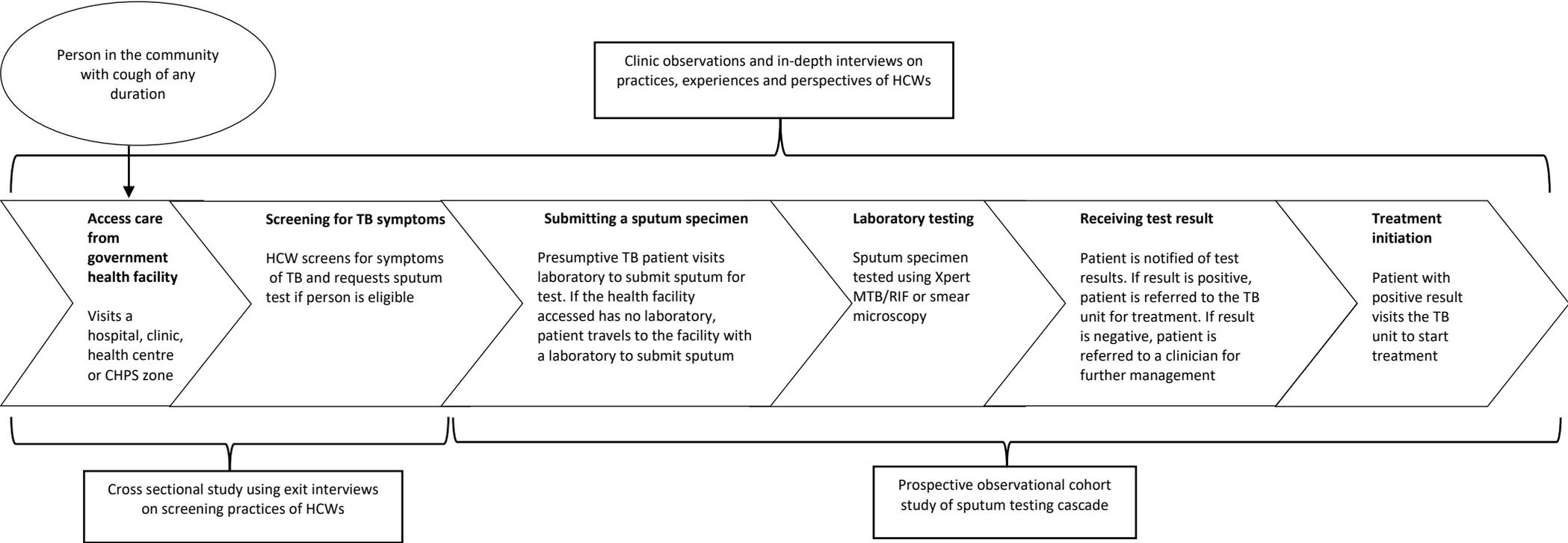
The second component was a prospective observational cohort study addressing objectives 2 and 3 which were to determine the proportion of patients with a request for sputum test who submitted a sputum for testing, the time from test request to submitting sputum, and factors contributing to non-submission of sputum for testing; and to compare the time from test request to submitting sputum among patients attending a health facility with vs. without a co-located laboratory. The study participants were patients presumed to have TB by a HCW and given a request for a sputum test as part of routine care. At enrolment, participants were interviewed using a standardized questionnaire. Participants were followed up for two months using

two-weekly phone calls or for those who had no telephone contact, a home visit was made once every month for the duration of follow up to find out if sputum had been submitted. The use of mobile phones for follow up for participants was inspired by my primary supervisor's experience of high loss to follow-up by two months after enrolment among people being investigated for TB if no contact calls were made and using mobile phones for follow ups in a previous randomized control trials evaluating the effectiveness of Xpert MTB/RIF in South Africa. Moreover, ownership of mobile phones in Ghana was about 80% [128] so it was a more convenient and cost-effective way to follow up on participants.

The third component was a qualitative study using clinic observations and in-depth interviews addressing objective 4 which was to explore HCWs' perspectives concerning barriers to TB case finding in health facilities, their experiences, practices and suggested solutions for improvement. Participants interviewed were HCWs involved in TB case finding at both urban and rural health facilities. Participants were interviewed using an interview guide and clinic observations were conducted at OPDs of the health facilities using a check list.

Figure 3.2 shows the TB diagnostic cascade and the steps covered by each component of the study.

Figure 3. 2: TB diagnostic cascade showing components of the study



CHPS= community health planning services (lowest level of care in the health system), HCW= healthcare worker, TB= tuberculosis

3.5 Data collection and management

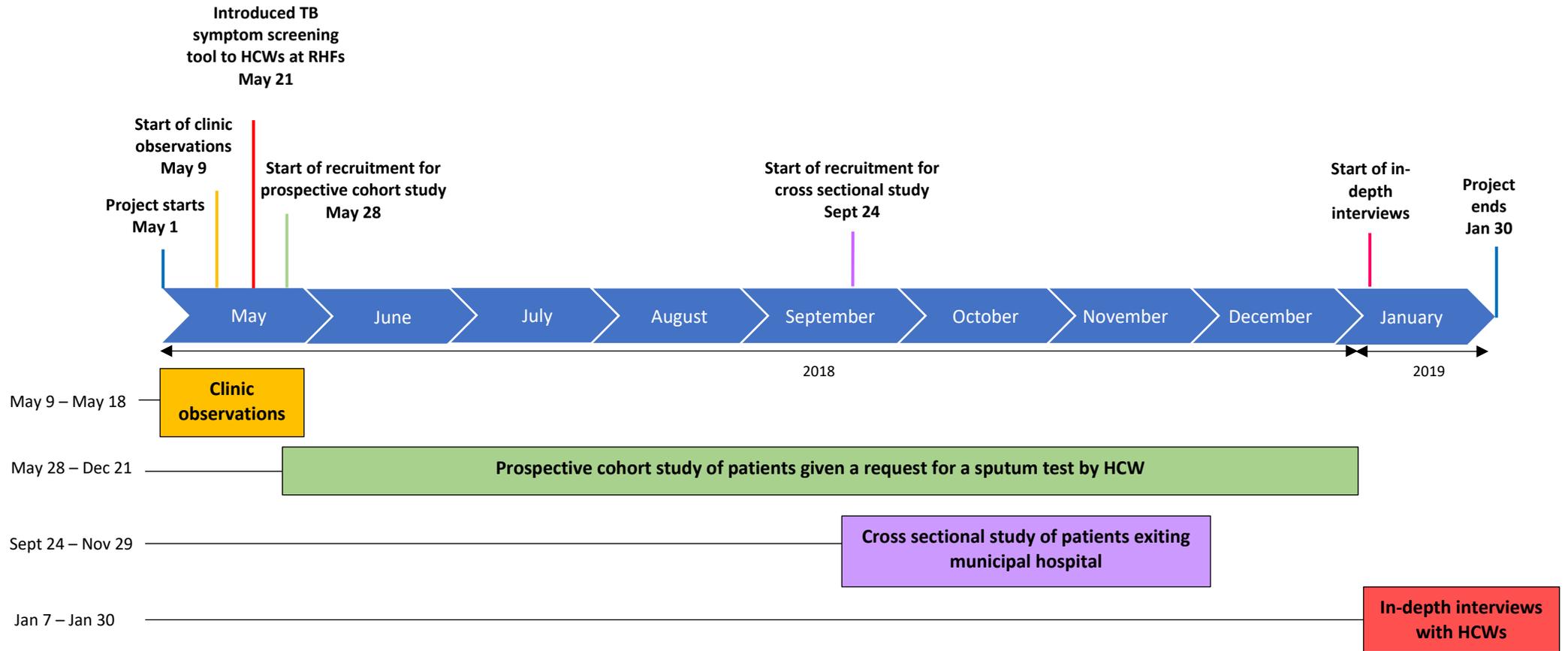
Data collection started in May 2018 and ended in January 2019. Six research assistants who were first degree holders in Public Health were recruited and trained for two weeks on all the study tools prior to commencement of the study. Clinic observations were the first to be conducted from May 9 to May 18, 2018 (figure 3.3) and this was done by myself and another colleague from the School of Public Health, University of Health and Allied Sciences in Hohoe, Ghana. Clinic observations were conducted first to ensure that the introduction of the other components of the study did not influence HCWs' practices in screening for symptoms of TB and requesting for a sputum test. On 21st May 2018, the TB-symptom screening tool was introduced to HCWs who attend to patients in the consulting room of the study rural health facilities. The prospective cohort study was then rolled out on May 28th because it had an element of follow-up of study participants and required more time. The cross-sectional study was the third to be rolled out and this was followed by the in-depth interviews with HCWs (figure 3.3). Most of the HCWs interviewed from rural health facilities were the ones the TB-symptom screening tool was introduced to at the beginning phase of the project.

All quantitative data were collected electronically using open data kit (ODK). Questionnaires for the quantitative data were piloted prior to commencement of the study. Data generated were stored on a secure server hosted by the London School of Hygiene & Tropical Medicine. Daily, data collected were checked for inconsistencies and missing data before uploading onto the server. Dashboards in Microsoft (MS) Excel were created for both the cross-sectional study and prospective cohort study to enable tracking of the numbers being recruited. To ensure data security, all study tablets were password protected and were stored in locked cabinets in an office at the municipal hospital during the period of data collection.

A check list was used for clinic observations and observations were done in the OPD of all the study health facilities including the laboratory and chest clinic of the municipal hospital. Findings from the clinic observations were used to modify the in-depth interview guide to seek explanation from HCWs on some findings during the observations. In-depth interviews were conducted in the health facilities and at times that were convenient for the HCWs. All interviews were audio-recorded. The audio records were stored in a locked cabinet to ensure data security.

Data from the quantitative components were intended to quantify progress through and losses from different components of the patient pathway. The quantitative data were used to inform questions that were asked during in-depth interviews with HCWs. Likewise, data from the qualitative component was intended to provide a more complete understanding of findings from the cross-sectional study on TB symptom screening and sputum test requesting practices of HCWs. The qualitative data was also to provide understanding of health system factors that could prevent presumptive TB patients who have been asked to submit a sputum for TB testing from submitting sputum. The qualitative data was then triangulated with the quantitative data in understanding where the barriers in the patient pathway were.

Figure 3. 3: Study implementation timelines



RHF=rural health facility, HCW=healthcare worker

3.5.1 Quality control for qualitative data

Reflexivity

In qualitative research, researchers need to increasingly focus on self-knowledge and sensitivity; better understand the role of the self in the creation of knowledge; carefully self-monitor the impact of their biases, beliefs, and personal experiences on their research; and maintain the balance between the personal and the universal [129]. In this regard, during the research process, I was continually reflective and ensuring that my presence during data collection and as facilitator of in-depth interviews did not influence responses given by the HCWs, but this could not be entirely eliminated. The type of relationship I had with the HCWs formed an important component of the study. Prior to conducting the in-depth interviews with HCWs, I had been living in the municipality for seven months conducting the other components of this PhD study in the selected health facilities. Therefore, by the time the in-depth interviews were conducted, the HCWs were familiar with me and used to seeing me in the health facilities on a daily basis. Also, as a Ghanaian woman who was familiar with the culture of the people and could converse with them in the local dialects made me acceptable and made it easy for me to develop rapport with HCWs. Participants were therefore comfortable talking to me about their experiences. I was mostly seen as a researcher from the London School of Hygiene & Tropical Medicine and not seen as a representative of the NTP or the Ghana Health Service who was there to find faults with their work, so participants felt relaxed and talked openly during interviews. However, it is still possible they modified some responses because I was an outsider. Moreover, as a former biomedical laboratory scientist who had worked in a TB laboratory in a regional hospital setting in Ghana, I could easily relate with some of the

issues on TB case finding raised by the HCWs during the interviews. This previous experience, coupled with what HCWs said, at times influenced the follow-up questions I asked during the interviews.

Once HCWs had the sense that I could relate with what they were saying, they became more open and shared their experiences. However, I was continuously reflexive about how my identity as a middle-aged woman doing a PhD and interviewing HCWs who were mostly younger than me could influence the data produced. This is because culturally, a woman studying for a higher degree is perceived to be very intelligent and this could have made participants conscious of how they expressed themselves. In addition, I recognise that my experience with previously working in a hospital setting and my views on how HCWs should conduct TB case finding in health facilities could influence the data collection, analysis, and interpretation.

3.6 Data analysis

Descriptive analysis, univariable and multivariable analysis using logistic regression were conducted for the quantitative data. In addition causal effect was assessed for the prospective cohort study data. Quantitative data were analysed using STATA v15 (Stata Corp, College Station TX, USA). All qualitative data were analysed manually. Clinic observations were summarized in MS Excel and used to describe the flow of presumptive TB patients in the health facilities and practices of HCWs. Audio-recordings were transcribed and analysed to generate themes relating to barriers in TB case finding in health facilities.

3.7 Ethical Considerations

The study received approval from the Ghana Health Service Ethics Review Committee (GHS- ERC:003/09/17) and the Ethics Committee of the London School of Hygiene & Tropical Medicine (LSHTM Ethics Ref: 14504). Permission to conduct the study in the health facilities was obtained from the regional and municipal health directorates. Written informed consent was obtained from literate participants and for those who could not read and write, consent was documented with a thumbprint in the presence of a literate witness.

Table 3.1 provides a summary of study objectives, methods used and expected outcomes.

Table 3. 1: Summary of objectives, study methods and outcomes

Objective(s)	Study type/design	Method of data collection	Primary outcome
<p>1a. To determine the proportion of health facility attendees eligible for sputum test according to national guidelines who were asked to do a sputum test by a HCW</p> <p>1b. To determine the prevalence of having sputum positive on Xpert MTB/RIF among health facility attendees who met the criteria for sputum test</p>	Quantitative/ cross-sectional study	TB symptom screening questionnaire plus enrolment questionnaire	<p>Proportion of health facility attendees eligible for sputum who were asked to do a sputum test</p> <p>Prevalence of TB among health facility attendees who met the criteria for sputum test according to study criteria</p>

<p>2. To determine the proportion of patients with a request for sputum test who submitted a sputum for testing, the time from test request to submitting sputum, and factors contributing to non-submission of sputum for testing</p>	<p>Quantitative/ prospective observational cohort study</p>	<p>Enrolment questionnaire plus short follow-up questionnaires</p>	<p>Proportion of participants who submitted a sputum specimen</p>
<p>3. To compare the time from test request to submitting sputum among patients attending a health facility with vs. without a co-located laboratory.</p>	<p>Quantitative/ prospective observational cohort study</p>	<p>Follow-up questionnaires</p>	<p>Time to submitting sputum among persons attending a health facility with vs without a co- located laboratory</p>
<p>4. To explore HCWs' perspectives concerning barriers to TB case finding in health facilities, their experiences, practices and suggested solutions for improvement</p>	<p>Qualitative/clinic observations and in-depth interviews</p>	<p>Observational checklist and in- depth interview guide</p>	<p>HCWs' TB symptoms screening and requesting for sputum test practices at the health facility</p> <p>Themes emerging on experiences of HCWs and their perceived barriers to TB case finding at the health facility level</p>

HCW = Healthcare worker

Chapter 4: Situation assessment at health facilities

This chapter describes the findings of the situation assessment on TB case finding at health facilities prior to the commencement of the study.

4.1 Municipal hospital

At the municipal hospital, we were introduced to the senior hospital administrator by the municipal director of health services. After explaining our mission, he in turn introduced us to the in-charge of the TB unit (chest clinic) with whom we had the discussion.

All TB services were provided at the hospital and these included screening of patients for TB- related symptoms, requesting of sputum test, laboratory testing of sputum specimen using Xpert MTB/RIF and providing treatment for all diagnosed TB patients. The in-charge explained that there was a designated HCW at the OPD called the task-shifting officer whose duty was to screen patients for TB-related symptoms and request for a sputum test if patient was eligible for the test. In addition to the task-shifting officer, all other HCWs in all departments of the hospital also screened patients for TB-related symptoms and requested for a sputum test when necessary. All TB care activities were provided according to the national guidelines.

4.2 Initial rural health centre selected for study

At the initial health centre selected for the study, we met with the in-charge of the facility and through the discussions, we found that no TB services were provided in the facility even though according to the national guidelines they were supposed to screen patients for TB-related symptoms and request for a sputum test if patient was eligible.

The in-charge explained that the facility's laboratory was only used to run test for malaria, haemoglobin and blood sugar levels and the laboratory had no capacity for sputum testing for TB. She mentioned that since she took over as the in-charge and clinician of the facility about a year ago, she had not referred any patient to the municipal hospital for TB testing and the reason was that she had not presumed TB in any patient to warrant referral to the municipal hospital.

4.3 Initial actions taken by the study team

After the discussions with the in-charge of the health facility, it was apparent that we needed to include other rural health facilities in the study to be able to recruit the required number of participants (patients routinely asked by a HCW to submit sputum for a TB test) for the prospective cohort study from rural health facilities. After consultations with the municipal director of health services and the municipal TB coordinator, six rural health centres were suggested, and the study team selected three based on high OPD attendance, representativeness of the sub-municipalities and being in rural areas of the municipality. A request for protocol amendment was submitted to the Ghana Health Service Ethics Review Committee and the London School of Hygiene & Tropical Medicine Ethics Committee for approval. Upon approval of the amendment, a visit was made to the three additional health facilities to assess the situation on TB services provided.

4.4 Findings from three additional rural health centres

At all the three health centres, we met with the in-charges of the facilities and through discussions, we found no TB services were provided in one of the facilities, however, in two of the facilities they did refer clients once in a while to the municipal hospital

for further assessment for TB but this was done without using the recommended TB symptom screening tool. The screening tool was not used because it was not available and HCWs had not been trained on how to use it. On average in a year about five patients were referred to the municipal hospital on suspicion of TB.

4.5 Actions taken by study team after situation assessment

It was agreed among investigators to introduce the TB-symptom screening tool to HCWs at the rural health facilities and explain to them how it was used. In all the four health centres, HCWs who attended to patients in the consulting room were trained on how to use the screening tool. It was necessary to do this so these facilities could start screening patients accessing care so we could identify eligible patients to recruit for the prospective cohort study. The study population for the prospective cohort study was presumptive TB patients who had a sputum test requested or were referred to the municipal hospital for further assessment for TB by a HCW through routine practice. If this intervention was not put in place, it would have taken a longer time period to recruit the required number of participants for the prospective cohort study based on the current numbers at the health facilities being referred for a sputum test. It might not have even been possible to do the study if action was not taken. Due to logistical challenges, the element of two months follow-up for the prospective cohort study and the timelines for this PhD study, we could not afford to have a very long recruitment period for the prospective cohort study.

The clinic observations component of the qualitative study was conducted before the TB- symptoms screening tool was introduced to nurse prescribers and in-charges of the rural health facilities. This was done to ensure that the findings of the clinic observations were not biased by the introduction of the TB-screening tool but rather to capture the true picture of the practices of HCWs relating to TB case finding.

Chapter 5: Research paper 1: Missed opportunities for tuberculosis investigation in a municipal hospital in Ghana: evidence from patient exit interviews

This chapter provides details on the TB symptom screening practices of HCWs in the municipal hospital and gives details on the proportion of health facility attendees eligible for sputum test according to national guidelines who were asked to do a sputum test by a HCW (objective 1). The methodology used to achieve the objective is outlined. Characteristics of study participants and predictive factors for requesting a sputum test for eligible participants by HCWs are also provided in this chapter.

This chapter was published on 24th August 2020 in Transactions of The Royal Society of Tropical Medicine & Hygiene [130]. The published manuscript is included in full below. The copyright is held by Oxford University Press and permission to reproduce the contents is included in appendix 10.3.



RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1514031	Title	Ms.
First Name(s)	Joyce Berkumwin		
Surname/Family Name	Der		
Thesis Title	Pathways to tuberculosis diagnosis and treatment in Ghana: identifying the gaps and seeking solutions		
Primary Supervisor	Alison Grant		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Transactions of The Royal Society of Tropical Medicine & Hygiene		
When was the work published?	24th August 2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	No	Was the work subject to academic peer review?	Yes

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was jointly responsible with Prof Alison Grant for the conceptualisation of the paper. I collected the data, conducted the data analysis and wrote the first draft of the paper. I prepared the subsequent revisions with consideration of comments from co-authors.
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SECTION E

Student Signature	[REDACTED]
Date	15th September 2020

Supervisor Signature	[REDACTED]
Date	16 September 2020

Missed opportunities for tuberculosis investigation in a municipal hospital in Ghana: evidence from patient exit interviews

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Received 27 April 2020; revised 23 July 2020; editorial decision 4 August 2020; accepted 5 August 2020

Background: We assessed coverage of symptom screening and sputum testing for tuberculosis (TB) in hospital outpatient clinics in Ghana.

Methods: In a cross-sectional study, we enrolled adults (≥ 18 years) exiting the clinics reporting 1 TB symptom (cough, fever, night sweats or weight loss). Participants reporting a cough ≥ 2 weeks or a cough of any duration plus ≥ 2 other TB symptoms (per national criteria) and those self-reporting HIV-positive status were asked to give sputum for testing with Xpert MTB/RIF.

Results: We enrolled 581 participants (median age 33 years [IQR: 24–48], 510/581 [87.8%] female). The most common symptoms were fever (348, 59.9%), chest pain (282, 48.5%) and cough (270, 46.5%). 386/581 participants (66.4%) reported symptoms to a healthcare worker, of which 157/386 (40.7%) were eligible for a sputum test per national criteria. Only 31/157 (19.7%) had a sputum test requested. Thirty-two additional participants gave sputum among 41 eligible based on positive HIV status. In multivariable analysis, symptom duration ≥ 2 weeks (adjusted odds ratio [aOR] 6.99, 95% confidence interval [CI] 2.08–23.51) and previous TB treatment (aOR: 6.25, 95% CI: 2.24–17.48) were the strongest predictors of having a sputum test requested. 6/189 (3.2%) sputum samples had a positive Xpert MTB/RIF result.

Conclusion: Opportunities for early identification of people with TB are being missed in health facilities in Ghana.

Keywords: Ghana, healthcare workers, missed diagnosis, screening practices, sputum request, tuberculosis

Introduction

According to the World Health Organization (WHO), in 2018, an estimated 3 million TB cases were missed globally.¹ Missed or delayed diagnosis of TB can have negative implications for patients and the community. Treatment delays increase the duration of infectiousness among people with TB, which can lead to ongoing transmission in the community.^{2,3} Patients may also suffer increased ill-health, increased costs or mortality.²

The 2013 national TB prevalence survey in Ghana showed a higher prevalence than anticipated (253/100 000 measured vs. 72/100 000 previously estimated), suggesting more missing cases than previously thought.^{4,5} The goal of the National TB Control Program (NTP) is to reduce TB prevalence by 25% by 2020

compared to the 2013 baseline level of 253/100 000 population.⁶ To achieve this goal, it is necessary to promptly identify people with active TB accessing care from health facilities and put them on treatment to reduce transmission. Moreover, Ghana's national standard operating procedures for TB case detection state that all adult patients attending outpatient departments and consulting rooms in clinics and hospitals, regardless of presenting symptoms, should be asked about cough by healthcare workers;⁷ and the criteria for requesting a sputum for TB testing is a cough longer than two weeks or a cough of any duration with at least two other TB-related symptoms (chest pain, weight loss, night sweat and fever). Patients who are HIV positive with a cough of any duration, fever, weight loss or night sweat should also be asked to submit sputum for a TB test.⁸

Studies in Ghana have measured patient and health system delay in TB care, but these recruited TB patients who were already on treatment.^{9,10} Much less is known about losses from the cascade of TB care prior to treatment in Ghana. We hypothesized suboptimal adherence to the national standard operating procedures for TB case detection in health facilities. We aimed to assess the coverage of TB symptom screening and sputum test-requesting practices among healthcare workers in a municipal hospital in Ghana.

Methods

Study setting

The study was conducted at outpatient clinics at the hospital in Ketu South Municipality of the Volta region, Ghana. In 2018, the municipality notified 172 TB cases out of a target of 546 estimated based on the 2013 national TB prevalence survey.¹¹ The municipality has eight health centres and one hospital. The hospital outpatient clinics provide several primary health care services. Persons identified in peripheral health centres as requiring further assessment or TB testing are referred to the hospital.¹² The hospital was chosen as the study site because it is the only testing centre for TB in the municipality with a laboratory that performs TB testing using Xpert MTB/RIF (Cepheid, Sunnyvale CA, USA). Tuberculosis diagnostic services are provided according to the national standard operating procedures for TB case detection.

Study design

We carried out a cross-sectional study using exit interviews.

Study population

We recruited adults aged 18 years and above with at least one symptom suggestive of TB defined according to WHO criteria (cough, fever, night sweats or weight loss),¹³ exiting the health facility after seeking care for their own health.

Sampling strategy and data collection procedure

Adults exiting the health facility on weekdays from September to November 2018, between 8am and 3pm, were approached by trained research assistants. Research staff attempted to approach consecutive adults; if the number of exiting adults exceeded the capacity of the research team to approach them, staff approached the closest individual. Those who reported seeking care for themselves were screened with a TB symptom questionnaire. Those who reported at least one symptom suggestive of TB were invited to be part of the study and those consenting were consecutively enrolled. A standardised questionnaire was used to collect data, including socio-demographic characteristics, reason for clinic visit, TB-related symptoms, whether these symptoms were reported to the healthcare worker and whether a sputum test was requested. In line with national criteria, study staff requested participants who reported a cough longer than two weeks, or a cough of any duration plus at least two other TB-related symptoms, to produce a single spot sputum sample for testing in the hospital

laboratory using the Xpert MTB/RIF assay. In addition, those self-reporting HIV-positive status with any TB-related symptom were asked to produce sputum for laboratory testing. Research assistants coached participants who were eligible for a sputum test on how to produce quality sputum before a sputum container was given to them. Participants then went into a sputum booth to produce sputum on their own. Those who produced a sputum sample were informed of their test result and those with a positive test result were referred to the chest clinic for TB treatment. We crosschecked with the TB laboratory register at the hospital to find out if participants who reported having a sputum test requested by a healthcare worker did submit a sputum for testing. All data were collected electronically using Open Data Kit (ODK) and uploaded onto a secure server hosted by the London School of Hygiene & Tropical Medicine.

Primary outcome

The primary outcome was the proportion of participants who had a sputum test requested by a healthcare worker in the outpatient clinic, among individuals who met the criteria for a sputum test according to Ghana's national standard operating procedures for TB case detection.

Sample size

We assumed that 25% of patients reporting a cough >2 weeks to a healthcare worker would be asked to submit sputum for a TB test;⁴ to estimate the 95% confidence interval with 8% precision, the minimum target sample size was 450 participants.

Data management and statistical analysis

Characteristics of study participants were described, and comparisons made using a chi-square test for categorical variables and a t-test for continuous variables. Logistic regression analysis was used to identify associations between being asked to give a sputum sample as the outcome variable and explanatory variables. Variables with likelihood ratio p -value <0.2 in univariable analysis were considered for inclusion in a multivariable model. However, adjusted analysis was limited by the relatively small number of outcomes and the multivariable model therefore included only covariates most strongly associated with the outcome. Data were analysed using Stata v15 (Stata Corp, College Station TX, USA).

Results

A total of 2516 people exiting the health facility were approached: 1652 (65.7%) of them had sought care at the hospital, of which 653/1652 (39.5%) were eligible for the study (Figure 1). The main reasons for ineligibility were not having any of the TB-related symptoms (865, 86.6%), being below 18 years (96, 9.6%) or being already on TB treatment (32, 3.2%). Among these 653 eligible individuals, 581 (89.0%) consented and were recruited. The main reasons for non-consent were not having time for the interview (53, 73.6%) and not being interested in the study (19, 26.4%).

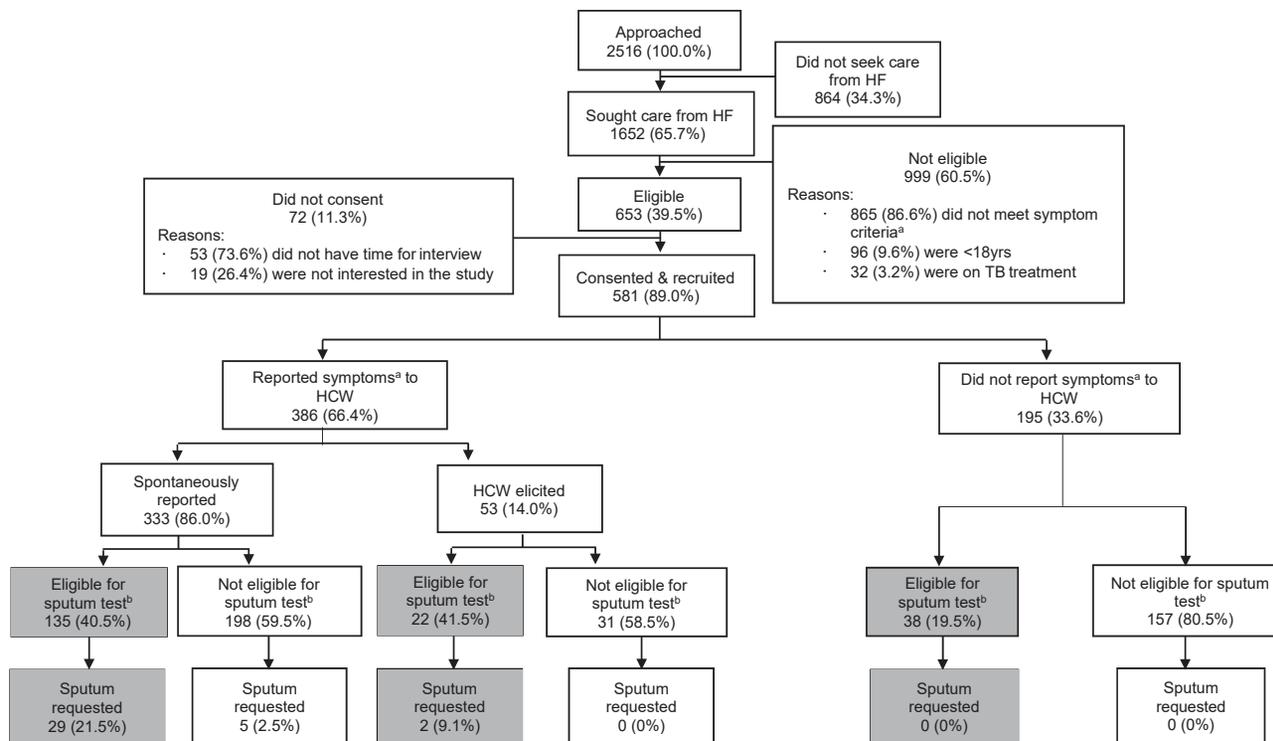


Figure 1. Flowchart of study recruitment of participants, reporting of symptoms and being asked to do a sputum test by HCW. HF: health facility; HCW: healthcare worker. ^a Symptoms considered suggestive of TB, i.e. cough, fever, weight loss, night sweats. ^b Criteria for eligibility for sputum test = cough >2 weeks or cough of any duration plus at least two other TB-related symptoms (fever, weight loss, night sweats).

Characteristics of study participants

The median age of the 581 recruited participants was 33 years (interquartile range [IQR] 24–48), most were women (510/581, 87.8%) and the majority had attained primary-level education (312/581, 53.7%) (Table 1). The most common TB-related symptoms were fever (348, 59.9%), chest pain (282, 48.5%) and cough (270, 46.5%). The main reason for visiting the hospital for most participants was for general medical care (237/581, 40.8%). There was strong evidence that those who reported symptoms to a healthcare worker had more TB-related symptoms ($p < 0.001$) and longer duration of symptoms ($p = 0.01$) compared to those who did not report their symptoms (Table 1).

Practices of healthcare workers

Of the 581 recruited participants, 386/581 (66.4%) had reported their symptoms to a healthcare worker. Among those who reported their symptoms, 333/386 (86.0%) had spontaneously reported their symptoms while 53/386 (14.0%) only reported their symptoms when elicited by a healthcare worker (Figure 1). Overall, 195 (33.6%) participants of the 581 recruited were eligible for a sputum test according to Ghana's national standard operating procedures for TB case detection, but only 31/195 (15.9%) had a sputum test requested by a healthcare worker. Among those who spontaneously reported their TB-related symptoms, 135/333 (40.5%) were eligible for a sputum test; however, only 29/135 (21.5%) had a sputum test requested

(Figure 1). Among the 53 participants whose symptoms were elicited by a healthcare worker, 22 (41.5%) were eligible for a sputum test, yet only 2/22 (9.1%) had a sputum test requested. Also, among participants who did not report their symptoms at all to a healthcare worker, 38/311 (19.5%) were eligible for a sputum test: none of them had a sputum test requested (Figure 1). All participants who had a sputum test requested by a healthcare worker were confirmed in the laboratory register to have submitted sputum for the test.

Reasons for not reporting symptoms to a healthcare worker

For participants (195/581, 33.6%) who did not report their TB-related symptoms to the healthcare worker, the reasons given were that the TB-related symptoms were not the reason they visited the hospital (156/195, 80.0%), they did not think it was important to report (32, 16.4%) and other reasons such as forgetting to report (7, 3.6%).

Factors associated with having a sputum test requested by a healthcare worker

In univariable analysis, there was a higher odds of having a sputum test requested by a healthcare worker among people with a longer duration of symptoms (≥ 2 weeks vs < 2 weeks, OR: 9.71, 95% CI 2.94–32.06), previous TB treatment (OR 8.52, 95%

Table 1. Characteristics of people exiting health facility and reporting at least one TB-related symptom in Ketu South Municipality, Ghana

Characteristics	Total N=581 n (column %)	Reported symptoms to HCW n=386		Did not report symptoms to HCW n=195 n (row %)	^a p-value
		Spontaneously reported n=333 n (row %)	HCW elicited n=53 n (row %)		
Age, years (IQR)	33 (24–48)	37 (25–51)	34 (22–48)	29 (22–39)	<0.001
Gender					0.28
Male	71 (12.2)	45 (63.4)	8 (11.3)	18 (25.4)	
Female	510 (87.8)	288 (56.5)	45 (8.8)	177 (34.7)	
Educational level					0.12
No formal education	148 (25.5)	97 (65.5)	8 (5.4)	43 (29.1)	
Primary/JHS	312 (53.7)	171 (54.8)	30 (9.6)	111 (35.6)	
Secondary/tertiary	121 (20.8)	65 (53.7)	15 (12.4)	41 (33.9)	
Symptoms (yes)^b					
Cough	270 (46.5)	180 (66.7)	28 (10.4)	62 (23.0)	<0.001
Fever	348 (59.9)	220 (63.2)	32 (9.2)	96 (27.6)	0.001
Chest pain	282 (48.5)	186 (66.0)	29 (10.3)	67 (23.8)	<0.001
Excessive night sweat	163 (28.1)	88 (54.0)	14 (8.6)	61 (37.4)	0.47
Weight loss	214 (36.8)	113 (52.8)	28 (13.1)	73 (34.1)	0.03
Number of symptoms					<0.001
1	208 (35.8)	98 (47.1)	16 (7.7)	94 (45.2)	
2	165 (28.4)	99 (60.0)	13 (7.9)	53 (32.1)	
3	116 (20.0)	71 (61.2)	11 (9.5)	34 (29.3)	
≥4	92 (15.8)	65 (70.7)	13 (14.1)	14 (15.2)	
Duration of symptoms					0.01
<2 weeks	252 (44.4)	155 (61.5)	13 (5.2)	84 (33.3)	
≥2 weeks	315 (55.6)	174 (55.2)	39 (12.4)	102 (32.4)	
HIV status					0.19
Positive	63 (10.8)	40 (63.5)	3 (4.8)	20 (31.8)	
Negative	307 (52.8)	163 (53.1)	30 (9.8)	114 (37.1)	
Don't know	211 (36.3)	130 (61.6)	20 (9.5)	61 (28.9)	
Health histories (yes)^b					
Diabetes	29 (5.0)	15 (51.7)	3 (10.3)	11 (37.9)	0.82
Hypertension	145 (25.0)	91 (62.8)	17 (11.7)	37 (25.5)	0.05
Ever treated for TB	22 (3.8)	13 (59.1)	3 (13.6)	6 (27.3)	0.67
Main reason for visit					<0.001
TB symptoms	96 (16.5)	92 (95.8)	4 (4.2)	0 (0.0)	
Routine ART clinic	40 (6.9)	26 (65.0)	3 (7.5)	11 (27.5)	
Antenatal care	129 (22.2)	54 (41.9)	10 (7.8)	65 (50.4)	
General medical care	237 (40.8)	133 (56.1)	30 (12.7)	74 (31.2)	
Other ^c	79 (13.6)	28 (35.4)	6 (7.6)	45 (57.0)	
Number of times ever sought care for TB symptoms					0.37
0	106 (18.2)	52 (49.1)	11 (10.4)	43 (40.6)	
1–2	408 (70.2)	240 (58.8)	35 (8.6)	133 (32.6)	
≥5	67 (11.8)	41 (61.2)	7 (10.5)	19 (28.4)	

ART: antiretroviral therapy; HCW: healthcare worker; HIV: human immunodeficiency virus; JHS (12–14 years): Junior High School; TB: tuberculosis.

^a p-value is for the comparison between those who reported their symptoms spontaneously, those whose symptoms were elicited by a health-care worker and those who did not report their symptoms at all.

^b Response is not mutually exclusive.

^c Diabetic clinic, hypertension clinic, mental health clinic, eye clinic and family planning unit.

Table 2. Factors associated with being asked to submit sputum by a healthcare worker, Ketu South Municipality, Ghana

Variable	N=581						
	Total (n)	Submitted sputum (n)	%	Univariable analysis		Multivariable analysis	
				OR (95%CI)	<i>p</i>	aOR (95% CI)	<i>P</i>
Gender					^a <0.01		
Female	510	25	4.9	Reference			
Male	71	11	15.5	3.56 (1.67–7.59)	<0.01		
Age group (years)					^a 0.07		
18–39	371	17	4.6	Reference			
40–60	143	11	7.7	1.74 (0.79–3.80)	0.17		
>60	67	8	11.9	2.82 (1.17–6.84)	0.02		
Educational level					^a 0.19		
No formal education	148	14	9.5	Reference			
Primary/JHS	312	16	5.1	0.52 (0.25–1.09)	0.08		
Secondary/tertiary	121	6	5.0	0.50 (0.19–1.34)	0.17		
Number of symptoms					^a <0.001		
1–2	373	11	3.0	Reference		Reference	
≥3	208	25	12.0	4.50 (2.16–9.34)	<0.001	^b 3.14 (1.47–6.71)	<0.01
Duration of symptoms					^a <0.001		
<2 weeks	252	3	1.2	Reference		Reference	
≥2 weeks	315	33	10.5	9.71 (2.94–32.06)	<0.001	^b 6.99 (2.08–23.51)	<0.01
HIV status					^a 0.54		
Negative	307	16	5.2	Reference			
Positive	63	5	7.9	1.56 (0.55–4.45)	0.40		
Don't know	211	15	7.1	1.39 (0.67–2.88)	0.37		
Ever treated for TB					^a <0.001		
No	559	29	5.2	Reference		Reference	
Yes	22	7	31.8	8.52 (3.23–22.54)	<0.001	^b 6.25 (2.24–17.46)	<0.001
Diabetes					^a 0.50		
No	552	35	6.3	Reference			
Yes	29	1	3.5	0.53 (0.07–3.99)	0.54		
Main reason for visit					^a <0.001		
General medical care	237	14	5.9	Reference			
TB symptoms	96	16	16.7	3.12 (1.49–6.82)	<0.01		
Routine ART clinic	40	3	7.5	1.29 (0.35–4.71)	0.70		
Antenatal care	129	1	0.8	0.12 (0.02–0.96)	0.05		
Other ^c	79	2	2.5	0.41 (0.92–1.86)	0.25		
Number of times sought care for TB symptoms					^a 0.02		
0	106	7	6.6	Reference			
1–2	408	19	4.7	0.69 (0.28–1.69)	0.42		
≥3	67	10	14.9	2.48 (0.90–6.88)	0.08		

ART: antiretroviral therapy; HIV: human immunodeficiency virus; JHS (12–14 years): Junior High School; *P*: *p*-value; TB: tuberculosis.

^a Log likelihood *p*-value.

^b In order to prevent overfitting of the adjusted model, it was restricted to the three covariates with the strongest association with the outcome.

^c Diabetic clinic, hypertension clinic, mental health clinic, eye clinic and family planning unit.

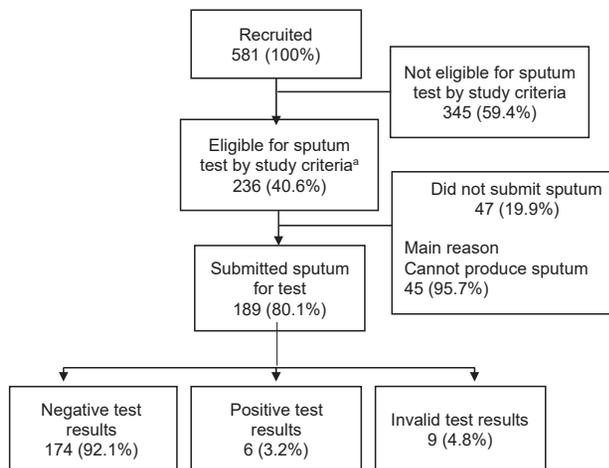


Figure 2. Flowchart for laboratory testing (Xpert MTB/RIF) using study criteria. ^a Eligibility for sputum test by study criteria = cough >2 weeks or cough of any duration plus at least two other TB-related symptoms (fever, weight loss, night sweats) or self-reporting HIV-positive status with any TB-related symptom.

CI 3.23–22.54), an increasing number of symptoms (≥ 3 vs 1–2, OR 4.50, 95% CI 2.16–9.34), males (OR 3.56, 95% CI 1.67–7.59), attending for TB-related symptoms vs general medical care (OR 3.12, 95% CI 1.49–6.82) and older age (OR 2.82, 95% CI 1.17–6.84 and 1.74, 95% CI 0.79–3.80 for >60 and 40–60 vs 18–39 years respectively, Table 2). After adjusting for confounders in multi-variable analysis, there remained strong associations between sputum being requested and duration of symptoms (adjusted OR [aOR] 6.99, 95% CI 2.08–23.51), previous TB treatment (aOR 6.25, 95% CI 2.24–17.46) and increasing number of symptoms (aOR 3.14, 95% CI 1.47–6.71) (Table 2). In addition, to explore any potential confounding effect of age and gender, a separate model was developed to assess the association of duration of symptoms with having a sputum test requested after adjusting for age and gender (data not shown). The strength of association was similar to that presented in Table 2, thus not suggesting confounding by age or gender. Similar models were run for previous TB treatment and number of symptoms, and similarly the strength of association remained the same (data not shown).

Laboratory findings

A total of 236/581 (40.6%) participants were eligible according to study criteria to produce a spot sputum sample for laboratory testing using Xpert MTB/RIF (Figure 2). Among these, 195 met the national criteria for sputum testing, and an additional 41 met study criteria based on self-reporting HIV-positive status who did not meet national criteria but reported any of cough, weight loss, fever or night sweats. Of those eligible, 189/236 (80.1%) produced a sputum sample for the test. The majority of the sputum samples (125/189, 66.1%) were salivary and 64/189 (33.9%) were mucopurulent. Test results showed 174/189 (92.1%) were negative, 6/189 (3.2%) were positive and 9/189 (4.8%) were invalid probably due to laboratory error (Figure 2). All positive results were without rifampicin resistance.

Discussion

Findings from this study show that patients with TB-related symptoms visiting outpatient departments for primary health-care services were not optimally screened for symptoms of TB, even though the national standard operating procedure for TB case detection specifies that people attending outpatient departments of health facilities should be asked about TB-related symptoms. Even among patients who reported symptoms and were eligible for a sputum test, a large proportion never had the test requested by a healthcare worker. This shows that there are missed opportunities for TB diagnosis in the health facility.

A study in Cape Town, South Africa in 2013 also showed that people with respiratory symptoms exiting primary health facilities were not asked about their symptoms and did not have a sputum test requested.¹⁴ They recommended that intensified case finding should not be limited to only those who report their respiratory symptoms. Other studies have demonstrated missed opportunities for early TB diagnosis in health facilities due to non-adherence to diagnostic guidelines.^{15–17} In a sub-study using exit interviews at clinics participating in a pragmatic cluster randomised trial evaluating programmatic roll-out of Xpert MTB/RIF in South Africa (XTEND), the change from sputum microscopy to Xpert MTB/RIF did not substantially influence healthcare workers' suboptimal practices in requesting sputum tests among patients presenting with TB symptoms.¹⁸

The main reason patients did not report their symptoms to a healthcare worker in our study was because they were not seeking care for these symptoms or did not find it important to report. The study in Cape Town conducted in primary health facilities also found that among study participants who tested positive for TB, none of them reported their symptoms to a healthcare worker when they visited the clinic.¹⁴ Several other studies have shown that patients delay in seeking care for their TB-related symptoms.^{3,19–21} It is imperative that we find ways to encourage patients to seek care early and to report all their symptoms when they visit a health facility.

Our study showed that persons with a longer duration of symptoms or prior TB treatment were more likely to be asked to submit sputum for a test. Studies in Uganda and South Africa have all shown that healthcare workers tend to request sputum tests in persons with longer duration of symptoms.^{18,22} However, a study conducted in the Greater Accra region of Ghana from 2010 to 2013 showed that more TB cases were identified when screening was done using the new diagnostic guidelines of a cough of any duration (>24 hours) and any other TB-related symptom compared to using just a cough >2 weeks.²³ This confirms that using longer duration of symptoms to investigate for TB could lead to missed opportunities for early diagnosis. This, however, has high cost implications for diagnosis. Therefore, there is the need to find efficient and cost-effective strategies for diagnosis.

In this study, the majority of participants were females, and this reflects the true outpatient department attendance where more women visit the outpatient department for care than men. This is supported by data from the district health information management system showing that from 2016 to 2019, 72.2–72.6% of outpatient department attendances were by women.²⁴

There are some limitations to this study. We depended on participants' self-report of having reported or not reported their symptoms to a healthcare worker, which we could not verify from clinic records. For those who said that they had had a sputum test requested, we crosschecked from the laboratory register to see if they had submitted a sputum sample. However, the use of exit interviews was a robust way to reduce recall bias since patients were interviewed immediately after consultation with a healthcare worker. The low yield of TB cases among participants submitting a sputum sample to the study team could be as a result of poor quality of sputum samples since most of the samples were salivary. This highlights the need for staff to supervise patients to ensure good quality sputum samples. In addition, the study was conducted in only the municipal hospital, and only during working hours, so findings cannot necessarily be generalized to other health facilities in the municipality.

Conclusion

Opportunities to identify people with TB were missed in this health facility; both coverage of TB symptom screening and testing of those fulfilling criteria for testing were low. This shows suboptimal adherence to national guidelines by healthcare workers in the study setting. There is the need to improve the system to maximise early detection of TB among people attending health facilities.

Authors' contributions: JD and ADG conceived and designed the study. Data capture tools were designed by JD, ADG, DG and CTN. Data collection was done by JD and CTN. Data analysis and interpretation were done by JD, DG, CTN and ADG. The first draft of the manuscript was written by JD. Critical comments were provided by ADG, DG, CTN and FB. All authors read and approved the final manuscript.

Acknowledgements: The authors are grateful to staff of the Municipal Hospital, the Municipal Health Directorate, research assistants and all study participants for their cooperation and support. Thanks to the Commonwealth Scholarship Commission for granting JD a scholarship funded by the UK government for her doctoral studies. The funder had no involvement in any aspect of the study or the decision to publish the manuscript.

Funding: None.

Competing interests: None declared.

Ethical approval: Ethical approval was obtained from the Ghana Health Service Ethics Review Committee and London School of Hygiene & Tropical Medicine Ethics Committee. Written informed consent was obtained from literate participants, and for those who could not read and write, consent was documented with a thumbprint in the presence of a literate witness.

Data availability statement: The data underlying this article cannot be shared publicly due to sensitive patient information. The data will be shared on reasonable request to the corresponding author.

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Chapter 6: Research paper 2: Where are patients missed in the tuberculosis diagnostic cascade? A prospective cohort study in Ghana

This chapter provides in-depth analysis of data to determine the proportion of patients with a request for sputum test who submitted a sputum for testing, the time from test request to submitting sputum, and factors contributing to non-submission of sputum for testing (objective 2). It also provides analysis of data to compare the time from test request to submitting sputum among patients attending a health facility with vs. without a co-located laboratory (objective 3). The methodology used, causal analysis and predictive analysis are also described in this chapter. This chapter was published on 19th March 2020 in PloS One [131]. The manuscript was published under a Creative Commons Attribution License, (CC BY 4.0) and the published manuscript is included in full below.

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed **for each** research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1514031	Title	Ms.
First Name(s)	Joyce Berkumwin		
Surname/Family Name	Der		
Thesis Title	Pathways to tuberculosis diagnosis and treatment in Ghana: identifying the gaps and seeking solutions		
Primary Supervisor	Alison Grant		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	PloS One		
When was the work published?	19th March 2020		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was jointly responsible with Prof Alison Grant for the conceptualisation of the paper. I collected the data, conducted the data analysis and wrote the first draft of the paper. I prepared the subsequent revisions with consideration of comments from co-authors.
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SECTION E

Student Signature	
Date	15th September 2020

Supervisor Signature	
Date	16 September 2020

RESEARCH ARTICLE

Where are patients missed in the tuberculosis diagnostic cascade? A prospective cohort study in Ghana

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OPEN ACCESS

Citation: Der JB, Grint D, Narh CT, Bonsu F, Grant AD (2020) Where are patients missed in the tuberculosis diagnostic cascade? A prospective cohort study in Ghana. PLoS ONE 15(3): e0230604. <https://doi.org/10.1371/journal.pone.0230604>

Editor: HASNAIN SEYED EHTESHAM, Jamia Hamdard, INDIA

Received: December 10, 2019

Accepted: March 3, 2020

Published: March 19, 2020

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: <https://doi.org/10.1371/journal.pone.0230604>

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Data Availability Statement: The data underlying this study contain sensitive patient information and cannot be made publicly available. The data have been deposited with the London School of Hygiene

Abstract

Background

Ghana's national prevalence survey showed higher than expected tuberculosis (TB) prevalence, indicating that many people with TB are not identified and treated. This study aimed to identify gaps in the TB diagnostic cascade prior to starting treatment.

Methods

A prospective cohort study was conducted in urban and rural health facilities in south-east Ghana. Consecutive patients routinely identified as needing a TB test were followed up for two months to find out if sputum was submitted and/or treatment started. The causal effect of health facility location on submitting sputum was assessed before risk factors were investigated using logistic regression.

Results

A total of 428 persons (mean age 48 years, 67.3% female) were recruited, 285 (66.6%) from urban and 143 (33.4%) from rural facilities. Of 410 (96%) individuals followed up, 290 (70.7%) submitted sputum, among which 27 (14.1%) had a positive result and started treatment. Among those who visited an urban facility, 245/267 (91.8%) submitted sputum, compared to 45/143 (31.5%) who visited a rural facility. Participants recruited at the urban facility were far more likely to submit a sputum sample (odds ratio (OR) 24.24, 95%CI 13.84–42.51). After adjustment for confounding, there was still a strong association between attending the urban facility and submitting sputum (adjusted OR (aOR) 9.52, 95%CI 3.87–23.40). Travel distance of >10 km to the laboratory was the strongest predictor of not submitting sputum (aOR 0.12, 95%CI 0.05–0.33).

and Tropical Medicine's Data Compass and are accessible using the following DOI: <https://doi.org/10.17037/DATA.00001529>. Interested researchers wishing to request access to the data can do by clicking the "request access" button to fill a form

which will be automatically submitted to the research data manager at London School of Hygiene and Tropical Medicine and to the first author. In addition, requests can be sent to researchdatamanagement@lshtm.ac.uk.

Funding: The author(s) received no specific funding for this work.

Competing interests: The authors have declared that no competing interest exist.

Conclusion

The majority of presumptive TB patients attending a rural health facility did not submit sputum for testing, mainly due to the long travel distance to the laboratory. Bridging this gap in the diagnostic cascade may improve case detection.

Introduction

Ghana is one of the tuberculosis (TB) and human immunodeficiency virus (HIV) high burden countries according to the World Health Organization (WHO) [1]. Ghana's TB case notification rate has declined from 56/100,000 in 2014 [2] to 52/100,000 in 2017 [3] compared to an estimated incidence of 152/100,000 based on the 2013 national TB prevalence survey [4]. Ghana's national TB prevalence survey also highlighted weaknesses in the care cascade where of persons with prolonged cough who visited a health facility, only 25% submitted sputum for testing [4].

In Ghana, TB diagnosis and treatment is mainly done at government health facilities. Until recently, sputum smear microscopy was the main diagnostic method, but Xpert MTB/RIF has now been introduced with 105 GeneXpert machines installed nationwide by 2017 [3]. Most diagnostic laboratories are located at secondary and tertiary levels of care but not at peripheral levels such as health centres mostly in rural areas. Therefore, a person with symptoms of TB might be identified at a health centre but will have to travel themselves to the district hospital for a sputum test to confirm the diagnosis. This creates an obstacle to diagnosis and treatment and potential loss within the cascade of TB care.

There is a wealth of literature on health facility contribution to delayed or missed diagnosis of TB and pre-treatment loss-to-follow up [5–9]; however, most are cross-sectional studies involving TB patients already on treatment, thus excluding those who never started treatment, or retrospective reviews of secondary data [10]. To better understand losses from the care cascade, we conducted a prospective observational cohort study to identify where and when potential TB patients are missed in the diagnostic cascade. We hypothesized that distance to the laboratory was a key determinant of whether sputum was submitted or not, therefore, persons with symptoms suggestive of TB (presumptive TB patients) were less likely to submit a sputum if they attended a rural health facility without a laboratory compared to those attending an urban facility with a co-located laboratory. Our aim was to determine if persons asked to submit sputum for testing for TB submitted sputum, and whether this was associated with urban vs. rural location of the facility; also whether they received test results, and if the results were positive, whether they started TB treatment.

Materials and methods

Study setting

The study was conducted in Ketu South Municipality in the Volta region of Ghana, which shares boundaries with the Republic of Togo. The municipality has one government hospital and eight health centres. In 2017, the municipality notified 290 TB cases out of a target of 534 estimated based on the 2013 national TB prevalence survey. In 2018, it notified 172 TB cases out of a target of 546, indicating a decreased case detection rate from 53.8% in 2017 to 31.5% in 2018 [11]. There is only one TB diagnostic laboratory in the municipality, located at the municipal hospital. All other health facilities in the municipality refer patients with symptoms

of TB to the municipal hospital for testing. The study was thus conducted in the municipal hospital, and four health centres without co-located TB diagnostic facilities in rural areas located 10 to 20 km from the municipal hospital. The four health centres were selected based on high outpatient department (OPD) attendance and to represent the different health demarcated sub-municipalities.

Study design

This was a prospective observational cohort study among adults aged ≥ 18 years with or without symptoms suggesting TB, self-presenting at the health facility, who were identified routinely by a health worker as needing TB investigation and given a laboratory request to do a sputum test or referred to the municipal hospital.

Sampling strategy. We consecutively invited eligible patients from the selected health facilities from May 2018 until the target study population had been enrolled in February 2019.

Data collection

At enrolment, trained research assistants collected baseline information on socio-demographic characteristics, symptoms of illness, health histories and date the sputum test was requested, using a standardised questionnaire. The questionnaire was pretested at the municipal hospital in a population similar to the study population. Following pretesting, revisions were made to improve comprehensibility and understanding. Participants were followed up for two months after the test request, via two-weekly phone calls to find out if sputum had been submitted, when and where it was submitted and the result of the test; and among those with a positive test result, to determine whether the patient had started TB treatment. Those without phones were visited at their homes once monthly for two months. Geographic positioning coordinates (GPS) of participant households and health facilities attended were collected. Coordinates were stored separately from participant information to ensure confidentiality. All data were collected electronically using Open Data Kit (ODK) and uploaded onto a secured server hosted by the London School of Hygiene & Tropical Medicine.

Sample size

Assuming 49% of participants attending an urban facility would submit sputum [7], we calculated that a sample size of 414 would provide 80% power to detect a difference of 15% in the proportion of participants who submitted a sputum in an urban versus a rural facility with alpha set to 5% and allowing 10% loss to follow up.

Measures and definitions

TB symptoms were defined as the four cardinal symptoms of TB (cough, fever, weight loss and night sweats) and/or other TB symptoms (chest pain, coughing up blood, tiredness, shortness of breath and/or lump in neck). Rural and urban residence was defined based on the municipal health directorate categorization. Socioeconomic status was generated using asset scores which included 33 items, based on methods used by demographic and health surveys [12].

Participants' attitudes of stigma towards people with TB were measured using a tool developed by Van Rie et al, based on 12 questions measured on a five-point Likert scale, with 1 being lowest score for stigma and 5 being the highest [13]. The mean score across the 12 questions was calculated and dichotomized to represent high perceived or low perceived stigma. Distance from a participant's residence to the TB diagnostic facility was generated from GPS coordinates.

Body mass index (BMI) was categorized according to WHO guidelines [14]. A Karnofsky

score was estimated as a measure of illness severity [15]. Diabetes and HIV status were defined based on participant self-report.

Primary outcome. This was the proportion of participants who submitted a sputum sample.

Data management and statistical analysis

Primary analysis assessed the causal effect of type of health facility attended (urban versus rural) on the probability of submitting sputum, using logistic regression. Any factor that changed the odds ratio by approximately 10% in bivariable analysis was considered a potential confounder and adjusted for in a final multivariable model. Kaplan-Meier analysis was used to compare the time to submitting sputum between urban and rural facility attendees. Predictive modelling was employed to assess risk factors associated with submitting sputum using logistic regression. Variables with likelihood ratio p-value <0.2 in univariable analysis were included in a multivariable model. Data were analysed using Stata v15 (Stata Corp, College Station TX, USA).

Ethical considerations

Ethical approval was obtained from the Ghana Health Service Ethics Review Committee and London School of Hygiene & Tropical Medicine Ethics Committee. Written informed consent was obtained from literate participants and for those who could not read and write, consent was documented with a thumbprint in the presence of a literate witness.

Results

A total of 468 persons were approached: of this number 437 (93.4%) were eligible, 428/437 (97.9%) consented and were recruited (285 from urban facility and 143 from rural facilities). The main reason for non-eligibility was being <18 years (28, 90.3%). Of the 428 recruited, 397 (92.8%) completed follow-up for two months, 13 (3.0%) died at some point in time within the two-month follow-up period and 17 (4.0%) were lost to follow up (Fig 1).

Baseline characteristics of study participants

Among 428 participants, the mean age was 48 years (standard deviation [SD]18.8) and this was similar among urban and rural facilities (Table 1). The majority of participants (288, 67.3%) were female and most (237, 55.4%) had attained primary level education. The median distance between participants' home and the laboratory was 17.3 km (interquartile range [IQR]16.7–19.4) for rural facility attendees and 2.6 km (IQR 1.3–10.0) for urban facility attendees. Most participants attending rural facilities were in the lowest socioeconomic tertile (58, 40.6%) compared to those attending urban facilities (85, 29.8%) and more than half (255, 59.6%) of study participants had a high perception of TB related stigma.

Cascade of care

Of 410 presumptive TB patients asked to do a sputum test who were followed up, 290 (70.7%) submitted sputum for the test; 194/290 (66.9%) received a test result; 27/194 (13.9%) had a positive test result and all 27 started TB treatment (Fig 2). Sixteen additional patients started treatment based on chest radiograph findings. Stratifying by type of health facility attended, 245/267 (91.8%) submitted sputum among those attending the urban facility and 45/143 (31.5%) among those attending rural health facilities (Fig 2).

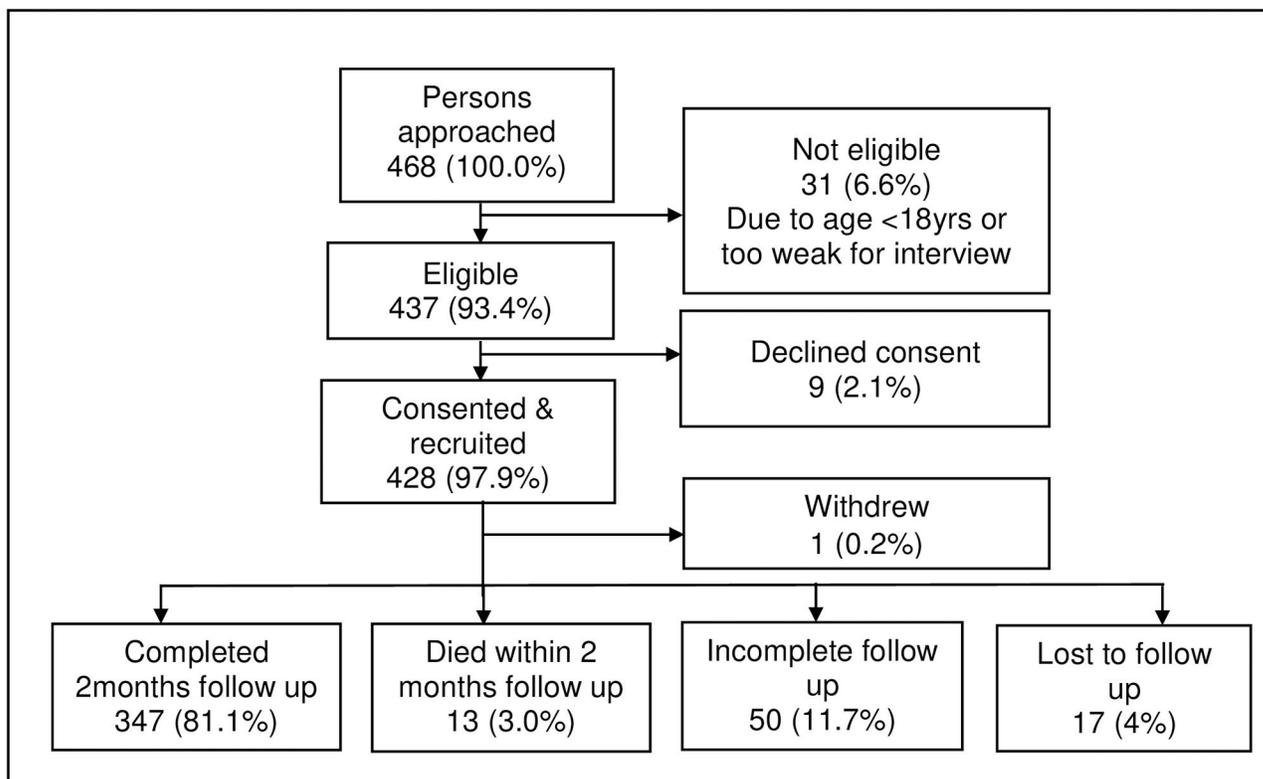


Fig 1. Flowchart of study recruitment and follow up of people requested to give sputum for TB investigation in Ketu South Municipality, Ghana.

<https://doi.org/10.1371/journal.pone.0230604.g001>

Time to submitting sputum among rural and urban health facility attendees

In Kaplan-Meier analysis, there was strong evidence for a difference in time to submitting sputum by location of health facility, where urban facility attendees submitted sputum earlier than rural facility attendees ($P < 0.001$) (Fig 3). Of urban facility attendees, 229 (80.4%) submitted sputum on the day the test was requested, 10 (3.5%) submitted within 7 days and 6 (2.1%) after 14 days. However, among rural facility attendees, only 6 (4.2%) submitted sputum on the day the test was requested, 18 (12.6%) within 7 days and 21 (14.7%) after 14 days (Fig 3).

Reasons for not submitting sputum

The main reasons given by participants for not submitting sputum were being too busy to go to the laboratory (58/116, 50.0%), feeling well so not seeing the need to do the test (19, 16.4%), having no money to travel to do the test (17, 14.7%) and being unable to produce sputum (15, 12.9%).

Association between type of health facility attended and submitting sputum

In causal analysis, participants recruited from the urban health facility had a much higher odds (unadjusted odds ratio [OR] 24.24, 95% CI 13.84–42.51) of submitting sputum compared to those recruited at a rural health facility. Adjusting for distance from participants' residence to the laboratory resulted in the biggest reduction in the odds of submitting sputum, comparing

Table 1. Baseline characteristics of participants (people requested to give sputum for TB investigation) in Ketu South Municipality, Ghana.

Characteristics	Variable	Urban health facility, n = 285	Rural health facility, n = 143	Total, N = 428	P-value
		n (%)	n (%)	n (%)	
Age (years)	Mean \pm SD	47.6 \pm 17.9	48.4 \pm 20.4	47.9 \pm 18.8	0.901
Gender	Male	99 (34.7)	41 (28.7)	140 (32.7)	0.207
	Female	186 (65.3)	102 (71.3)	288 (67.3)	
Educational level	No formal education	70 (24.6)	34 (23.8)	104 (24.3)	0.982
	Primary/JHS	157 (55.1)	80 (55.9)	237 (55.4)	
	Secondary/Tertiary	58 (20.4)	29 (20.3)	87 (20.3)	
Place of residence	Urban	205 (71.9)	1 (0.7)	206 (48.1)	<0.001
	Rural	80 (28.1)	142 (99.3)	222 (51.9)	
Distance to laboratory (km)	Median (IQR)	2.6 (1.3–10.0)	17.3 (16.7–19.4)	10.0 (1.6–17.3)	<0.001
Socioeconomic status (tertiles)	High	114 (40.0)	28 (19.6)	142 (33.2)	<0.001
	Middle	86 (30.2)	57 (39.9)	143 (33.4)	
	Low	85 (29.8)	58 (40.6)	143 (33.4)	
TB symptoms (yes)	Cough	279 (97.9)	142 (99.3)	421 (98.4)	0.279
	Fever	204 (71.6)	115 (80.4)	319 (74.5)	0.048
	Night sweat	70 (24.6)	24 (16.8)	94 (22.0)	0.067
	Weight loss	79 (27.7)	22 (15.4)	101 (23.6)	0.005
Symptoms duration (days)	Median (IQR)	19 (7–31)	7 (7–14)	14 (7–28)	<0.001
HIV status	Positive	32 (11.2)	0 (0.0)	32 (7.5)	<0.001
	Negative	72 (25.3)	17 (11.9)	89 (20.8)	
	Don't know	181 (63.5)	126 (88.1)	307 (71.7)	
Diabetes	No	273 (95.8)	142 (99.3)	415 (97.0)	0.046
	Yes	12 (4.2)	1 (0.7)	13 (3.0)	
BMI (kg/m ²)	Median (IQR)	24.6 (19.7–34.1)	25.1 (22.0–30.3)	24.8 (20.3–32.6)	0.077
Severity of illness (Karnofsky score)	Mean \pm SD	81.2 \pm 10.8	86.1 \pm 6.4	82.9 \pm 9.8	<0.001
Stigma	Low perceived stigma	138 (48.4)	35 (24.5)	173 (40.4)	<0.001
	High perceived stigma	147 (51.6)	108 (75.5)	255 (59.6)	

N = total number, n = number within facility, SD = standard deviation, IQR = interquartile range, BMI = body mass index, TB = tuberculosis, HIV = human immunodeficiency virus, JHS (13–15 years) = junior high school

<https://doi.org/10.1371/journal.pone.0230604.t001>

urban and rural facility attendees (adjusted OR [aOR] 12.98, 95% CI 5.95–28.30) (Table 2). After adjusting for all other confounders, in the final adjusted model, a strong association between attending the urban versus rural health facilities and submitting sputum remained (aOR 9.52, 95% CI 3.87–23.40) (Table 2).

Factors associated with submitting sputum among study participants attending an urban or rural health facility

In univariable analysis (Table 3), rural versus urban residence (OR 0.08, 95% CI 0.05–0.15); longer travel distance to the laboratory (OR 0.06, 95% CI 0.03–0.11 for 10–20 km and OR 0.17, 95% CI 0.07–0.41 for >20 km versus <10 km); and high versus low perception of TB-related stigma (OR 0.39, 95% CI 0.24–0.62) were associated with a lower odds of submitting sputum. Prior TB treatment (OR 4.00, 95% CI 1.19–13.460); more reported symptoms (OR 2.87, 95% CI 1.47–5.59 for >4 versus 1–2), longer symptom duration (OR 2.20, 95% CI 1.39–3.50 for >14 versus \leq 14 days); and visit to at least one care providers prior to current clinic visit (OR 3.18, 95% CI 1.88–5.10) were predictors of submitting sputum.

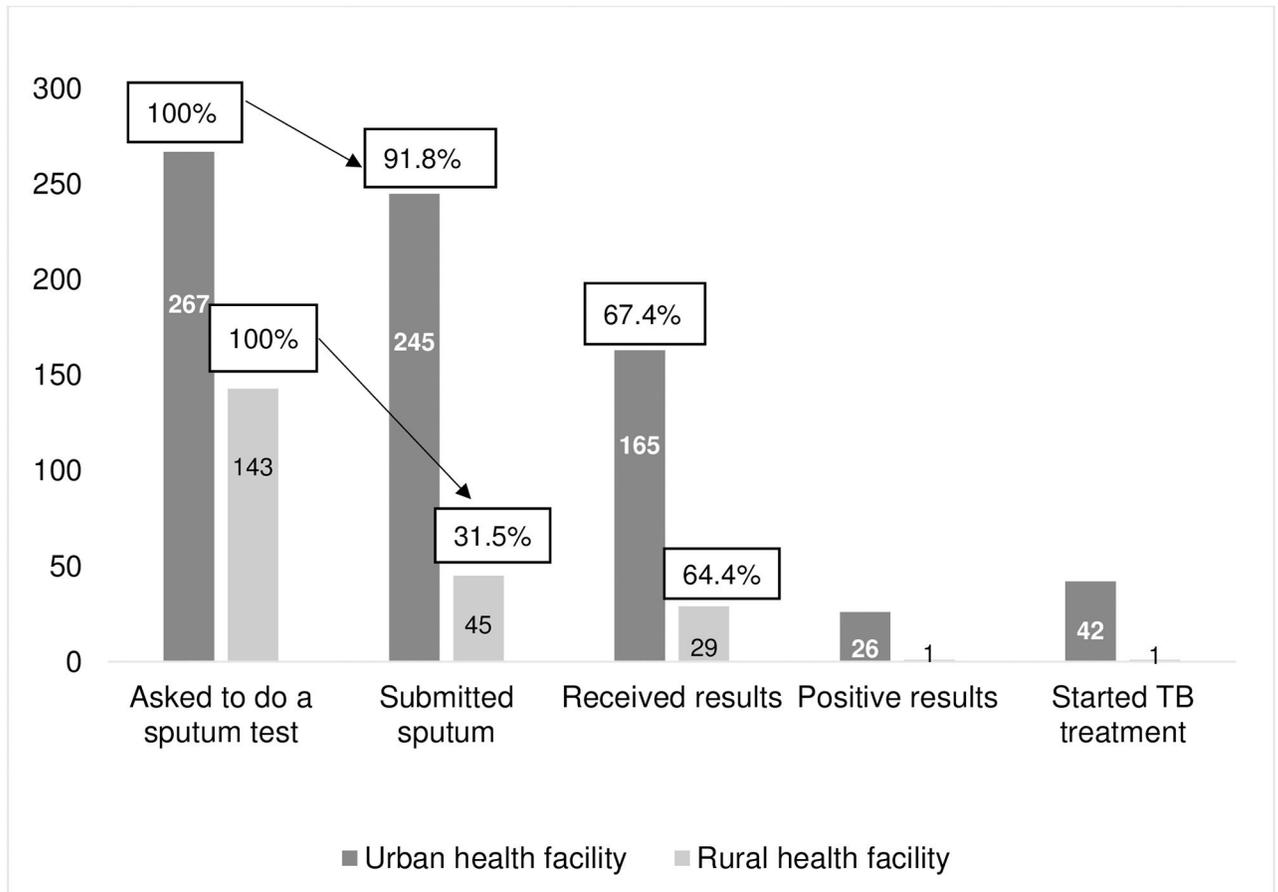


Fig 2. Cascade of TB care among people requested to give sputum for TB investigation in Ketu South Municipality, Ghana.

<https://doi.org/10.1371/journal.pone.0230604.g002>

In predictive multivariable analysis, longer travel distance to the laboratory and high perception of TB-related stigma remained associated with a lower odds of submitting sputum (Table 3).

Discussion

In south-east Ghana, more than a quarter of presumptive TB patients never submitted a sputum, and non-submission of sputum was most strongly associated with longer distance to the laboratory. Studies from Zimbabwe, India and Tanzania have also reported high pre-diagnosis loss-to-follow, 25%, 30.4% and 44% respectively [16–18], and some studies, including one from Ghana, showed that attending rural health clinics and long travel distance were risk factors for delay or pre-diagnosis loss to follow-up [7, 10, 17, 19]. In contrast, pre-diagnosis attrition was lower in South Africa and China (5% and 11% respectively) [20, 21], perhaps because in South Africa, sputum specimens are transported free to a central laboratory for diagnosis.

TB-related stigma was independently associated with non-submission of sputum, consistent with findings from a study in India [22]. Several studies have reported high perception of TB-associated stigma [23–27], and specific actions are needed to counter this [28, 29].

An encouraging finding was that all patients with a positive TB result on their sputum were promptly put on treatment. This contrasts with a study of routine data from a regional hospital

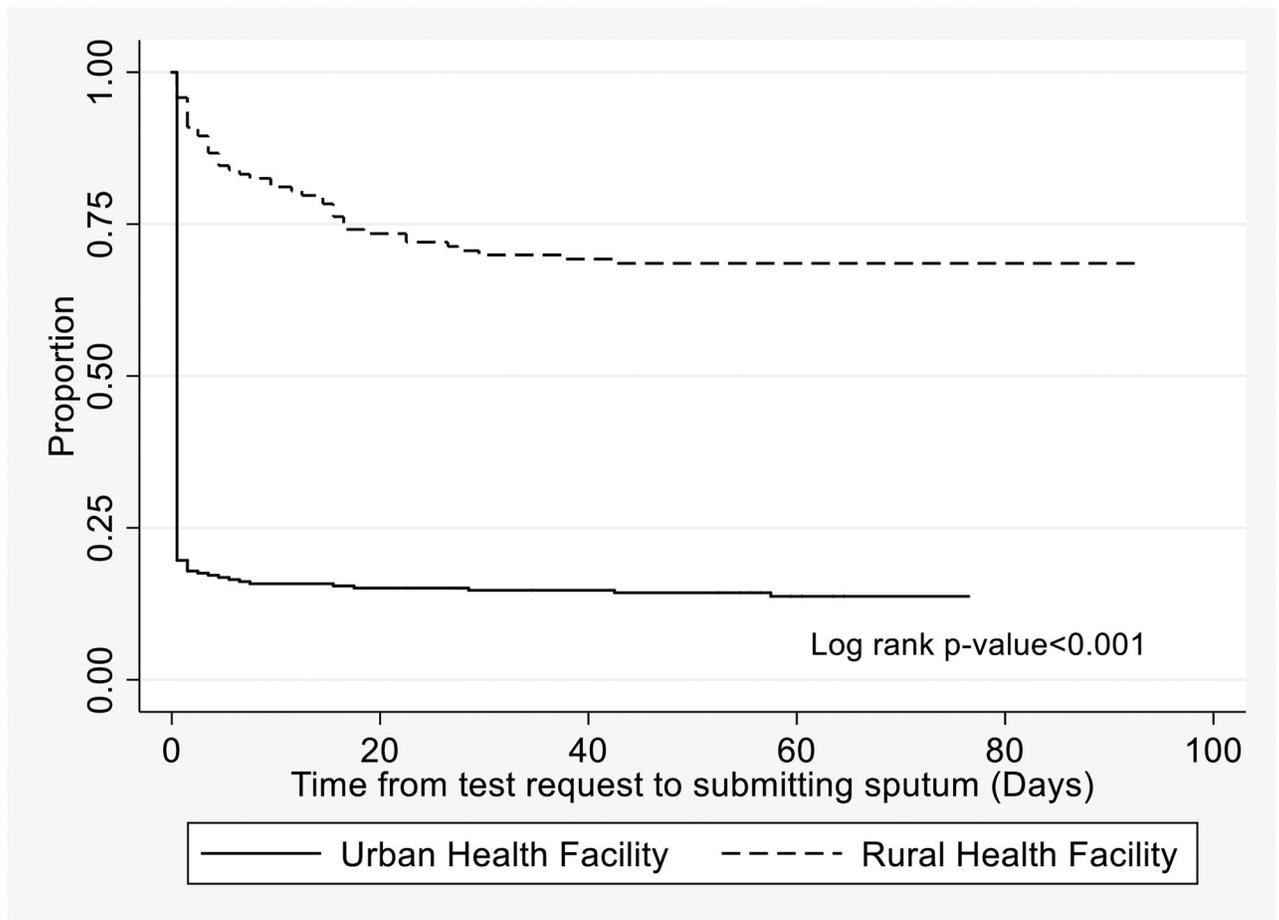


Fig 3. Time from test request to submitting sputum for people requested to give sputum for TB investigation in Ketu South Municipality, Ghana.

<https://doi.org/10.1371/journal.pone.0230604.g003>

in Ghana in 2011 where pre-treatment loss-to-follow up was 38% [30], and a systematic review which found an 18% pre-treatment loss to follow-up in Africa [31]. The difference could be due to the presence of a “task-shifting officer”, dedicated to TB screening and follow-up in our study hospital’s main outpatient department, supporting the value of this role.

Table 2. Causal analysis showing association between the type of health facility attended and submitting a sputum for a TB test, Ketu South Municipal—Ghana.

Association between type of health facility attended and submitting sputum	OR	CI	P
Univariable+	24.25	13.84–42.51	P<0.001
Confounder adjustment			
Adjusted for longer distance from residence to laboratory	12.98	5.95–28.30	P<0.001
Adjusted for rural residence	18.25	8.08–41.21	P<0.001
Adjusted for negative HIV status	22.07	12.35–39.44	P<0.001
Adjusted for high perceived stigma	22.46	12.73–39.61	P<0.001
Adjusted for increasing number of symptoms	22.64	12.85–39.88	P<0.001
Final: adjusted for all of above	9.52	3.87–23.40	P<0.001

†bivariate analysis between type of health facility (rural or urban) and sputum submission as an outcome.

OR = odds ratio, CI = 95% confidence interval, P = p-value

<https://doi.org/10.1371/journal.pone.0230604.t002>

Table 3. Factors associated with submitting sputum among study participants attending rural and urban health facilities in Ketu South Municipality, Ghana.

Variable	N = 410				
	Number submitting sputum (%)	OR (95% CI)	P	aOR (95%CI)	P
Age group (years)			*0.689		
18–38	99/145 (68.3)	1			
39–59	107/150 (71.3)	1.15 (0.70–1.90)	0.567		
≥60	84/115 (73.0)	1.26 (0.73–2.16)	0.403		
Gender			*0.177		
Male	102/136 (75.0)	1		1	
Female	188/274 (68.6)	0.73 (0.46–1.16)	0.182	0.90 (0.48–1.69)	0.739
Educational level			*0.706		
No formal education	65/96 (67.7)	1			
Primary/JHS	162/228 (71.1)	1.17 (0.70–1.96)	0.549		
Secondary/Tertiary	63/86 (73.3)	1.31 (0.69–2.48)	0.414		
Place of residence			*<0.001		
Urban	182/197 (92.4)	1		1	
Rural	108/213 (50.7)	0.08 (0.05–0.15)	<0.001	0.41 (0.16–1.03)	0.058
Distance to laboratory (Km)			*<0.001		
<10	184/197 (93.4)	1		1	
10–20	74/168 (44.1)	0.06 (0.03–0.11)	<0.001	0.12 (0.05–0.33)	<0.001
>20	32/45 (71.1)	0.17 (0.07–0.41)	<0.001	0.29 (0.10–0.86)	0.025
Socioeconomic status (tertiles)			*0.002		
Low	92/134 (68.7)	1		1	
Middle	86/138 (62.3)	0.76 (0.46–1.25)	0.272	0.59 (0.30–1.13)	0.113
High	112/138 (81.2)	1.97 (1.12–3.45)	0.018	1.03 (0.47–2.24)	0.945
Ever treated for TB			*0.008		
No	263/380 (69.2)	1		1	
Yes	27/30 (90.0)	4.00 (1.19–13.46)	0.025	2.02 (0.45–9.07)	0.359
Number of symptoms			*<0.001		
1–2	34/56 (60.7)	1		1	
3–4	123/191 (64.4)	1.17 (0.63–2.16)	0.615	1.33 (0.60–2.96)	0.488
>4	133/163 (81.6)	2.87 (1.47–5.59)	0.002	2.00 (0.83–4.80)	0.12
Duration of symptoms (days)			*<0.001		
≤14	158/245 (64.5)	1		1	
>14	132/165 (80.0)	2.20 (1.39–3.50)	0.001	0.83 (0.43–1.62)	0.589
HIV status			*0.037		
Positive	28/28 (100.0)	1		1	
Negative	66/85 (77.7)	1.79 (1.02–3.15)	0.043	0.85 (0.40–1.83)	0.678
Don't know+	196/297 (66.0)	-	-	-	-
Severity of illness (Karnofsky score)			*0.024		
Less severe (≥90)	136/217 (62.7)	1		1	
Moderately severe (70–80)	133/167 (79.6)	2.70 (1.24–5.92)	0.013	1.84 (0.68–4.98)	0.228
Severe (≤60)	21/26 (80.8)	0.92 (0.17–5.10)	0.924	0.14 (0.01–2.28)	0.165
Number of previous care providers visited			*<0.001		
0	173/272 (63.6)	1		1	
≥1	117/138 (84.8)	3.18 (1.88–5.40)	<0.001	2.05 (1.02–4.13)	0.045
Stigma			*<0.001		
Low perception	134/164 (81.7)	1		1	

(Continued)

Table 3. (Continued)

Variable	N = 410				
	Number submitting sputum (%)	OR (95% CI)	P	aOR (95%CI)	P
High perception	156/246 (63.4)	0.39 (0.24–0.62)	<0.001	0.54 (0.30–0.98)	0.043

*Log likelihood P-value,

†Omitted from model due to collinearity,

OR = odds ratio, aOR = adjusted odds ratio, P = p-value, JHS (13–15 years) = Junior high school

<https://doi.org/10.1371/journal.pone.0230604.t003>

Mortality among study participants was high, with 3% documented to have died within two months of enrolment, which is high for a population of presumptive TB patients but supports data from Zimbabwe [32]. An additional, 4% of participants recruited were lost to follow-up, if all these had died, two-month mortality would have been 7%. This further emphasizes the need for better access to prompt diagnosis and treatment for TB and other conditions.

Findings from this study have both programmatic and health system implications. This study clearly shows there is a gap in the cascade between a sputum test being requested and sputum being submitted, particularly among persons attending rural health facilities, and this can be attributed to the distance people need to travel to submit a sputum. An effective specimen transport system might bridge the gap in the diagnostic cascade.

Limitations

The study was designed to be observational rather than interventional and so the follow-up calls aimed to find out whether the participant had given a specimen and/or started TB treatment rather than motivating them to give a specimen; however, follow-up calls could have prompted some participants to give a sputum specimen, and thus we may have underestimated the true pre-diagnostic delays or losses.

Strengths

The prospective cohort design of our study allowed us to determine pre-diagnostic losses directly and explore the reasons for losses, whereas previous studies have been based on secondary data analysis, or recruited patients already on TB treatment, thus excluding those who never started treatment.

Conclusion

Almost 30% of patients asked to give a sputum specimen for TB testing in Ketu South municipality, Ghana, did not submit sputum: this was primarily determined by longer distance to the TB diagnostic laboratory. Closing this gap in the TB diagnostic cascade is an important step in reducing treatment delay and reducing TB transmission.

Acknowledgments

The authors thank the staff of the Municipal Health Directorate, all participating health facilities, research assistants and all study participants for their cooperation and support. Thanks to the Commonwealth Scholarship Commission for granting JD a scholarship for her doctoral studies. The Commission had no involvement in any aspect of the study and manuscript.

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Methodology: Joyce B. Der, Daniel Grint, Clement T. Narh, Alison D. Grant.

Project administration: Joyce B. Der.

Supervision: Daniel Grint, Frank Bonsu, Alison D. Grant.

Writing – original draft: Joyce B. Der.

Writing – review & editing: Daniel Grint, Clement T. Narh, Frank Bonsu, Alison D. Grant.

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Additional material for chapters 5 and 6

Additional material for chapters 5 and 6 is presented in this section to provide more explanation for some of the statistical methods used and other limitations of these methods.

Confounder selection

There are several strategies that can be used to determine factors or potential confounders that should be included in a multivariable model. No single one of these strategies is best in all situations. Every strategy has limitations and defects that depend on the context in which it is applied [132]. In the quantitative studies presented in chapters 5 and 6 of this thesis, factors/potential confounders for inclusion in the multivariable models were selected using change-in-estimate and p-values. The advantage of using these is that they show the size and strength of an association between an outcome and an exposure. However, this strategy has several limitations compared to other methods such as the use of causal diagrams or directed acyclic graphs (DAG). A causal diagram or DAG is a visual representation of the causal relationships believed to exist between the variables of interest, including the exposure, outcome and potential confounding variables [133]. One of the advantages of using DAGs is that they help to differentiate between confounders, mediators (intermediate variables on the causal path between exposure and outcome), and colliders (variables influenced by both the exposure and the outcome) and therefore makes it easier to select which variables need to be controlled for [134]. Colliders are not to be adjusted for as doing that will introduce bias and mediators are rarely adjusted for unless the interest is to quantify different causal pathways between the exposure and the outcome [133, 135].

Therefore, the limitation of using change-in-estimate and p-values for confounder selection is that colliders and mediators might be included in the multivariable model because they meet the set criteria for change-in-estimate or p-value for inclusion whereas important confounders might not be included in the multivariable model because they do not meet the inclusion criteria. The potential impact of this on the study findings is that the associations or causal relationship between study outcomes and exposures reported might be distorted or biased. For example, we could have overestimated or underestimated the causal relationship between attending a rural health facility and not submitting sputum just by using change-in-estimate in selecting potential confounders to control for.

On the other hand, specifying a DAG to use as the basis for which variables to control for requires specialist knowledge of the causal question. This may or may not be easy to do and misspecification of the causal DAG can also lead to a biased or misspecified causal effect estimate. For instance, given that we were exploring factors that could influence whether a healthcare worker requested a sputum test or not and because we did not know what these factors were, it would have been difficult to correctly specify a DAG for this analysis.

Chapter 5: Research paper 1: Missed opportunities for tuberculosis investigation in a municipal hospital in Ghana: evidence from patient exit interviews

Evidence of association

Initially it was reported in Chapter 5 from table 1 that there was strong evidence that persons who reported their symptoms to a healthcare worker had longer duration of symptoms compared to those who did not report their symptoms, however upon review, that statement only holds for those whose symptoms were elicited by a HCW (75% vs 54.8% as shown in table below).

Duration of symptoms	Spontaneously reported, n=333 (column %)	HCW elicited n=53 (column %)	Did not report n=195 (column %)	P-value
<2 weeks	155/333 (47.1)	13/53 (25.0)	84/195 (45.2)	0.01
>2 weeks	174/333 (52.9)	39/53 (75.0)	102/195 (54.8)	

HCW= healthcare worker

Multivariable models

In the results section of chapter 5, it was mentioned that to prevent overfitting of the multivariable model due to the small number of outcomes, only three covariates with the strongest association with the outcome were adjusted for; that model was presented in table 2. It was also mentioned in the text that to explore for any potential confounding effect by age and sex, separate models were developed to assess the association of duration of symptoms, number of symptoms and ever treated for TB with having a sputum test being requested by a healthcare worker after adjusting for age and sex. The four multivariable models are shown below:

Model 1: Multivariable model showing the association between number of symptoms, duration of symptoms and whether ever treated for TB with having a sputum test requested

N=581					
Variable	Total (n)	Submitted sputum (n)	%	Multivariable analysis	
				aOR (95% CI)	P-value
Number of symptoms					
1-2	373	11	3.0	Reference	
≥3	208	25	12.0	3.14 (1.47-6.71)	<0.01
Duration of symptoms					
<2 weeks	252	3	1.2	Reference	
≥2 weeks	315	33	10.5	6.99 (2.08-23.51)	<0.01
Ever treated for TB					
No	559	29	5.2	Reference	
Yes	22	7	31.8	6.25 (2.24-17.46)	<0.001

In model 1, persons with increasing number of symptoms, longer duration of symptoms and those ever treated for TB were more likely to have a sputum test requested by a HCW.

Model 2: Multivariable model showing the association between duration of symptoms and having a sputum test requested, after adjusting for age and sex

N=581					
Variable	Total (n)	Submitted sputum (n)	%	Multivariable analysis	
				aOR (95% CI)	P-value
Gender					
Female	510	25	4.9	Reference	
Male	71	11	15.5	3.10 (1.41-6.83)	<0.01
Age group (years)					
18-39	371	17	4.6	Reference	
40-60	143	11	7.7	1.62 (0.72-3.63)	0.24
>60	67	8	11.9	2.40 (0.95-6.03)	0.06
Duration of symptoms					
<2 weeks	252	3	1.2	Reference	
≥2 weeks	315	33	10.5	8.94 (2.69-29.68)	<0.001

In model 2, after adjusting for age and sex, persons with longer duration of symptoms were more likely to have a sputum test requested by a HCW.

Model 3: Multivariable model showing the association between number of symptoms and having a sputum test requested, after adjusting for age and sex

N=581					
Variable	Total (n)	Submitted sputum (n)	%	Multivariable analysis	
				aOR (95% CI)	P-value
Gender					
Female	510	25	4.9	Reference	
Male	71	11	15.5	2.98 (1.36-6.55)	<0.01
Age group (years)					
18-39	371	17	4.6	Reference	
40-60	143	11	7.7	1.77 (0.79-3.97)	0.16
>60	67	8	11.9	2.96 (1.17-7.47)	0.02
Number of symptoms					
1-2	373	11	3.0	Reference	
≥3	208	25	12	4.35 (2.07-9.16)	<0.001

In model 3, after adjusting for age and sex, persons with increasing number of symptoms were more likely to have a sputum test requested by a HCW.

Model 4: Multivariable model showing the association between whether ever treated for TB and having a sputum requested, after adjusting for age and sex

N=581					
Variable	Total (n)	Submitted sputum (n)	%	Multivariable analysis	
				aOR (95% CI)	P-value
Gender					
Female	510	25	4.9	Reference	
Male	71	11	15.5	3.06 (1.39-6.76)	<0.01
Age group (years)					
18-39	371	17	4.6	Reference	
40-60	143	11	7.7	1.66 (0.74-3.72)	0.22
>60	67	8	11.9	2.40 (0.95-6.05)	0.06
Ever treated for TB					
No	559	29	5.2	Reference	
Yes	22	7	31.8	6.80 (2.48-18.71)	<0.001

In model 4, after adjusting for age and sex, persons who had ever been treated for TB were more likely to have a sputum test requested by a HCW.

The number of parameters that could be included in the multivariable model was limited by the number of outcomes (36), to prevent overfitting of the model. The choice of using p-values for selection of variables to be moved to a multivariable level could have led to some variables that might be associated with the outcome to be excluded in the final model. Not including these variables could imply the true association between the outcome and factors in the multivariable model could be masked.

Chapter 6: Research paper 2: Where are patients missed in the tuberculosis diagnostic cascade? A prospective cohort study in Ghana.

Methods

Sample size

In calculating the sample size for the cohort study presented in chapter 6, the aim was to detect an absolute difference of 15% in the proportion of participants who submit a sputum among those attending a rural health facility and those attending an urban facility.

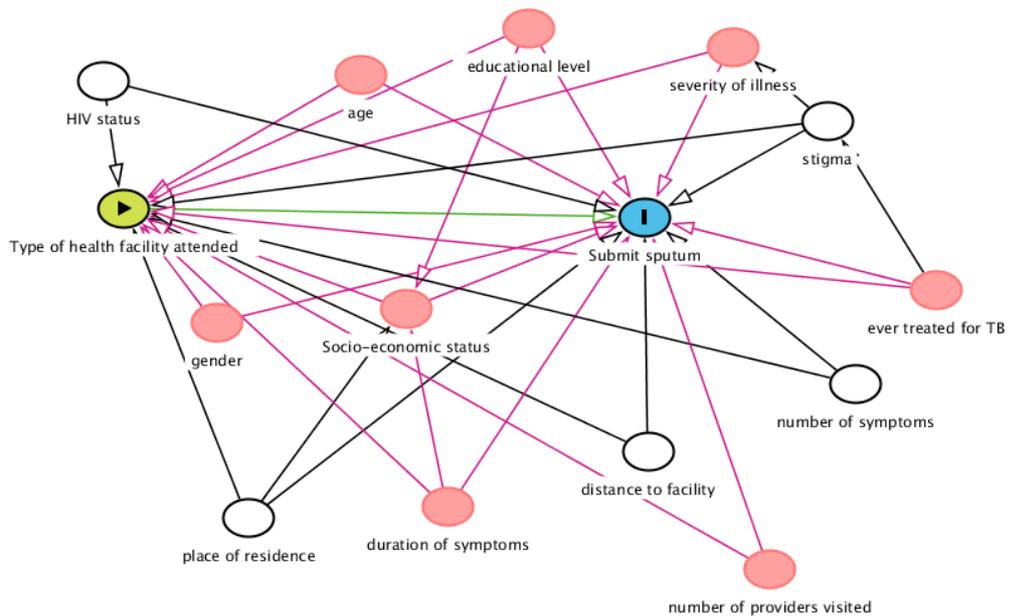
Data analysis

In the analysis even though we recruited from four rural health facilities, we did not adjust for clustering because of the small number of participants recruited from some of the rural health facilities. The small numbers could produce biased estimates in adjusting for clustering. Out of a total of 428 participants enrolled, 285 were from the urban facility and 143 were from the four rural facilities. Of the number recruited from the rural health facilities, 105, 6, 5 and 27 were recruited from the four respective rural health facilities.

Limitations of multivariable model

There could be potential limitations to the multivariable model in table 2. As explained earlier in this additional material, the choice of using the change-in-estimate method for selection of variables to be included in the multivariable model could have led to other potential confounders being excluded in the final model. For example, socio-economic status could be a potential confounder for the association between type of health facility attended and submitting a sputum sample for a TB test (figure 6.1). This is because people with a low socio-economic status may be the ones living in rural areas and therefore will visit a rural health facility (table 1 of published paper presented in chapter 6). Also because of their low socio-economic status they might not have money to travel to the municipal hospital to submit a sputum. Likewise, a person's educational level could determine the type of health facility they attend and also whether they will submit a sputum specimen. For instance, people with a low educational level are likely to reside in rural areas and will attend a rural health facility. Due to their low educational level, they might not see the need to travel to the municipal hospital to submit a sputum for the test. Other factors such as age, gender, severity of illness etc which could be potential confounders are shown in the causal diagram in figure 6.1. All these potential confounders were not included in the multivariable model because they did not meet the 10% change-in-estimate and this could have led to an over- or underestimation of the association between the type of health facility attended and submitting a sputum sample for a TB test. There could be residual confounding based on the method used in selecting variables for the multivariable model.

Figure 6.1: Causal diagram showing relationship between the type of health facility attended and submitting sputum for a TB test with potential confounders



- Key**
-  exposure
 -  outcome
 -  adjusted variable
 -  causal path
 -  biasing path

Figure 6.1 shows the potential confounders of the relationship between the type of health facility attended by a presumptive TB patient and submitting sputum for a TB test.

Interpretation of findings

In as much as distance seems to be the main determinant of patients not submitting sputum for a test, it is important to note that other factors relating to travel distance could account for this, for example, people of low socio-economic status may not have money to travel a long distance to the municipal hospital to submit a sputum. Also,

people who are severely ill or in the older age category may not be able to travel a long distance to submit a sputum for a test. In addition, the size of the odds ratio does not necessarily mean that longer distance of travel is the main cause of patients not submitting a sputum, it only shows there is a strong relationship between travel distance and submitting sputum, but other factors could influence this association.

Limitations of follow up methods used

Even though it has been stated as part of the limitations in chapter 6 that the frequency of follow up might have influenced people to submit a sputum, it is worth mentioning that this could be more prominent among those with mobile phones since they were followed up four times compared to those without mobile phones who were followed up twice in their homes during the two months follow up period. Moreover, the effect size for participants in the high wealth tertile could have been overestimated since this category of people were more likely to own phones and therefore were followed up more frequently in the study.

Chapter 7: Research paper 3: Barriers to tuberculosis case finding in health facilities in Ghana: perceptions, experiences and practices of healthcare workers

This chapter provides in-depth analysis of qualitative data to explore barriers to TB case finding in health facilities (objective 4). It provides details of the experiences and practices of HCWs.

This chapter is prepared as a manuscript to be submitted to BMC Health Services Research. The final manuscript to be submitted is included in full below.

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1514031	Title	Ms.
First Name(s)	Joyce Berkumwin		
Surname/Family Name	Der		
Thesis Title	Pathways to tuberculosis diagnosis and treatment in Ghana: identifying the gaps and seeking solutions		
Primary Supervisor	Alison Grant		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	BMC Health Services Research
Please list the paper's authors in the intended authorship order:	Joyce B. Der, Alison D. Grant, Daniel Grint, Clement T. Narh, Frank Bonsu, Virginia Bond
Stage of publication	Not yet submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I was jointly responsible with Prof Alison Grant for the conceptualisation of the paper. I collected the data, conducted the data analysis and wrote the first draft of the paper. I prepared the subsequent revisions with consideration of comments from co-authors.
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SECTION E

Student Signature	
Date	15th September 2020

Supervisor Signature	
Date	16 September 2020

Barriers to tuberculosis case finding in health facilities in Ghana: perceptions, experiences and practices of healthcare workers

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Abstract

Background: Ghana's national tuberculosis (TB) prevalence survey conducted in 2013 showed higher than expected prevalence indicating that many people with TB were not being identified and treated. Responding to this, we assessed barriers to TB case finding from the perspective, experiences and practices of healthcare workers (HCWs) in rural and urban health facilities in south eastern Volta region, Ghana.

Methods: We conducted clinic observations and in-depth interviews with 12 HCWs (including five trained in TB) in four rural health facilities and a municipal hospital. Interviews were transcribed. Transcripts and clinic observations summaries were manually analysed, triangulated and organised by health system-related and HCW-related barriers.

Results: The key health system barriers identified included lack of TB diagnostic laboratories in rural health facilities and no standard referral system to the municipal hospital for further assessment and TB testing. In addition, missed opportunities for early diagnosis of TB were driven by suboptimal screening practices of HCWs linked to not adhering to the national standard operating procedures (SOP) for TB case detection. Infection prevention and control measures in health facilities were not implemented as recommended by the same SOP. HCW-related barriers were mainly lack of training on case detection guidelines, fear of infection (exacerbated by lack of appropriate personal protective equipment) and apathy among HCWs for TB work. Solutions to these barriers suggested by HCWs included provision of at least one diagnostic facility in each sub-municipality, laboratory staff going round to collect sputum samples from rural health facilities and training of newly recruited staff on case detection guidelines.

Conclusion: Findings portray the complexity of barriers within the health system that affects TB case finding. There is the need for efforts from the national TB control

programme and health facility managers to ensure continuous quality monitoring of TB diagnosis and treatment with focus on patient-centred care. An effective specimen transport system and standard referral linkage at peripheral health facilities are needed.

Background

Tuberculosis (TB) is a major global public health threat and in 2018, an estimated ten million people developed the disease with 1.2 million deaths among human immunodeficiency virus (HIV) negative people (1). It was also estimated that three million TB cases were missed globally in the same year and this could be due to under-reporting of detected cases or under-diagnosis. Under-diagnosis could arise from people with TB not accessing health care and/or being missed by the health system when they seek care (1). Prompt diagnosis and treatment of TB is essential to prevent spread of infection.

Ghana is among the 30 TB and HIV high burden countries according to the World Health Organization (WHO) (1). A national TB prevalence survey conducted in 2013 showed higher than expected TB prevalence. The survey also revealed that a large number of people with TB had visited public health facilities but only 5% had been diagnosed with TB (2). The national standard operating procedures (SOP) developed in 2010 for TB case detection, outlines what health facilities and healthcare workers (HCW) should practice to ensure clients with symptoms of TB who access care are identified promptly and initiated on treatment (3). However, HCWs may encounter barriers that hinder their ability to detect people with TB promptly when they seek care from health facilities.

Qualitative studies in Africa and other low- and middle-income countries have evaluated barriers to TB diagnosis and treatment in health facilities that can be classified as health system-related or patient-related barriers (4-8). Several quantitative studies have assessed reasons for health systems delay in diagnosing TB such as first seeking care from private health providers (9), primary healthcare facilities (10) or general

practitioners (11) and multiple healthcare contacts (12, 13). In our study setting, no qualitative study has been conducted to assess barriers to TB case finding in health facilities. This study was part of a larger project where qualitative research activities were conducted before and after quantitative components. Specifically, clinic observations were carried out before cohort and cross-sectional studies (14, 15) and in-depth interviews were carried out as the final research activity of the project. Some findings from these quantitative studies showed gaps which were health system- and HCW-related. We conducted this qualitative study to assess barriers to TB case finding from the perspective, experiences and practices of HCWs and explore their suggestions for sustainable ways to improve TB case finding in health facilities in Ghana.

Methods

Study setting

The study was conducted in the south eastern part of the Volta region, Ghana, in a municipality that has one of the highest burdens of TB in the region (16). In 2018, the municipality notified 172 TB cases out of a target of 546 estimated based on the 2013 national TB prevalence survey (17). We selected for the study four of the municipality's eight rural health facilities that were geographically spread and had the highest outpatient department (OPD) attendance, along with the OPD of the municipal hospital, where the only TB diagnostic laboratory and chest clinic were based.

Study design and population

We employed qualitative methods using clinic observations and in-depth interviews. Participants were HCWs involved with TB case finding in the selected health facilities. The participants were purposefully chosen and included one medical doctor, two physician assistants, eight nurses and one task-shifting officer. There were four women

and eight men participants. Their ages ranged from 27-42 with a mean age of 32 (standard deviation: 4.8) years. Four of the participants were from rural health facilities. The number of years of experience in TB work ranged from six months to three years.

Data collection and procedure

Clinic observations were conducted in May 2018. The observations were done by JBD and CTN at the OPD waiting area, triage area, consulting rooms of the study health facilities including the laboratory and chest clinic of the municipal hospital. Observations were done using a checklist and included: waiting time of clients at the OPD waiting area; procedures at the triage area; interaction between HCW and clients in the consulting room; waiting time and dropping samples at the laboratory; and procedures at the chest clinic (supplementary table 1). These observations were done between 7am and 12pm on days that the health facilities were very busy (usually market days). Two days were spent at each facility and on each of the days, two researchers followed client flow by observing clients as they moved from one area to the other. The researchers dressed casually and were introduced to HCWs at the facilities before they started the observations.

Based on an initial assessment of health facilities in April 2018 before the start of data collection, we found that there were no TB case finding activities in the rural health facilities. This made it necessary to introduce the screening tool to HCWs who attended to patients in the consulting rooms of the study rural health facilities to facilitate enrolment for the cohort study (15) and also as an ethical obligation to help improve TB services. The TB symptom screening tool was introduced just after the clinic observations at the beginning of May 2018, the quantitative studies were then

conducted from May to December 2018 followed by the in-depth interviews that were conducted in January 2019.

In-depth interviews were held in the health facilities at a time that was convenient for the HCW and lasted on average 50 minutes. Some of the HCWs in the rural health facilities to whom the TB symptom screening tool was introduced were among those interviewed. Interviews were led by JBD, and a trained research assistant observed and took notes. All interviews were conducted in English and audio recorded. An interview guide based on findings from clinic observations was used and included training in TB control, practices in TB diagnosis and treatment, experiences in TB case finding, barriers to TB diagnosis and treatment and suggested solutions by the HCWs.

Data analysis

Data from clinic observations were entered in Excel spreadsheet by JBD with columns representing observations done per area of the health facility and rows representing each health facility. This was done immediately after the observations were carried out. Data were organized by the type of health facility and patterns across the different areas of the health facilities observed were noted. Narrative data based on the observed patterns were used to show the workflow and practices of HCWS when clients reported to the health facility. Also, frequencies on number of patients screened for TB symptoms, numbers reporting a cough and numbers asked to submit a sputum for TB test were computed. Subsequently, with the data presented in this manner, the observations from the facilities could be used to validate the findings from the in-depth interviews and to thus triangulate, enrich and deepen the understanding of the data. All audio recordings were transcribed by JBD and reviewed by listening to the recordings as a quality control step. The transcripts were also

reviewed by VB who was the senior qualitative expert on the team. Transcripts and field notes were summarized and read over to identify emerging themes. JBD and VD then discussed and agreed on the themes. Summaries from clinic observations and transcripts were triangulated to generate the final analytical themes. Themes were organized in a framework that categorized barriers into two main areas: (i) health system-related factors, which are factors relating to the operations of the health system; and (ii) HCW-related factors relating to attitudes of HCWs. These categories were adopted from models used by Cattamanchi *et al* and Chimbatata *et al* (4, 18).

Ethical approval

Ethical approval was obtained from the Ghana Health Service Ethics Review Committee and London School of Hygiene & Tropical Medicine Ethics Committee. Permission to conduct the study in the health facilities was obtained from the regional and municipal health directorates. Written informed consent was obtained from all study participants.

Results

We first present the TB client flow and standard TB management in the two types of health facilities, before presenting findings about barriers that were categorized as health system-related and HCW-related barriers. A summary of barriers to TB case detection in health facilities is shown in figure 2 and a table of illustrative quotes (supplementary table 2) is presented as supplementary material.

TB client flow and standard TB management in health facilities

In every health facility, the standard practice is that there should be a TB team made up of facility stakeholders that is responsible for planning, monitoring and evaluating

adherence to TB case detection protocols. The regional and district TB teams are supposed to visit health facilities quarterly to monitor case detection activities.

The national SOP for TB case detection indicates that all clients attending OPDs should be asked about cough, irrespective of presenting symptoms. Those who report a cough should be screened with a TB symptom questionnaire (a screening tool) (3). Clients who report a cough of two weeks or more, or clients with cough of any duration plus two or more TB-related symptoms (fever, chest pain, weight loss and night sweats), should be asked to do a sputum TB test, and be recorded into a cough register. Also health talks on basics of TB and TB infection control should be given to clients at the OPD.

Figure 1 shows the TB client flow and actions that are taken at each step of the pathway in rural health facilities and the municipal hospital. Client flow in all facilities is similar until after triaging where, in the municipal hospital, clients first see a task-shifting officer before queuing to see a clinician. The task-shifting officer is a HCW designated to screen for symptoms of TB and request sputum tests.

Rural health facilities

Health system-related barriers

Lack of diagnostic facilities in rural health facilities

In the study setting, the only TB diagnostic facility was in the municipal hospital. Therefore, HCWs in rural health facilities had to refer all presumed TB clients to the municipal hospital for further assessment and testing. However, HCWs in all the four rural health facilities complained that most clients who are referred never reach the municipal hospital. In addition, there was no standard referral system for presumed

TB clients. Two facilities gave clients a referral letter to the chest clinic at the municipal hospital, one facility referred clients to the task-shifting officer and the other facility referred clients to the general OPD at the municipal hospital. Study observations documented that clients who are referred to either the chest clinic or the task-shifting officer are attended to more quickly than those referred to the general OPD. In one facility, a HCW said at times they need to threaten clients to go and do the test.

“I have experienced that, most of them don’t go [...] unless we tell them that maybe they will die before they will just rush to go and come”. (Male HCW, Rural health facility [RHF])

HCWs said some of the health system reasons that clients do not go to the municipal hospital when they are referred are extensive waiting times at the municipal hospital and being treated badly by staff at the municipal hospital.

HCWs relayed how consequently sometimes people could die and/or some clients would suppress their cough or would not report their TB-related symptoms to the HCW because they do not want to be referred to the municipal hospital.

“[...] sometimes patients want to suppress the symptoms because they know you will refer them and if you refer them, they won’t go because of financial constraints. So, when you start going deeper, they tend to refrain from answering you more and that way we don’t get to capture the whole history about the patient. A patient could be coughing like two weeks and will come and tell you it started three days ago [...]”. (Female HCW, RHF)

One reason for which HCWs might not refer clients for a TB test was lack of money for clients to travel to the municipal hospital for further assessment and/or to do a TB test. These rural facilities were about 10 to 20 km from the municipal hospital.

“[...] if they hear the name X (municipal hospital) they will start crying because they don’t have money for T&T (travel and transportation)”. (Female HCW, RHF)

Another reason especially in fishing communities was migration. During the peak of the fishing season, most fisherfolk migrate to Benin, Togo, or Ivory Coast where there are big fishing vessels. They go to work on these fishing vessels for better income and only return after several months. If they have symptoms of TB and are referred to the municipal hospital, they may never go and do the test but will rather migrate and cannot be traced. Therefore, HCWs are reluctant to refer such clients during the fishing season.

“Some of them you will not see them again after you refer them [...] they will travel to Benin, Togo or Ivory Coast. Those are the places they have been going because of the fishing, they will go to fish there and it makes follow up difficult”. (Female HCW, RHF)

Suboptimal screening for TB symptoms and sputum test request

Clinic observations showed that in three of the four rural health facilities, HCWs at the triage area were not asking clients about cough. In the consulting rooms, clients were asked about cough as part of a routine set of symptoms asked to all clients. However, clients who reported a cough were not screened with the TB symptom questionnaire to determine their eligibility for a sputum test. Of 78 clients observed across the four rural health facilities in May 2018, 27 (34.5%) reported a cough to a HCW in the consulting room but none of them was screened with the screening tool. During HCW interviews conducted in January 2019, after the symptom screening tool that had been introduced, some of them said all clients in the consulting room are asked about cough and that the screening tool is used when appropriate. However, no observations were conducted after to triangulate whether this change in practice had been made. Other HCWs shared that they do not ask all clients about a cough.

“A patient could come with hypertension, we don’t ask for cough so I won’t say all patients, but I will say majority of patients, especially with the malaria cases [...] but not all patients”. (Female HCW, RHF)

Asked why HCWs were not asking about cough or using the screening tool, they responded that there was shortage of staff leading to heavy workload.

“We don’t have enough staff [...] Actually the one who was doing this is no longer in the facility”. (Female HCW, RHF)

HCWs said they had never seen the screening tool until the study team introduced it to them. During clinic observations, the screening tool was not found in any of the consulting rooms of the health facilities.

“I think the first time we had it (screening tool) was when you provided it, to be very frank. We never had any guideline (screening tool) for TB until you provided the TB guideline (screening tool)”. (Female HCW, RHF)

Sub-optimal infection prevention and control practices

In all the rural health facilities, we observed that health talks on TB and other health conditions were not given at the clients’ waiting area. When we interviewed HCWs, they said health talks are provided on one-on-one basis with clients who report a cough and they normally advise them to cover their mouths when they are coughing. Again, in all health facilities, we observed that clients in the waiting area who were visibly coughing were not isolated from the crowd and attended to as required by the national SOP for case detection. In one rural health facility, the HCW admitted that they did not have enough space to isolate clients with cough. Further, fast-tracking them through the process created misunderstanding with other clients already in the queue.

“You only tell them to use their handkerchief to cover their mouth when they are coughing because this place is just too small so you can’t be isolating [...] and sometimes too some came to meet others so if they are overpassing it will bring confusion”. (Female HCW, RHF)

Insufficient monitoring and supervision of TB work

None of the rural health facilities had a TB team or focal person to ensure HCWs were following protocols. Also, there was poor documentation in cough registers at all the rural health facilities, and no supervision of TB case finding activities. The last record

of cough was entered more than a year ago prior to this research. HCWs explained this as due to “*laziness*”, not enough staff to do entries, heavy workloads and inadequate registers.

“You see this place that we are working, the workload is too much for us, because you are the only person consulting, dispensing at the same time dressing wound and other things. So, most times doing recordings in the book is difficult. So if you take one client and you do all these kind of things by the time you realize the day is over”. (Male HCW, RHF)

Healthcare worker-related barriers

Gaps in TB knowledge and lack of training in case detection guidelines

HCWs believed some of their colleagues might have less knowledge about TB, especially the signs and symptoms. Therefore, when they examine clients with symptoms of TB, they do not think of TB but rather other health conditions. To compound this problem, the majority (75%) of the HCWs interviewed had received no training on TB and had no idea about the national SOP for TB case detection. Indeed, prior to this study, the SOP was not available in any of the health facilities. HCWs believed the lack of training on the SOP led to majority of them not knowing what to do when they see a client with cough or TB-related symptoms. They believed that training should be done regularly because of the high turnover of staff.

In addition, the lack of training on the SOP for case detection led to different criteria being used by different rural health facilities to refer a client to the municipal hospital for further assessment or for a TB test. In one facility, cough ≥ 2 weeks was used as criterion for referring clients for a TB test, in another facility, cough and weight loss were used. In the two other facilities, they used cough and other TB-related symptoms. A respondent at one rural health facility felt lack of training should not prevent HCWs from identifying people with symptoms of TB.

Municipal Hospital

Health system-related barriers

Suboptimal screening for TB symptoms and sputum test request

At the municipal hospital, clients are supposed to be asked about cough during triaging and those who report a cough should be referred to the task-shifting officer to be screened for TB-related symptoms and if eligible be asked to submit sputum for a TB test. However, clinic observations showed that after being triaged patients were not sent to the task-shifting officer to be screened for TB-related symptoms. Rather, the task-shifting officer either actively identified clients who were coughing in the waiting area and approached them to be screened and have a sputum test requested if they were eligible, or clients identified in consulting rooms of the municipal hospital who required screening were referred to the task-shifting officer. Some HCWs said the reasons they were not asking about cough or using the screening tool were that it was not their job, that it was extra work and at times they forget to ask about cough.

“They are complaining that it’s not their job and they sometimes forget to ask. They cannot be checking the vital signs and at the same time remember to be asking about cough”. (Male HCW, Municipal hospital [MH])

All the clinicians at the municipal hospital said they had never seen the screening tool or sputum test request forms in the consulting room. However, HCWs at the chest clinic disagreed with their colleagues saying all HCWs were trained on how to use the screening tool and all forms needed were distributed to all the departments but they refused to use them.

“They don’t ask about cough, but they are supposed to ask the clients, but they are not doing it, meanwhile they’ve been trained but yet still they are not doing it. Apart from the task- shifting officer asking about cough, the screening tool was sent to every unit, consulting rooms but now they are not doing it at all, [...] now everything is on the task- shifting officer and the TB unit”. (Male HCW, MH).

Many HCWs in the municipal hospital alluded that TB diagnosis would be more efficient if they were also screening for symptoms of TB and requesting for sputum test directly instead of referring to the task-shifting officer.

Sub-optimal infection prevention and control practices

HCWs from the chest clinic complained that when they try to let clients who are coughing see the doctor quickly to prevent potential spread of infection, they face opposition from their colleague HCWs at the OPD. Also, entry to the isolation wards for TB clients was not restricted and the time spent in the ward by client relatives was not regulated.

“[...] mostly I try my best to let them see the doctor fast but sometimes it brings some kind of argument between I and the nurses because they will say they can’t allow me to jump the person over other people in the queue [...], this person just came some few minutes ago [...]”. (Male HCW, MH)

In the municipal hospital, there was a TB team in theory, but it was described by some key HCWs as non-functional for the past two years. HCWs with TB responsibilities felt that the ineffectiveness of the team was what was causing other HCWs not to adhere to the SOP for TB case detection.

“Previous minutes from the files show the team used to meet [...] and discuss the challenges and find some ways of resolving them but since I joined the team in 2016, frankly speaking the team is not working well, is not working, it was working previously but now is not working since they had different administration [...], it is no more effective again”. (Male HCW, MH)

Shortage of staff

Some HCWs said they could not adequately and effectively screen for symptoms of TB because they did not have enough staff.

“Fair enough! We are supposed to be asking every patient about cough but I mean

sometimes too the workload I mean you can't be asking every patient whether the patient is coughing". (Male HCW, MH)

Shortage of staff led laboratory staff to batch sputum specimen for the day and perform the test at the end of the day. Therefore, patients who submitted a sputum at the laboratory had to return the following day to the hospital for their test results. This caused some patients not to return for their results. Some HCWs reported that laboratory staff did not give priority to TB work.

"[...]sometimes the samples delay so you get the test results late [...] sometimes they even misplace the samples [...] we are having a problem with the lab in terms of human resource. If you look at the number of cases I mean we see at the lab and even in the day the number of people working there are not enough, I mean it's a human resource challenge". (Male HCW, MH)

Also, because laboratory results were not given to patients on the day of sputum submission, the task-shifting officer on a daily basis at the start of work would go to the laboratory and collect all sputum test results from the previous day. The task-shifting officer then called all patients with a positive test result immediately and asked them to come and start TB treatment. He reported that at times he had difficulty convincing patients with positive result to return to the hospital to start TB treatment. Also, when he could not reach patients with a positive test result on phone, he traced them to their homes using the contact address provided during screening. HCWs at the chest clinic reported that availability of a vehicle to trace some patients with positive test result who cannot be reached via telephone was often a challenge.

"[...] most of them [...] if you call them [...] they come but some of them you have to keep on calling them convincing them, talking to them and they will say, they don't have money to come or their place is far they cannot come. Sometimes you have to walk to the house because you took their address, you have to make sure you go to the house and look for them and tell them that please you have to come for the medication [...]" (HCW, MH).

Those with a negative test result were not called to inform them of their result, and the reason given was that no call credit was given to the task-shifting officer to call

patients and inform them of their test result.

“Those who are negative [...] I don’t call them. I will not call them but we tell them to come back for the results the following day and they themselves will come or later on if they come back for review and they will come to me for the result [...] because there is no money given for calling, but I just sacrifice my own money to buy the credit and be calling the positive ones”. (Male HCW, MH).

Shortage of diagnostic logistics

HCWs at the chest clinic of the municipal hospital complained that there were intermittent shortage of sputum containers or Xpert MTB/RIF cartridges. When this happened it affected the diagnosis of TB because once the presumed patient leaves the hospital, it is normally difficult to get them to return to do the test. The main reason attributed for these shortages was that the laboratory staff were not proactive in requesting for these items when their stock levels were low. Therefore, to prevent shortage of sputum containers, the containers were usually kept with the task-shifting officer at the OPD or kept at the chest clinic. When containers were kept at the chest clinic, it was inconvenient for patients as the chest clinic was quite a distance from the OPD.

Healthcare worker-related barriers

Fear of infection and attitude towards TB work

Fear of infection was one of the main barriers affecting TB case detection in the municipal hospital. Nurses in the wards were reluctant to attend to TB clients admitted to the isolation wards of the hospital because they were worried about getting infected. This fear also prevented other HCWs from being interested in TB work. The fear was attributed to the lack of essential personal protective equipment (PPE) like N95 respirators. HCWs claimed the hospital management said N95 respirators were expensive and not readily available. This had led to some HCWs refusing to see clients with productive cough or TB clients.

“So everybody is on the alert, I don’t want to be infected, I don’t want to get infected and that thing has brought in some reluctance in getting closer to TB clients or TB unit [...]” (Male HCW, MH)

HCWs at the chest clinic said the presence of a task-shifting officer, coupled with lack of motivation, had undermined the interest of other HCWs in TB work. Perceived incentives for the task-shifting officer and other staff of the chest clinic from the national TB control programme reinforced that they should be the only ones screening for symptoms of TB and requesting for sputum test. It was reported that at times that the task-shifting officer was not available, for instance on sick leave, no one did his job. They also said this responsibility shifting could lead to delay in diagnosis and more inconvenience and cost for presumed TB clients.

“[...] I’ve heard statements whereby somebody is coughing, and they will say they should call the task-shifting officer because he is being paid to do that work, that one I’ve heard it several times”. (Male HCW, MH)

Solutions suggested by healthcare workers

In rural health facilities, some HCWs mentioned that if there could be a diagnostic facility in each sub-municipality, then clients would not have to travel to the municipal hospital for the TB test. Other HCWs thought that laboratory personnel going round the rural facilities and collecting sputum specimen from presumed TB clients would also help to reduce the loss to follow-up due to referrals to the municipal hospital.

Most of the HCWs in both rural and urban facilities mentioned sensitization and training of HCWs on SOP for TB case detection. They recommended that training should be routinely held because of the high turnover of staff. Providing logistics such as N95 respirators to ensure HCWs feel safe in dealing with clients with cough or TB were prioritized.

HCWs felt that there should be a functional TB team or focal person in every health facility to monitor TB case detection activities and to ensure HCWs adhere to the guidelines. Apart from a functional TB team, there should be regular monitoring and supervisory visits from the national, regional and district TB teams to ensure that guidelines are followed and also to serve as motivation for the HCWs to know that their work is appreciated. Other HCWs suggested directors from the national level should come to the health facilities and talk to HCWs and let them know TB case detection is part of their work and that this would let HCWs adhere to the guidelines. Provision of funds to health facilities to support patients with their transportation cost to the municipal hospital would be helpful.

Discussion

This study explored HCW perceptions and experiences in TB case detection in rural and urban health facilities in south eastern Volta region, Ghana. These perceptions and experiences were supplemented with findings from observations in these health facilities. We found there were barriers to TB case detection, presented using a framework of health system-related and HCW- related barriers.

The main health system-related barrier was the lack of TB diagnostic laboratories in rural health facilities. This caused HCWs in rural health facilities to refer presumed TB clients to the municipal hospital for further assessment and testing. This system could contribute to high pre-treatment loss to follow-up since these facilities are mostly located far from the municipal hospital and, according to the HCWs, most clients are not able to afford the cost of transportation to the municipal hospital. This was substantiated by our linked quantitative study in the same facilities (15). Ereso *et al* in their study in Ethiopia also demonstrated that the absence of TB diagnostic

laboratories in facilities and subsequent referral of clients often led to delayed care seeking by these clients (5). Limited access to diagnostic facilities, mostly in rural settings, and long travel distance were similar barriers experienced by presumed TB clients in other parts of the world (6, 18-22). Rural health facilities in this study referred clients either to the chest clinic, task-shifting officer or to the general OPD. The lack of a standard referral system in our rural study facilities also led to extensive waiting times for some referred clients at the municipal hospital and this further underscored their reluctance to go to the municipal hospital for further assessment and testing.

Suboptimal TB screening practices in both rural health facilities and the municipal hospital imply non-adherence to national SOP for TB case detection. This was a barrier in this study as related by HCWs and from clinic observations. This can result in missed opportunities for early identification of clients with TB that could further impact on the spread of TB in the community. The lack of training and absence of the screening tool that we observed in this study could account for the HCWs not asking clients about cough as required by the national SOP for case detection. Harper *et al* in their study in The Gambia also revealed through observations that HCWs did not adhere to the stated health policy on asking about cough and referral of presumed TB patients to the national TB control programme (NTP) for further assessment (19). Similarly, in China, Xu *et al* found that HCWs were not alert to symptoms of TB and did not screen for other TB-related symptoms or request for a sputum test (23). The “Stop TB partnership’s” “Action framework for higher and earlier TB case detection” recommends training of all HCWs and not just HCWs in the TB unit to ensure comprehensive implementation of existing diagnostic algorithms in health facilities to improve TB case detection (24). Both this study and other research identified HCWs not being appropriately trained as a barrier to TB case detection (6, 18). Shortage of

staff and heavy workload were mentioned by HCWs as explanations for this non-adherence to TB case detection SOP, similar to other studies (4, 18, 25, 26).

The absence of a dedicated TB team could be one of the reasons for the non-adherence to the SOP. We found insufficient monitoring and supervision of TB work in the health facilities because there were no TB teams or focal persons in any of the rural health facilities and the one in the municipal hospital was described as non-functional. HCWs in the rural health facilities and those in the chest clinic of the municipal hospital perceived that if there was a team regularly supervising and monitoring the activities of HCWs then that would prompt them to ask about cough and request for sputum test where necessary. Lisboa *et al* in their study in Mozambique found that the lack of a motivated TB taskforce to supervise and monitor TB control activities in the health facility was a potential factor contributing to poor quality TB care (22). In addition, HCWs in our study were of the view that if TB teams from the district, regional or national levels regularly visited the health facilities to monitor and encourage staff, this appreciation of their efforts combined with knowing their activities are going to be monitored would serve as a motivation for them to pay attention to TB case detection. HCWs in another region in Ghana expressed similar sentiments (27). Moreover, in our study, HCWs were not putting into practice the recommended infection control measures which could lead to transmission of infection within the health facility. Comparably, in Nigeria, Tobin-West *et al* found poor TB infection control practices in both rural and urban health facilities (28).

The main HCW-related barrier identified in this study was fear of infection that affected attitudes to TB work and undermined effective screening for symptoms of TB. A study from Malawi in 2015 also reported that fear of infection by HCW led to underassessment

of clients for symptoms of TB (4). The lack of PPE for HCWs compounds this fear. This same challenge was reported by Dordor *et al* in Ghana and Lisboa *et al* in Mozambique (22, 27). In some rural health facilities, clients who were coughing at the OPD could not be isolated due to lack of space. This creates a complex barrier because the SOP states that it has to be done but no provisions are made. In the municipal hospital, the lack of interest in TB work led to all the work being left to the task-shifting officer and HCWs at the chest clinic. This could lead to clients with symptoms of TB going through the health system without being identified by other categories of staff. Contrarily, in the Mozambican study, HCWs were advocating for task shifting in TB work where auxiliary staff can be trained to screen for symptoms of TB and believed that this would solve the problem of TB case detection (22). In addition, HCWs' perceptions that some incentives were given to the task-shifting officer and chest clinic staff meant that they were not responsible to screen for symptoms of TB and request for sputum test. These findings conformed to findings from other parts of Ghana where perceived incentives for frontline TB staff and lack of interest in TB work by clinicians were identified as barriers to TB control (29). HCWs need to be provided with the right PPE to alleviate their fear of infection when dealing with presumed or TB clients and motivated to implement TB case detection activities in health facilities. This could subsequently lead to improved TB case detection.

Many health care organizations have embraced patient-centred care as central to their strategic missions and values (30). Patient-centred care involves providing care that is compassionate, empathetic, and responsive to the needs, values, and expressed preferences of each individual patient (31). The care providers must understand the patient's context and provide services to meet their needs. TB case finding in health facilities is impeded by complex barriers, and solutions should be patient centred. For

instance in rural health facilities, a specimen transport system should be implemented where presumptive TB patients will be asked to produce sputum at the rural health facility. The sputum specimen is then transported to the diagnostic laboratory for testing instead of referring patients to travel to the diagnostic laboratory to submit sputum. In South Africa, Naidoo *et al* found only 5% of TB patients could not access testing (32). The authors suggested that the effective sputum specimen transport system in South Africa could have accounted for the low proportion of patients not accessing testing. Ghana's NTP could adopt such patient-centred strategies to improve TB case finding in rural facilities. Also, implementation of a standard patient referral system between rural health facilities and the municipal hospital might improve TB case finding.

Our study had potential limitations. HCWs might have been more comfortable highlighting some barriers than others. The dominance of one health professional category (nurses) in the study population might affect the diversity of the information obtained. However, the strength of this study was the use of both interviews and health facility observations to validate our findings.

Conclusion

In south eastern Volta region, Ghana, the main health system barriers to TB case detection reported by HCW were lack of TB diagnostic laboratories in rural health facilities, fear of infection and suboptimal adherence to case detection protocols. These barriers likely contribute to poor TB case detection rates in the municipality. The barriers identified portray a complicated health system with no "one size fits all" solution. There is a need for appropriate interventions that focus on patient-centred care such as to improve TB symptom screening, an effective sputum transport system

and standard referral linkage to bridge the gap between rural health facilities and laboratories so that people with TB are not lost even before diagnosis. Also, hospital management especially in the municipal hospital should provide the appropriate PPE to HCWs to alleviate their fears of infection and encourage TB symptom screening.

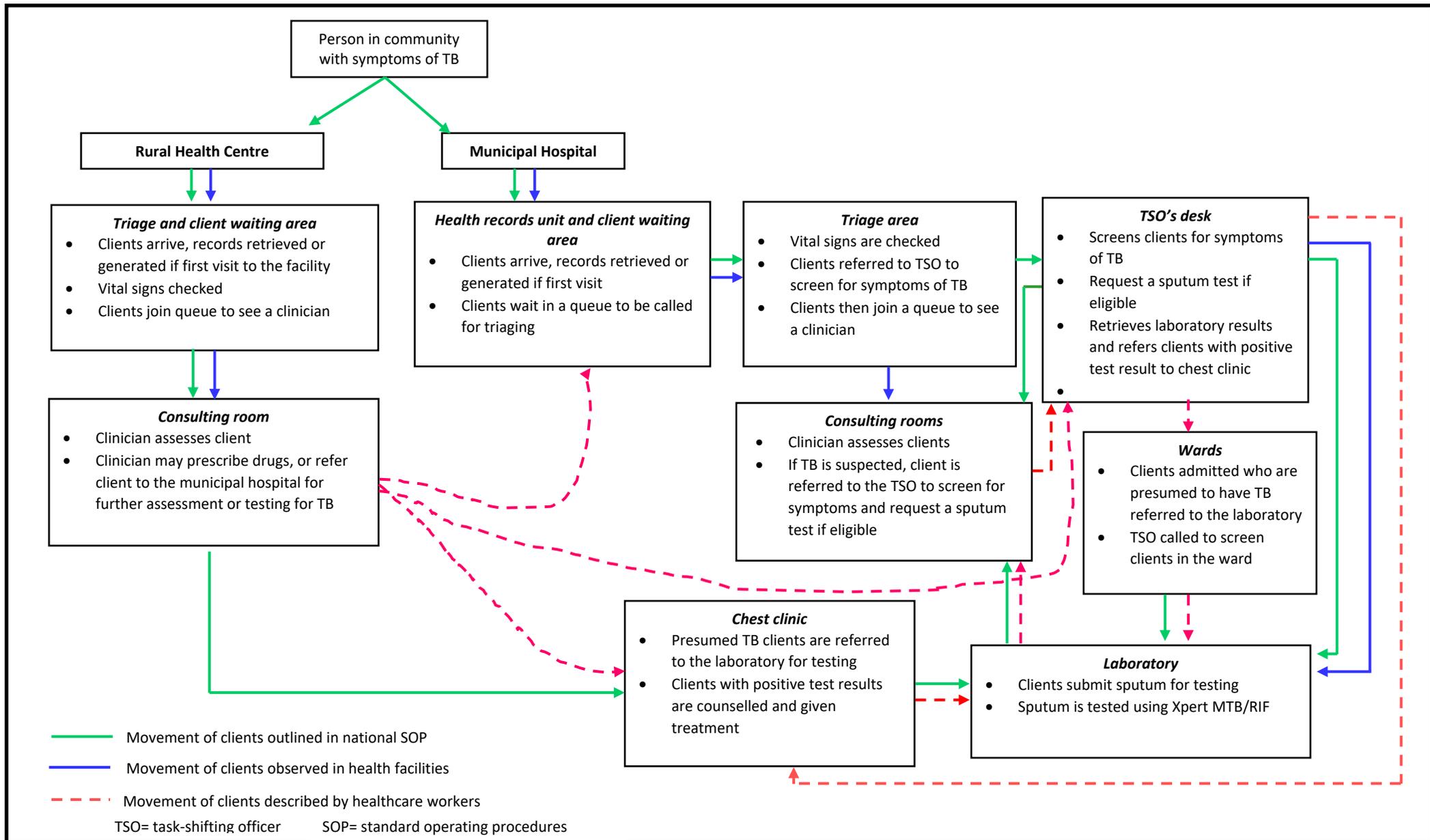
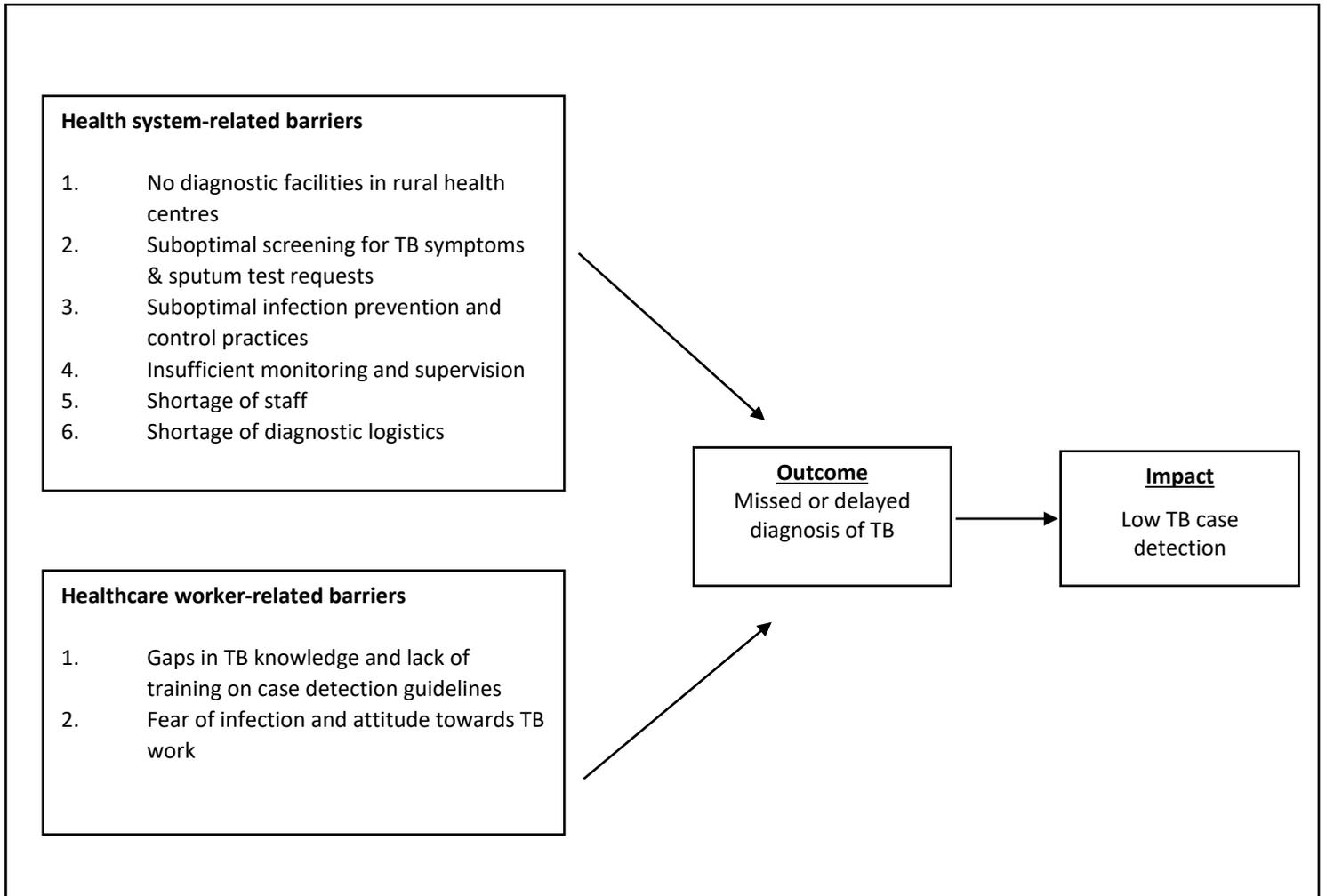


Figure 1: TB client flow and management in rural health facilities and the municipal hospital.

Ideally, in the municipal hospital, after triaging, clients should be referred to the TSO but this is not done in practice. Also, the TSO is not supposed to go to the ward to screen clients, but this is done in practice.

Figure 2: Summary of barriers to TB case detection in health facilities in south eastern Volta region Ghana.



The diagram shows that health system-related and healthcare-worker related barriers lead to missed or delayed diagnosis of TB and the impact of these is low TB case detection.

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Supplementary Table 1: Summary of checklist used for clinic observation

Location within health facility	Observations done
OPD waiting area	Presence of TB posters, whether health talks were held, waiting time of clients, behaviour of clients as they waited, whether visibly coughing clients were separated from other clients, and communication style of HCWs and clients
Triage area	Number of HCWs present, HCWs asking clients about cough and other TB related symptoms, use of TB symptom screening tool, number of clients who reported a cough, recording of cough in a cough register, requesting/referral for sputum test, providing education on cough etiquette and how to produce sputum samples, escorting clients to the laboratory for sputum test or allowing them to go on their own, behaviour and communication style of HCWs and clients
Consulting room	Number of HCWs present, HCWs asking clients about cough and other TB related symptoms, use of TB symptom screening tool, number of clients who reported a cough, recording of cough in a cough register, requesting/referral for sputum test, providing education on cough etiquette and how to produce sputum sample, escorting clients to the laboratory for sputum test or allowing them to go on their own, behaviour and communication style of HCWs and client
Laboratory	Number of HCWs present, providing education on cough etiquette and how to produce sputum samples, waiting time to submit sputum, handling of sputum sample by client and how laboratory staff collected sputum from client, behaviour and communication style of laboratory staff and clients
Chest clinic	Number of HCWs present, clients escorted to chest clinic by HCW or arriving alone, providing education on cough etiquette, counselling of clients with positive test results, explaining treatment procedure to clients, serving of medication, behaviour and communication style of HCWs and client
General observation	General facility layout and workflow, whether any significant event was happening at the health facility on the day of observation

OPD= outpatient department, TB=tuberculosis, HCW= healthcare worker, RHF= rural health facility, MH= municipal hospital

Supplementary Table 2: Illustrative quotes on barriers to TB case detection

Study results	Illustrative quotes
Health system related barriers	
Suboptimal screening for TB symptoms and sputum test request	“Every client whether the person is a BP (blood pressure) client, [...] because sometimes they easily forget something unless you remind them before they will say that oh yesterday, I was even coughing. So, we ask them”. (Male HCW, RHF)
Shortage of diagnostic materials	“[...] sometime sputum container will get finish, cartridge will get finish and sometimes what marvels me is that on days containers are in the lab they will be giving the containers out without checking their stock levels but will wait when I send a patient to them for sputum test before they will tell me that containers are finished. Sometimes containers will get finish and because the clients are coming plenty and everybody is at risk, so I have to go and [...] have to give me some money to go and look for containers [...]”. (Male HCW, MH)
Poor documentation in cough registers	“We don’t have enough staff to record cough in the register. Actually the one who was doing this is no longer in the facility”. (Female HCW, RHF)
Sub-optimal infection prevention and control practices	“Here the relatives can enter anytime they want, maybe in the night that I don’t know but for daytime the relatives enter the isolation ward anytime they want [...], that’s one of our challenges in this premises, the regulation is not there”. (Male HCW, MH)
Insufficient monitoring and supervision of TB work by TB team	“There is a name to that effect, yes in quote a TB Team, but we don’t conduct any meetings I mean nothing really happens so I really don’t know if that team is functional or not but it’s just a name [...]”. (Male HCW, MH)
Healthcare worker related barriers	
Gaps in TB knowledge and lack of training in case detection guidelines	“The nurses at the hospital here we are many and if all of us we know something about tuberculosis and about tuberculosis detection, if all of us we are aware and we know much about it, we will be able to identify more cases but because most of us don’t know anything about tuberculosis when a person is even coughing they will ignore the person until those experience ones capture the person”. (Male HCW, MH)
	“Not all the health workers have gone for the training, but TB is a common thing [...], we have been learning about it so even if you don’t go for training at least you have to identify cases”. (Female HCW, RHF)
Fear of infection	“If the health worker doesn’t have so much knowledge about TB and has just this knowledge that TB is infectious, [...] then getting closer to the person and even how to handle yourself before the person so that you will not also get infected is one issue. Also, if the nurse doesn’t have much knowledge then stigmatization then comes in and fear of infection comes in too so you will not be able to assess the client very well”. (Female HCW, RHF)
	“[...] so, the ones who are not coughing I mean we can do our normal examination but most of the time I mean we don’t wear any PPEs. There have been few times which I have declined to see TB patients [...]”. (Male HCW, MH)

Attitude towards TB work	“Some of our laboratory staff, who show much concern for this screening issue, sometimes if accidentally they are not there and those who are around are the less concerned ones, sometimes we don’t get test result. [Therefore we] sometimes have to recall the clients to come and reproduce the sputum, sometimes you have to pay their T&T (travel and transportation)”. (Male HCW, MH)
Suggested solutions by HCWs	“If we get laboratory in any of the four facilities in the sub-district, it will solve the referral problem”. (Female HCW, RHF)
	“[...] instead of we referring directly to the laboratory at the municipal hospital, there could be a focal person at the laboratory who could come and take the sample and then when the person is diagnosed positive, the person can now go to the bigger facility for treatment [...]”. (Female HCW, RHF)

TB=tuberculosis, HCW= healthcare worker, RHF= rural health facility, MH= municipal hospital

Chapter 8: Discussion

This chapter provides a synthesis of this thesis. It presents a summary of the key findings, reflections on the findings in relation to literature and the implications of the findings to TB case detection in health facilities. It also presents the strengths and limitations of the research and lastly it gives the conclusions and recommendations.

8.1 Summary of key findings

8.1.1 Situation assessment at health facilities

Findings from a situation assessment at health facilities prior to the start of the study (chapter 4) revealed that some rural health facilities were not screening patients for symptoms of TB or requesting sputum tests. Also, in the facilities that were screening for TB-related symptoms, this was not done regularly. The reasons given for not screening for TB-related symptoms and requesting a sputum test were that HCWs were not trained on the use of the screening tool and the tool was not available in the health facilities. Since the prospective cohort component of this PhD study required patients who had a sputum test requested routinely by a HCW, the screening tool was introduced and HCWs at the rural health facilities selected for the study were trained by the study team on how to use it. This action likely influenced HCWs to screen for TB-related symptoms and request a sputum test. The likely impact on the results of the study is that, had the study not happened, there would have been even less TB case finding at these rural health facilities.

8.1.2 Objective 1

To determine the proportion of health facility attendees eligible for sputum test according to national guidelines who were asked to do a sputum test by a HCW and the

prevalence of having sputum positive on Xpert MTB/RIF among health facility attendees who met the criteria for sputum test according to study criteria.

The findings of this objective are detailed in chapter 5. The key findings were that among patients attending outpatient clinics at the municipal hospital and had at least one symptom of TB and did not report these symptoms to a HCW, most were not asked about TB-related symptoms even though the national SOP for TB case detection states they should be asked. In addition, among patients who reported their TB-related symptoms to a HCW and were eligible for a sputum test, only about a fifth (21.5%) of them were asked to submit sputum for a TB test. Likewise, among patients whose TB-related symptoms were elicited by a HCW and were eligible for a sputum test, only 9.1% were asked to submit a sputum. Some patients did not report their TB-related symptoms at all to a HCW and among this category, 20% were eligible for a sputum test but none was asked to submit a sputum. The factors positively associated with being asked to submit a sputum by a HCW were increasing number and longer duration of symptoms as well as having been previously treated for TB. The prevalence of TB among patients who were eligible for a sputum test according to the study criteria was 3.2% which was surprisingly low.

8.1.3 Objective 2

To determine the proportion of patients with a request for sputum test who submitted a sputum for testing, the time from test request to submitting sputum, and factors contributing to non- submission of sputum for testing.

Findings for this objective are detailed in chapter 6. In summary, about 70% of patients with a request for a sputum test submitted a sputum for the test. Stratifying by the type of health facility attended, only 31.5% of rural facility attendees submitted sputum compared to 91.8% of urban facility attendees who submitted a sputum. The

main predictors of not submitting a sputum were travel distance greater than 10 km and a high perception of TB stigma.

8.1.4 Objective 3

To compare the time from test request to submitting sputum among patients attending a health facility with vs. without a co-located laboratory.

The majority of urban facility attendees submitted sputum earlier than rural facility attendees. In rural facilities where there was no co-located laboratory, only 4.2% submitted sputum to the laboratory on the day the test was requested compared to 80.4% of urban facility attendees who submitted sputum on the day the test was requested.

8.1.5 Objective 4

To explore HCWs' perspectives concerning barriers to TB case finding in health facilities, their experiences, practices and suggested solutions for improvement.

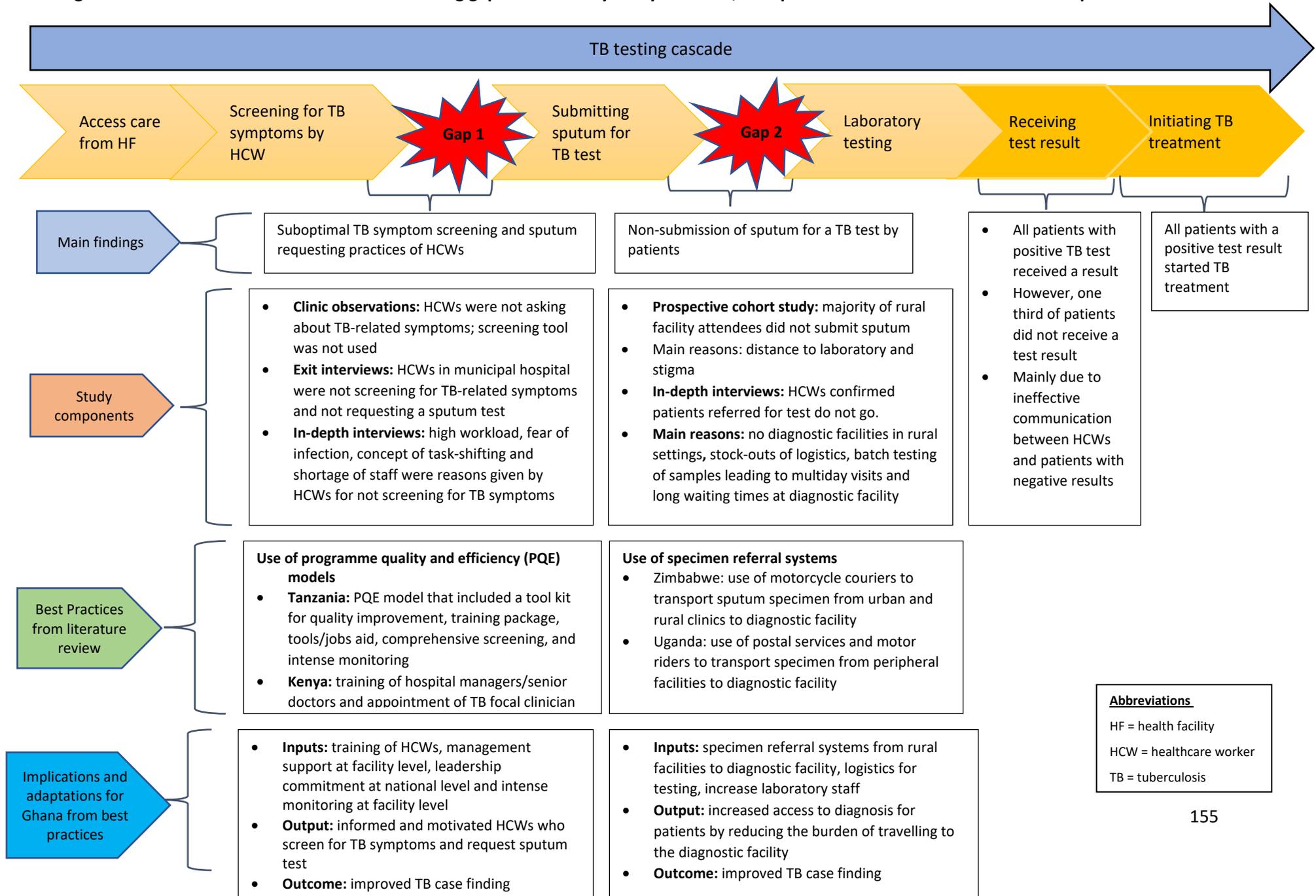
The findings of this objective are detailed in chapter 7. Barriers to TB case finding in health facilities were classified into two thematic areas: health system-related and HCW-related barriers. The main health system-related barriers were lack of access to diagnostic laboratories for patients attending rural health facilities, suboptimal screening for TB-related symptoms and sputum test request, lack of implementation of infection control measures according to the standard guidelines and insufficient monitoring of TB case detection activities in health facilities. The main HCW-related symptoms were lack of training on case detection guidelines and fear of infection causing a lack of motivation to carry out TB work. HCWs interviewed suggested that provision of diagnostic facilities in sub-municipalities, training on case detection guidelines and intensified supervision would help improve TB case detection in health facilities.

In summary, findings from this thesis show there are gaps in the pre-diagnostic steps of the TB care cascade. These gaps need to be closed to ensure patients with active TB accessing health facilities for care are promptly identified and initiated on treatment.

8.2 Reflections on findings

I have organised the discussion of these findings using a framework modelled around the steps of the TB care cascade. The framework was adapted from the conceptual framework of Bitton et al [136] and is shown in figure 8.1. It shows the gaps identified using the different components of the study, best practices from other countries to address similar gaps and what Ghana's national TB control program can adapt from these best practices. The gaps identified, best practices from other countries, implications and adaptations for Ghana are discussed below:

Figure 8. 1: Framework of TB care cascade showing gaps identified by study methods, best practices from other countries and implications for Ghana



Two main gaps were identified mainly in the pre-diagnostic steps of the TB care cascade. The gaps identified are:

8.2.1 Gap 1: Suboptimal TB symptom screening and sputum requesting practices of HCWs

Screening for symptoms of TB is the first important step required to identify people with TB. The WHO's principles and recommendations for systematic screening for active TB states that the primary objective of screening for active TB is to ensure early detection of active TB and prompt initiation of treatment, with the ultimate aim of reducing the risk of poor treatment outcomes, health sequelae and the adverse social and economic consequences of TB, as well as helping to reduce TB transmission [38]. The WHO's document outlines different recommendations for systematic screening for different risk groups. Different countries have adapted the WHO's recommendations to suit their local context. In Ghana, the SOP for TB case detection states that all adult patients visiting OPD of health facilities should be asked about cough and those reporting a cough should be screened for TB-related symptoms, if eligible they should have a sputum test requested. Findings from the cross-sectional study using exit interviews showed that HCWs in the municipal hospital were not screening for TB-related symptoms and not requesting a sputum test among persons who spontaneously reported their symptoms and were eligible for a sputum test. Studies in South Africa and Zimbabwe using similar methodologies also reported that patients with TB symptoms seeking care in health facilities were not screened and sputum was not requested [82, 137-141]. The details of how some of these studies compare with our study are discussed in chapter 5. In one of these studies [140], the authors found through exit interviews that, of patients reporting a history of cough of two weeks or more only 21% were asked to submit a sputum for testing. This was comparable to our study where we reported a similar proportion of 21.5% asked to submit a sputum among those eligible

for the test. Kweza *et al* in their exit interview study in South Africa, also reported that of 5% of patients exiting the facility who tested positive for TB by study team, 38.5% were never screened for TB-related symptoms by clinic staff and 61.5% were screened but not tested for TB [139]. Others similarly reported that HCWs were only prompted to request a sputum test if symptoms were obvious as TB related such as prolonged cough [137, 141].

These findings from the cross-sectional study were supported by findings from the clinic observations in health facilities where we noticed HCWs were not systematically screening for symptoms of TB and requesting sputum tests. During the in-depth interviews in the qualitative study of this thesis, HCWs reported that shortage of staff leading to heavy workload were some of the reasons they do not screen for symptoms of TB. Others too felt screening for TB symptoms was extra work and not their duty. HCWs not screening for TB clearly showed non-adherence to standard guidelines and typically meant missed opportunities for identifying patients with TB. In 2010 when the NTP introduced systematic screening of patients attending OPDs for TB-related symptoms as part of routine practices, HCWs started complaining of heavy workload leading to non-adherence to the guidelines. In response to this complaint, the NTP introduced the concept of “task-shifting” in some selected health facilities where a designated HCW is assigned and stationed at the OPD to support in the screening of patients for TB-related symptoms and request for a sputum test [142]. In 2016, task-shifting officers were employed and posted to all district/municipal and regional hospitals. Findings from clinic observations and in-depth interviews in this study showed the presence of the task-shifting officer was helpful in identifying patients with TB, but the main challenge was that the presence of the task-shifting officer caused other HCWs not to screen for TB-related symptoms, because they felt it was not their

job leading to lack of attention to TB case finding. This made it difficult for the task-shifting officer to take leave from work. We found during the clinic observations that at any point in time that the task-shifting officer fell sick, no one took over their role and this could lead to missed TB diagnoses. In a qualitative study among HCWs in the northern part of Ghana on barriers and facilitators to bidirectional screening of TB and diabetes (TB-DM), HCWs said the presence of a task-shifting officer had increased TB case finding compared to the low case detection they had prior to the institution of this position [143]. However, similar to what was found in our study, the task-shifting officer said the main challenge was that even though it was mandatory to screen all patients at the OPD for TB, other HCWs were not doing it, because the screening had not been fully incorporated in the triage routines at the OPD [143]. Despite the fact that the NTP has tried to solve the problem of non-adherence to screening guidelines by introducing the task-shifting concept, the challenges still exist as evidenced by our study and the TB-DM study. Project planners need to be aware that task shifting programmes are limited by the health system of which they are a part. Therefore, there is the need to consider the entire health system in the implementation of such programs most especially the professions affected by these programs [144]. These professions must be an active component of the change process rather than being alienated from it, such that they can provide the needed support for successful implementation. When they are excluded, then challenges such as those observed in our study arise. Based on the experiences of HCWs on the concept of task shifting in sub-Saharan Africa reported in a systematic qualitative review [144], Ghana's NTP needs to provide training for all HCWs at OPDs of health facilities on the concept of task shifting in TB case finding. HCWs should be educated on the limitations of the concept and made to know that it is a complimentary practice hence, the need for them to all be supportive instead of leaving the work for the task-shifting officer. The

training of HCWs should be accompanied by strong supervision of the TB screening practices of HCWs and the task-shifting officer.

Moreover, among HCWs we interviewed, most of them were not trained on the SOP for TB case detection. They acknowledged that lack of training led to poor knowledge of TB and a low index of suspicion. In chapter two, I detailed in the literature review several studies that also identified poor knowledge and low index of suspicion as factors causing delayed or missed diagnosis of TB [33, 39, 51, 63, 145]. Fear of infection was another reason for which HCWs did not screen for symptoms of TB or were reluctant to attend to TB patients admitted to the TB ward. HCWs need to be educated on the fact that TB patients on treatment and admitted in wards are unlikely to be infectious especially after two weeks of anti-TB treatment [146, 147] but rather it is the unidentified, untreated TB patient who is most likely to be infectious. Therefore, it will be in their interest to rather screen for symptoms of TB among patients so that those with the disease can be identified early and put on treatment to reduce the infectiousness of the disease and keep everyone safe.

In Tanzania and Kenya, after their national prevalence surveys were conducted in 2013 and 2015 respectively, they found higher than expected TB prevalence, showing that their case detection rates were low indicating persons with TB were missed, similar to what was found in Ghana [148]. In order to solve the problem, they conducted national assessments to identify the barriers and best practices in TB case finding. In Tanzania, the barriers included low index of suspicion among HCWs, low usage of diagnostic algorithms and unequal distribution of laboratory diagnostic services; and in Kenya, limited hospital managers' and HCWs' involvement in TB case detection and treatment were their main barriers. Both countries developed programme quality and efficiency

(PQE) models to solve the challenges. In Tanzania, the PQE included a toolkit for quality improvement in TB case detection, training package, tools and job aids, comprehensive screening and intense monitoring of health facilities. Training of hospital managers and senior doctors and the appointment of a TB focal clinician whose duty was to keep TB on the agenda of discussions and meetings where components of the PQE implemented in Kenya. In addition, the Minister of Health sent a memo directing the practice of active TB case finding in all health facilities and this was a significant action that changed things. Peer mentorship visits were also carried out. After 18 months of implementation in Tanzania, the key results of the intervention were increased notification in facilities that implemented PQE compared with the control facilities; and increased index of suspicion of TB among HCWs. In Kenya, after a year of implementation, there was an increase of 158 percent in case detection in the 13 country hospitals that benefitted from the intervention [148]. The key lessons learnt were that management support at the facility level and leadership commitment at the national level were essential in changing HCWs' practices in TB case finding [148]. These were success stories shared at a workshop organized as part of a collaborative initiative designed to bring countries together to share experiences and support their efforts to reach the common goal of ending TB by 2030, in line with the WHO End TB strategy [148]. During our qualitative study, some HCWs mentioned that if leadership from the NTP and regional health directorate could come to the facility and talk to HCWs then they would comply with TB case finding guidelines in the facility, emphasizing the role of leadership, as demonstrated in Kenya. Ghana's NTP could adapt some of these strategies based on what is feasible and meets the country's need to improve TB case finding in health facilities. However, there is the need to bear in mind that these programme quality and efficiency models may not be sustainable [149]. Thus, an understanding of how to ensure sustainability and the factors that

affect it is of fundamental importance to prevent wasted effort [150]. These should be incorporated into the project design at the earliest stage of its development. It requires a supportive management structure from national, regional, district and facility level as well as a robust, transparent feedback systems to make it work [150].

As mentioned above in the summary of findings, the action taken after the situation assessment of health facilities was to ensure that the recruitment period for the prospective cohort study was not extended or the study could not be done. The assessment also portrayed the magnitude of the challenges with TB case finding in rural health facilities in the study setting. If prior to the study rural health facilities were not regularly referring presumptive TB patients for a sputum test, then the potential number of missed diagnoses of TB could be huge and this has implications for patient outcomes, transmission of disease in the community and national programme goals. This finding from the initial situation assessment was confirmed by findings from the clinic observations in the qualitative study where we found that even though HCWs in the consulting rooms of rural health facilities asked a routine set of symptoms questions to all patients, they did not continue to ask about other TB-related symptoms when a patient responded they had cough. Even though they asked about duration of cough, there were instances when patients reported durations of two weeks or more but they were not referred to the municipal hospital to submit a sputum for a TB test. This showed a gap in TB symptom screening practices of HCWs. Several reasons were given for why HCWs did not screen for TB-related symptoms as part of routine practices and these were discussed in detail in chapter 7. One of the reasons was that they had not been trained on the SOP for TB case detection and did not know there was a TB-symptom screening tool they needed to use. This was evident during in-depth interviews when some HCWs alluded to the fact that the first time they saw

the screening tool was when the study team introduced it to them. One-off training of HCWs on the SOP might not necessarily change their behaviour in screening for symptoms and requesting for sputum test. Ghana's NTP could consider adapting one of the many programme quality and efficiency models used by other countries especially one that incorporates involvement of high level management and leadership, as was done in Kenya (discussed above) [148], to motivate HCWs to show more interest in TB case finding activities. This also implies the district TB management team should monitor closely the data that is reported by health facilities. This would enable them to know which facilities are screening for symptoms of TB and requesting sputum tests. If there is close monitoring of the data, once a facility is not reporting or the numbers are decreasing, they can intervene early to determine what the challenges are and resolve them.

8.2.2 Gap 2: Non-submission of sputum for a TB test by patients

In the TB care cascade, once a person is eligible for a sputum test, the HCW normally gives a request for a sputum test. The patient needs to produce a sputum sample and the sample submitted to the laboratory to be tested to confirm if the patient has TB or not. Submitting a sputum for testing is an essential step in the care cascade; however, it is not always easy to submit a sputum to the laboratory depending on where a patient accessed care. In our study setting, there was only one TB diagnostic laboratory at the municipal hospital and all patients with a request for a sputum test had to travel to the municipal hospital to submit a sputum for a TB test. In the prospective cohort study of this thesis, we followed up on patients to find out if they did submit a sputum after it was requested by a HCW and we found that the majority of rural health facility attendees did not submit a sputum for the test. In our qualitative study, HCWs in rural health facilities reported that when they referred patients to the municipal hospital

for a sputum test, most of them did not go to submit a sputum, leading to losses from the care cascade. The main predictor of patients not submitting a sputum was longer distance to the diagnostic laboratory. In the study setting, most of the rural areas were located about 10- 20 km from the municipal hospital and so patients need to reach the hospital either by using commercial motorbikes or public transport which they must pay for. As part of findings in the prospective cohort study, most study participants attending rural health facilities were in the lower wealth tertile. This implied they did not have money to pay for the transportation to the diagnostic laboratory for the test. In fact, one of the reasons mentioned by participants in the prospective cohort study as to why they did not submit a sputum was that they did not have money to travel to the hospital for the test. This also came out strongly during the qualitative study where HCWs said most patients were constrained financially and that is the reason why when they refer them for a sputum test, they do not go. On some occasions, HCWs had to pay the transportation cost for patients to go and submit a sputum at the municipal hospital. HCWs also mentioned that patients at times think they need to pay for services at the municipal hospital even though the TB test is free and for this reason, they are reluctant to go to the hospital. Studies in Ghana and Zimbabwe have reported long travel distance and its associated cost as risk factors for pre-diagnosis loss to follow-up [26, 28, 151].

Aside the direct out of pocket cost that prevented rural facility attendees from submitting sputum, there was also the opportunity cost. In the qualitative study, HCWs mentioned long waiting times at the municipal hospital as a reason for which patients they referred did not go. This was because patients felt they would waste time at the hospital and would rather prefer to do their work than to go to the hospital and lose income. This was also evident in the prospective cohort study where some patients who

did not submit sputum said the reason was because they did not have time to go to the hospital. In the literature review (Chapter 2), I detailed studies that reported how patients would prioritize their work over going to the hospital to seek health care [53, 58, 62, 152]. During the qualitative study, we found that there was no standard referral system used at rural health facilities to refer presumptive TB patients to go for a sputum test or for further assessment at the municipal hospital. Presumptive TB patients were referred to different departments at the municipal hospital, and depending on the department the patient was referred to, it could lead to long waiting times. For instance, patients who were referred to the OPD of the municipal hospital had long waiting times compared to those referred to the chest clinic or directly to the task-shifting officer. A standard referral system could reduce the waiting time which might motivate patients to submit a sputum when they are referred. In Tanzania and Kenya, during national assessment of barriers to TB case detection, they found weak referral systems as a reason for missed diagnosis of TB [148].

Rather than asking patients to travel to the laboratory to submit a sputum, there could be innovative ways of transporting the sputum specimen to the laboratory. For instance in Zimbabwe, the NTP with the support of the United States Agency for International Development (USAID) and the International Union Against Tuberculosis and Lung Disease (The Union) initiated a medical specimen transport system in 2010 to ensure universal and early access to TB diagnosis, care, and treatment [153]. The mainstay of the innovation was that it used a cadre of motorcycle couriers, enlisted to conduct specimen transport full-time. The couriers picked up sputum specimens from clinics and sent them to the laboratory for testing and they picked up the test results and delivered them back to the clinics. Clinics were visited on a daily basis in urban areas, and on a weekly basis in rural areas. The couriers used logbooks to track

specimens and results transported and HCWs and laboratory staff endorsed the logbooks daily, which fostered a high level of accountability for the couriers and implementers alike. In 2014, when they evaluated the programme, they found that the specimen transport system had strengthened TB diagnosis by decentralizing diagnostic services from district to peripheral health facilities. This increased access to diagnosis for patients by reducing the burden of traveling to district facilities to receive services. It also empowered HCWs to collect sputum specimens regularly instead of referring patients to district facilities and resulted in increased patient trust in the health system [153].

In Uganda, they also implemented an innovation to strengthen the TB specimen referral network for diagnosis of multi-drug resistant TB between 2008–2011 [154]. In their programme they used the postal services where on a daily basis, sputum specimens were transported from TB units to the local post office and the post office in turn transported the specimen to the national TB reference laboratory for testing. They found that the system led to increased numbers of patients receiving the necessary diagnostic testing and substantial reductions in transport delays [154]. Transport of sputum specimen which is an infectious material may require specific regulations and permits to be transported through the post office in most countries and specimen will require special packaging [155]. The authors mentioned that all the necessary consultations and permits were obtained from the relevant institutions before implementation of the intervention. HCWs and post office staff were trained on how to safely package specimen and the specimen transport containers used were the ones with triple packaging capacity which were validated by South African national standards [154].

Again, between 2015-2018, when Uganda realized there remained significant gaps along the cascade of care for patients undergoing TB diagnostic evaluation at peripheral health centres (i.e. considerable costs and time required to complete health centre visits), they initiated a system similar to the one implemented in Zimbabwe using motor riders [156]. They found it significantly improved the provision of high-quality care for patients undergoing TB diagnostic evaluation.

Specimen referral systems play a critical role in ensuring access to laboratory services by allowing patients to receive care and treatment at one location, while their specimens are transferred to various levels of a tiered laboratory system for testing [155]. Referral systems can efficiently increase access to diagnostics in areas where testing is not available, prevent the need and associated costs for patients to travel, and lead to equity in access to health care [155]. It is time Ghana's NTP took a cue from these success stories in other countries and adopt a specimen referral system instead of asking patients to travel all the way to district or municipal hospitals to submit a sputum. There is no doubt that these innovations do have limitations and some of the limitations include getting to hard-to-reach areas in rural communities especially during the rainy season when roads are unmotorable [154] but these innovations still have the potential to reduce losses in the care cascade than asking patients to travel to the diagnostic laboratory to submit a sputum. Other factors in our study which contributed to pre-diagnostic delay or loss to follow-up such as rural facility attendance will be reduced by the institution of a specimen referral system.

Other findings from the diagnostic and post-diagnostic steps of the TB care cascade are discussed below:

8.2.3 Laboratory testing of sputum samples

Laboratory testing is another important step in the TB care cascade. During clinic observations in our qualitative study, we observed at the municipal hospital that patients who were given a request for a sputum sample had to either collect a sputum container from the task-shifting officer or the laboratory or the chest clinic. The location of containers kept changing because HCWs at the chest clinic claimed when the containers were given out at the laboratory, laboratory staff did not monitor the usage and this at times led to stock-outs. When this happened, patients who travelled in from rural health facilities to submit sputum would return home without submitting the sputum and some never returned to the hospital to submit a sputum. This added to the financial cost to the patients as was mentioned by HCWs of the chest clinic during in-depth interviews. Some of these inconveniences caused to patients could also be the reason for their reluctance to travel to the municipal hospital to submit a sputum. Also, when the sputum containers were kept at the chest clinic, it increased the time patients spent in the hospital and caused more inconvenience. This is because the chest clinic was located about 200-300 metres from the OPD and patients had to walk all the way to the chest clinic to collect a container, produce sputum and returned to the OPD to submit it at the laboratory. This made the whole process of sputum submission very cumbersome for patients. Allowing the task-shifting officer to keep the containers would make it simpler for patients to submit sputum.

At the time of planning the study, the main diagnostic method was smear microscopy but by the time we were executing the study, the main diagnostic method had changed to Xpert MTB/RIF. At the planning stage of the study, we considered the fact that

presumed TB patients needed to submit a sputum the first day and return the next day to submit a second specimen, so we anticipated more losses than observed from the testing cascade in our prospective cohort study. However, the change to Xpert MTB/RIF did not affect this because presumptive TB patients submitting a sputum at the laboratory still needed to visit the hospital a second time to receive their results. The reason for this multi-day visit was because the laboratory batched all sputum specimens and performed the testing towards the end of the working day. In order not to let patients wait a long time to receive their results on the day of sputum submission, they were asked to return the next day for the results or told they would be called by the hospital to inform them of their results. The reason for which sputum specimens were batched and the test performed at the end of the day was because of heavy workload and few laboratory staff as reported during in-depth interviews with HCWs. The laboratory doubled as the main laboratory for performing all laboratory tests for all other diseases with the same staff performing all the tests. Laboratory staff did not give priority to performing sputum test as reported by some HCWs during in-depth interviews and this at times led to delay in the release of test results. This reflects the tension between laboratory organization and patient-centred care. These multi-day visits contribute to losses from the care cascade as has been shown by several studies [97, 99]. Davids *et al* in their cross-sectional survey of primary healthcare providers on use of rapid tests and TB diagnostic practices in South Africa reported that despite implementation of Xpert MTB/RIF there was still long turnaround times to receiving TB test results (median: 3 days) [99]. This was similar to our qualitative finding where patients had to visit the hospital a second time after sputum submission to receive a test result even though Xpert MTB/RIF was the main diagnostic tool. Davids *et al* explained that the long turnaround time was due to backlogs created by the centralized testing system and that primary healthcare facilities required the

appointment of additional staff to ensure same-day results [99].

In the cross-sectional exit interview study, we asked patients who were eligible for a sputum test according to our study criteria to submit one spot sputum specimen for laboratory testing to determine the prevalence of TB among patients exiting the hospital after seeking care for themselves and reporting at least one TB-related symptom. The yield of TB was low (3.2%), and several reasons could account for this but one of the reasons could be because most of the sputum specimen submitted were salivary. At the municipal hospital there was a sputum booth for sputum collection and although routinely patients were educated on how to produce a sputum specimen, there was no direct supervision of sputum production. The study team too did not supervise sputum collection though education on how to produce quality sputum was provided to patients. The study criteria used for eligibility for sputum submission was the same as the national criteria being used by the hospital except that the study criteria included patients self-reporting to be HIV-positive. Since study staff did not supervise patients to produce sputum which could have resulted in a lot of salivary specimen then it could be that since routinely in the hospital patients are equally not supervised to produce sputum then it is possible most of the specimen submitted to the laboratory for routine testing might also be salivary. This could result in missed diagnosis of TB. We would advise that patients should be supervised to produce quality sputum for testing. In Botswana, Mathebula *et al* conducted a study in 2013 to improve sputum collection processes to increase TB case finding among HIV-positive persons by introducing sputum collection job aids and assisting patients to produce sputum [157]. They found that enhanced sputum collection significantly improved the quality of sputum collected. The number of salivary sputa decreased significantly, and the proportion of mucoid and muco-purulent sputum specimen

increased. The rates of TB diagnosis also increased from 9.7% to 12.5% but the evidence for this difference was weak ($P=0.143$) [157]. The authors however, did not comment on sustainability of the intervention strategies, although they mentioned that they did not assess the cost-effectiveness of the intervention strategies, but they believed it would be a low-cost intervention [157].

8.2.4 Receiving test results and initiating TB treatment

In the prospective cohort study of this thesis, we found that about 33% of study participants who submitted a sputum for a TB test did not receive a test result. During clinic observations and in-depth interviews, we discovered that in the municipal hospital, the task-shifting officer on a daily basis picked up the test results from the laboratory of all patients who submitted sputum the previous day. He then called those with positive test results to inform them of the results and asked them to come to the hospital to start TB treatment. Those with a negative test result had to visit the hospital to pick up their results. It is possible that some of those who did not return to the hospital were those who had not received their results. This implied there was no further follow up of these patients with negative test results. In the SOP for TB case detection, the TB diagnosis and treatment algorithm outlines that patients with a negative TB result should be treated with broad spectrum antibiotics and if they did not get better, the sputum test should be repeated and chest radiograph taken and if both are negative then the clinician should make a clinical judgement to treat or not treat for TB. During follow-up calls as part of the prospective cohort study, when we asked participants why they had not received their test results, some said they felt better from their symptoms and did not see the need to return for the results but others said they were told by the task-shifting officer they will be called to inform them of the results but no one had called them. Some of them were quite upset that they had not

heard anything from the hospital about their results. This lack of communication from the hospital reduced their trust in the health system. When the task-shifting officer was asked during in-depth interviews why the hospital did not call patients to inform them of their test result as communicated to them, the task-shifting officer said no call credit was provided by the hospital or district management to call patients to inform them of their test results. In a study in South Africa where they used standardized patients' analysis to measure the quality of TB screening at primary healthcare facilities, they found only 28% of standardized patients were effectively communicated to on receiving their results [158]. This showed a lack of information-sharing, particularly in terms of continuity of care.

A positive finding however was that all patients with a positive test result were initiated on TB treatment promptly, usually within a day or two. This could be attributed to the commitment of the task-shifting officer in calling those with positive test results using his own call credit to come and start treatment. If the laboratory confirmed a positive test result and the task-shifting officer was not available, staff at the chest clinic were notified of the positive results and they would call the patient to come for treatment. In instances where a patient with a positive TB test result had no telephone number or could not be reached on the telephone number provided, the task-shifting officer traced them to their homes using the contact address they provided to inform them of the results and asked them to come and start treatment. At times, he used his own resources to do this but at other times he informed the staff at the chest clinic who would request for a vehicle from the hospital administration to follow up on the patient with positive test result and bring them in for treatment. Unfortunately, sometimes they were informed by the hospital administrator that there is no vehicle available. This highlights the institutional challenges HCWs sometimes

encounter in carrying out TB case finding activities. There is the need for facility management commitment to TB case finding in health facilities.

Also, the task-shifting officer accompanied positive TB patients to the chest clinic for them to start treatment. A challenge was that at times patients with positive test result were not told to come with a treatment supporter and in such instances, they had to go and find a treatment supporter before they were initiated on treatment. A treatment supporter was a person chosen by the TB patient whose main role was to make sure that the patient took the TB drugs regularly, on schedule, for the full duration of the treatment [159]. A TB patient having to go and look for a treatment supporter before TB treatment is initiated can lead to loss to follow-up. Since pre-treatment loss to follow-up was not the main focus of this study, we did not explore this further, but it could be an area for future research.

The time between a positive test result and treatment being started in this thesis was comparable to a cross-sectional study in Italy on determinants of patient and health care services delays for TB diagnosis where the authors found the median treatment delay was zero days with an interquartile range of zero to three days [46]. Also, a systematic review and meta-analysis involving 78 countries on empirical evidence of delays in diagnosis and treatment of pulmonary TB showed that the pooled mean treatment delay was 7.9 days compared to pooled mean patient delay of 81 day [34]. Although most studies on delay define health system delay as the time a patient first contacts a health facility to the time TB treatment is initiated, there are few studies that sub-categorize health system delay into diagnostic delay and treatment delay as reported in this systematic review. The definitions for diagnostic delay and treatment delay were discussed in the literature review in chapter 2. The systematic review

showed that treatment delay was not the main contributor of delay in TB diagnosis and treatment but rather patients not accessing care early for their TB-related symptoms.

This PhD study was designed to focus on the pre-diagnostic steps and not the pre-treatment step of the TB care cascade because we envisaged that the challenges in TB case finding in health facilities would be at the pre-diagnostic phase. Also, the pre-diagnostic steps in health facilities are less often studied and perhaps less well understood.

8.3 Thesis limitations and strengths

8.3.1 Limitations

Some limitations of the different studies that make up this thesis are discussed in chapters 5, 6 and 7. Here I present some additional limitations.

8.3.1.1 Potential biases in cross-sectional study using exit interviews

Selection bias: in determining the prevalence of TB among patients with at least one TB-related symptom, we only asked patients who were eligible for a sputum test according to the study criteria (cough > 2 weeks or cough of any duration plus any two other TB-related symptoms or self-reported HIV positive status with any TB-related symptom) to submit one spot sputum sample for testing instead of asking all study participants. It is possible we missed out on some participants who were not eligible to submit a sputum but could have tested positive for TB. We restricted sputum testing to only those eligible because the study did not have sufficient funding to test all participants. It is also inevitable that the study would have missed out on subclinical TB patients (persons with active TB who do not report clinical TB-related symptoms

but have other abnormalities that can be detected using existing radiologic or microbiologic assays [9]) who would not have reported a TB-related symptom and therefore would not have been asked to take part in the cross-sectional study.

Non-response bias: among symptomatic patients exiting the hospital who were eligible for the study, about 11% did not consent to take part in the study. If characteristics of these patients were different from those recruited in the study, then that could potentially affect the findings; for instance assuming all those who did not consent to be part of the study had reported their TB-related symptoms to a HCW and had a sputum test requested then the proportion of patients who had a sputum test requested by a HCW would have been higher than reported by the study. Research assistants did their best to encourage all eligible patients to take part in the study but because these were exit interviews and patients had already spent long hours at the hospital, they were in a hurry to leave the hospital. This is evident in the reasons for which consent was declined as 74% of eligible patients who declined said they did not have time for an interview.

The cross-sectional study was only conducted at the municipal hospital due to logistical constraints. It is possible that the proportion of patients eligible for a sputum test who were not asked to submit a sputum would have been much higher if we had included the rural health facilities in this component of the study.

8.3.1.2 Potential biases in prospective observational cohort study

Loss to follow-up bias: some participants recruited were lost to follow up and this could have affected the outcome since we did not know whether they submitted a sputum sample or not, even though for most of them we cross-checked from the

laboratory TB register to find out if they submitted a sputum sample. We did our best to minimize loss to follow-up by collecting two telephone numbers from study participants: their personal number and the number of another person they felt comfortable that we could call to check on them. For participants without telephone numbers, we collected a traceable home address using landmarks so we could visit them in their home for the follow up. We maintained participants' interest in the study by letting them know that the follow up calls or visits were to check on their health condition rather than just soliciting for information. Participants were also given call credit of 0.50 pence (0.25p at recruitment and 0.25p at the last follow up call) of any mobile network of their choice to keep in touch with the study team. This was equally to maintain their interest in the study. The loss to follow-up for this study was 4% which was unlikely to affect the point estimate of the primary outcome.

Response bias: since we kept calling participants regularly and each time asking whether they had submitted a sputum or received a test result, some of them could have responded yes to these questions without actually submitting sputum or receiving a test result. To minimize this, we cross-checked from the presumptive TB register and with the task-shifting officer to find out if a sputum had been submitted or a result collected. In instances where we found otherwise from the register or task-shifting officer, at the next follow up we probed further the initial response given by the participant during the last follow up call or visit.

8.3.1.3 Qualitative study

An additional limitation in the qualitative study was that the study participants did not include a member of staff from the laboratory to give their experiences and perceptions since laboratory testing is an essential step in the TB care cascade. That

notwithstanding, HCWs interviewed were able to talk about barriers relating to laboratory testing for TB. We could not include a member of laboratory staff because during the period of the in-depth interviews, the laboratory staff operating the GeneXpert was not available.

Also, having the national TB control programme manager as the local supervisor of the study, which was indicated on the study information sheet, could have influenced what HCWs said about their experiences and perceptions for fear of being victimized. To minimize any biases, participants were assured of confidentiality of their identity and information they provided. I acknowledge that my prior experience of working in a regional hospital laboratory and coordinating TB laboratory work at a regional level could have influenced my interpretation of the study findings. Because I have worked in a leadership role in TB control, my expectation was that, once guidelines are given to health facilities to follow, then HCWs will follow these guidelines but as study findings were contrary to this, I was tempted to blame HCWs. However, based on what I learnt during the study, I acknowledge that some of the challenges are health-system related where policies are made without making provision for the system to accommodate them. Also, being a middle-aged Christian woman going to conduct research in an area where many people hold traditional beliefs could have influenced how I perceived the study participants and their responses to some questions asked when these were contrary to my belief as a Christian.

We did not do in-depth interviews with presumptive TB or TB patients to find out their experiences and perceptions of barriers to TB diagnosis and treatment. This was due to logistical challenges and time constraint for the study. Therefore, we could not get first-hand information on barriers TB patients encounter in getting a TB diagnosis and

initiating treatment, which is a limitation. However, in the prospective cohort study, we did get comments from patients on their perception of the TB diagnostic pathway. These are not qualitative data but at least gave some insight into their perspectives of the diagnostic pathway.

8.3.2 Strengths

The main strength of this thesis was the use of mixed methods to achieve the study objectives. Findings from the qualitative study were used to validate some of the findings in the quantitative studies. The different studies thus complemented each other to improve the validity of the study findings.

The use of a prospective observational cohort design, as discussed in chapter 6, enabled us to measure the direct losses from the testing cascade and factors accounting for these losses. This was also quite novel since most studies on delayed or missed diagnosis of TB use retrospective cross-sectional designs or secondary data from TB patients already on treatment thus missing out on those who never got a diagnosis or started TB treatment. The prospective cohort design reduced selection bias, improved validity and provided unusual data since this approach is not often used.

As previously discussed (chapter 5), the use of exit interviews in the cross-sectional study reduced recall bias since participants had just sought care and were more likely to remember what had happened in the clinic that day. The use of clinic observations and in-depth interviews in the qualitative study to triangulate findings was the main strength of the qualitative study as previously discussed in chapter 7.

8.4 Reflective commentary

Prior to starting a PhD in 2016, I had been involved with research at different stages of the research process but this thesis gave me the opportunity to be involved at all stages of the research process: developing a protocol, seeking ethical approval, planning and executing data collection, coordinating fieldwork, data management and analysis, writing reports and manuscripts for publication. It has been a learning process where I learnt not only the challenges inherent in the research process but also the fulfilling moments when a major milestone was achieved.

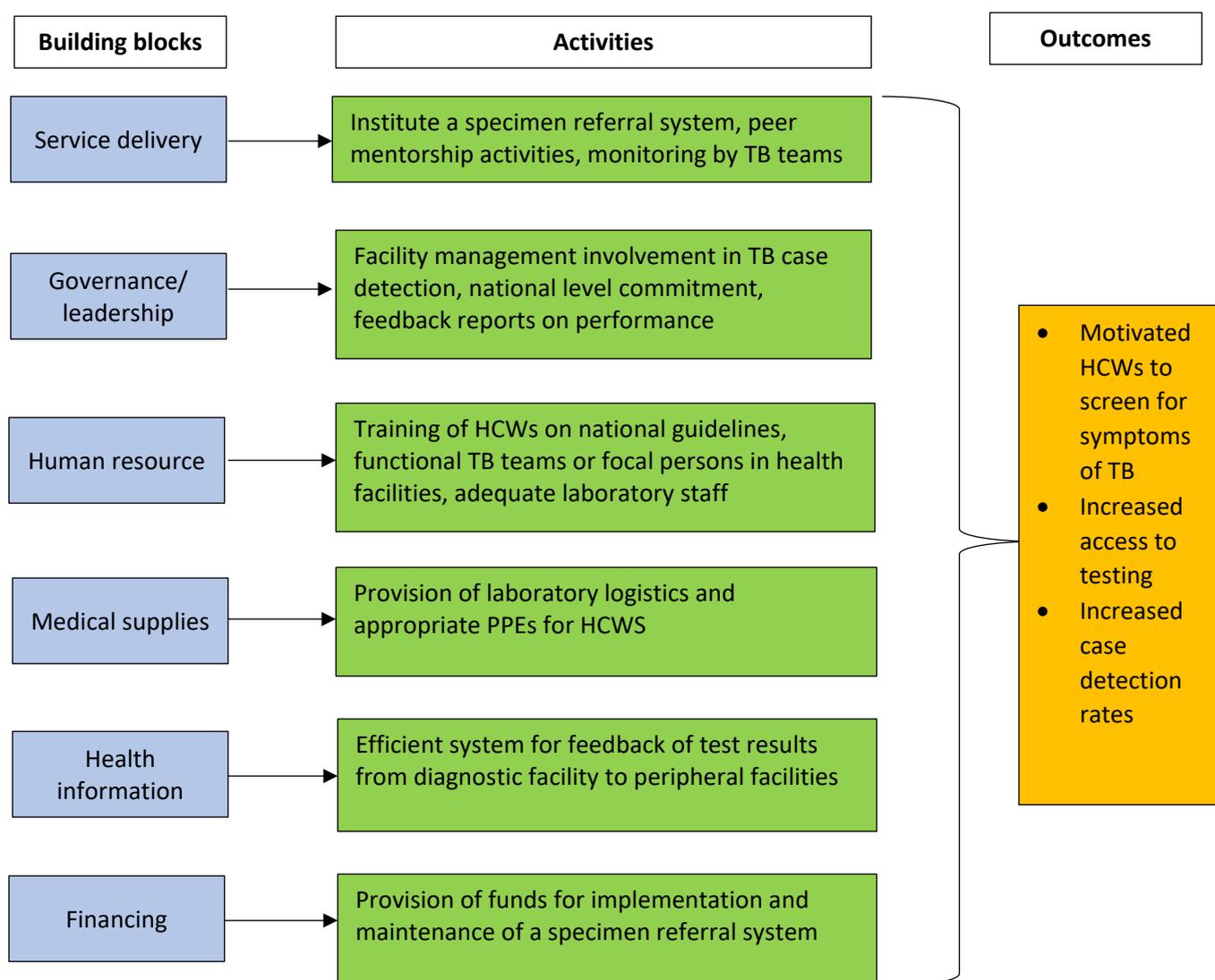
Throughout the process, I worked with different teams notably my supervisory, study and health facility teams, all of whom were very helpful. During fieldwork, I understood the importance of establishing good working relationships with members of the various teams including study participants. This was particularly important for the prospective cohort study because of the follow up element, as this made them more cooperative. Listening to stories told by study participants during interviews and relating to their circumstances was a good way to establish rapport and maintain their interest in the study. The follow up calls and home visits were novel to study participants as most of them said they never had people call them from the hospital to check on their health and they were very grateful. This gave the study team a sense of fulfilment. In Ghana and particularly in the study setting there was no formal address system so tracing participants without telephone numbers to their homes using landmarks during follow up was challenging. On numerous occasions we got lost in villages and there were times we needed to walk long distances because the roads were not accessible in a motor vehicle. But this made me appreciate better the challenges HCWs encounter in tracing TB patients and likewise the challenges faced by some patients in accessing health care services.

Despite all the challenges, the project was executed successfully. The whole process was a learning experience for me, and I learnt something new daily. I believe with the experience gained, module courses I took as well as different transferable skills I gained has made me a better researcher compared to the experience I had before the start of this PhD journey.

8.5 Recommendations

Ghana's national TB control program can seek to bridge the gaps identified in this thesis by employing a systems thinking approach where the gaps can be viewed as part of a wider dynamic system. Systems thinking enables a deeper understanding of the linkages, relationships, interactions and approach to illuminate the full range of effects behaviours among the elements that characterize the entire system [160]. This will enable a better and realistic understanding of what works for whom and under what circumstances [161]. Health systems thinking can be modelled along the building blocks of the WHO's health systems framework [160]. The WHO's health systems framework has six building blocks that contribute to the strengthening of health systems in different ways [162]. Interventions implemented at systems level target one or multiple system building blocks directly or broadly rather than just one specific health problem [160]. A systems thinking approach to bridge the gaps in the TB care cascade within the health system should consider inputs, outputs, initial, intermediate and eventual outcomes that can strengthen the health system [161]. The recommendations from this thesis follow the concept of health systems thinking modelled along the building blocks as shown in figure 8.2 below:

Figure 8. 2: Recommended health systems framework building blocks for implementation of possible interventions to bridge the gaps in the TB care cascade



TB= tuberculosis, HCW= healthcare worker, PPE= personal protective equipment

Figure 8.2 shows the six building blocks, the activities that can be implemented to bridge the gaps and the possible outcomes. Recommendations for each gap are stated below:

8.5.1 Recommendations for health system improvement

8.5.1.1 Gap 1: Suboptimal TB symptom screening and sputum requesting practices of HCWs

- i. **Service delivery:** effective monitoring of TB case finding activities in health facilities should be carried out regularly by TB teams to ensure screening for symptoms of TB and requesting for sputum becomes a permanent, routine, and

consistent activity carried out in all departments of the facility. Peer mentorship programs can be instituted in health facilities to motivate HCWs to screen for symptoms of TB and request for sputum test where necessary. The concept of task shifting should be fully integrated in the triaging process at the OPD of health facilities being mindful of existing professional identities.

- ii. **Governance/leadership:** health facility managers should be involved in TB case finding activities so they can provide the necessary logistics and high-level leadership that will ensure HCWs adhere to the standard guidelines for TB case detection. Teams from the national, regional and district levels should pay regular visits to health facilities to encourage HCWs to screen for symptoms of TB.
- iii. **Human resource:** all HCWs in all units of health facilities should be adequately trained on the standard guidelines for TB case finding. Functional TB teams should be formed, or TB focal persons appointed in health facilities and they should develop a plan outlining activities that should be carried out, sensitize HCWs on the plan, screening tool and sputum request form, and encourage them to comply and use the tools. The team should meet on a regular basis to review progress of implementation of the plan.
- iv. **Medical supplies:** health facility managements should provide N95 respirators for HCWs to alleviate their fears of infection and encourage screening for symptoms of TB.

The different programme quality and efficiency models employed by Tanzania and Kenya to improve TB case detection discussed in section 8.2.1 could be adapted and modified by Ghana depending on the local needs to improve TB case finding in health facilities.

8.5.1.2 Gap 2: Non-submission of sputum for a TB test by patients

- i. **Service delivery:** Ghana's NTP should possibly institute a specimen referral system so that presumptive TB patients identified in rural health facilities will not have to travel to the municipal hospital to submit a sputum for a TB test. Several success stories of implementing specimen referral systems have been shared by LMICs as discussed in section 8.2.2. Ghana could adapt one of the innovations that is feasible and suits the local needs.
- ii. **Governance/leadership:** high level support from the NTP by periodic evaluation of the system will enable them to identify challenges early which can be addressed to ensure the system is effective.
- iii. **Human resource:** more laboratory staff should be employed to handle the increase in sputum submission for testing to ensure timely release of test results.
- iv. **Medical supplies:** with an expected increase in sputum submission, the NTP should ensure adequate supply of sputum containers and GeneXpert cartridges to prevent stock outs and ensure the specimen referral system remains functional.
- v. **Health information:** an implementation of an efficient system for feedback of test results to the rural health facilities will be essential. Once HCWs get feedback from specimen they refer for testing, they will probably be motivated to screen for symptoms of TB and request for sputum test. Presumptive TB patients might also be encouraged to submit sputum for testing once they know they will receive a test result timely.
- vi. **Financing:** Ghana's ministry of health and the NTP should commit funding to the implementation of a specimen referral system to reduce losses in the diagnostic cascade.

The possible outcomes from these recommendations could be adequately trained HCWs who are motivated to screen for symptoms of TB and request for sputum test when a patient is eligible, increased access to testing for presumptive patients who seek care from rural health facilities, and all these could lead to increased case detection rates (figure 8.2).

8.5.2 Recommendations for future research

Since we could not conduct in-depth interviews with patients to explore their experiences and perceptions on barriers to TB case finding in health facilities, this could be an area for further research. Findings from this research could be used to inform patient-centred interventions for improved case finding.

In this PhD study, we found that newly diagnosed TB patients being initiated on treatment needed to have a treatment supporter before treatment can be initiated. Since this area was not the main focus of our study, we could not explore more the usefulness of treatment supporters. Further research is needed to answer the research question: does having a treatment supporter improve treatment outcomes? It will also be worth exploring whether chest clinics rigidly enforce the requirements for a treatment supporter. If they do, does this mean that some people do not start treatment? Findings will justify or refute the insistence of chest clinic staff on TB patients having a treatment supporter before treatment is initiated.

8.6 General conclusion

This thesis highlights the gaps in the pre-diagnostic steps of the TB care cascade in health facilities in Ghana. HCWs' suboptimal adherence to the national SOP for TB case detection is one of the causes of gaps in the pre-diagnostic cascade. Also, the majority of presumptive TB patients attending rural health facilities not submitting sputum for testing due to lack of a specimen transport system to facilitate sputum testing is another cause of the gaps. The factors contributing to these gaps are multifaceted and require commitments from the NTP, health facility managers, HCWs and presumptive TB patients to address. High-level leadership endorsement of TB symptom screening in health facilities will motivate HCWs to adhere to the SOP for TB case detection and a system to facilitate referral of specimen from rural health facilities to the diagnostic laboratory may bridge the gaps and possibly improve TB case detection.

Chapter 9: References

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Chapter 10: Appendices

Appendix 10.1 Ethics approvals

Appendix 10.1.1 Ghana Health Services Ethics Review Committee

GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

In case of reply the number and date of this letter should be quoted.


Your Health - Our Concern

Research & Development Division
Ghana Health Service
P. O. Box MB 190
Accra
Tel: +233-302-681109
Fax + 233-302-685424
Email: ghserc@gmail.com
2nd January, 2018

My Ref. GHS RDD/ERC/Admin/App/256
Your Ref. No.

Joyce Der
London School of Hygiene and Tropical Medicine
UK

The Ghana Health Service Ethics Review Committee has reviewed and given approval for the implementation of your Study Protocol.

GHS-ERC Number	GHS-ERC: 003/09/17
Project Title	Pathways to Tuberculosis Diagnosis and Treatment in Ghana: Identifying the Gaps and Seeking Solutions
Approval Date	18 th December, 2017
Expiry Date	17 th December, 2018
GHS-ERC Decision	Approved

This approval requires the following from the Principal Investigator

- Submission of yearly progress report of the study to the Ethics Review Committee (ERC)
- Renewal of ethical approval if the study lasts for more than 12 months,
- Reporting of all serious adverse events related to this study to the ERC within three days verbally and seven days in writing.
- Submission of a final report **after completion** of the study
- Informing ERC if study cannot be implemented or is discontinued and reasons why
- Informing the ERC and your sponsor (where applicable) before any publication of the research findings.

Please note that any modification of the study without ERC approval of the amendment is invalid.

The ERC may observe or cause to be observed procedures and records of the study during and after implementation.

Kindly quote the protocol identification number in all future correspondence in relation to this approved protocol

SIGNED.....
DR. CYNTHIA BANNERMAN
(GHS-ERC CHAIRPERSON)

Cc: The Director, Research & Development Division, Ghana Health Service, Accra

Appendix 10.1.2 London School of Hygiene & Tropical Medicine Ethics Committee

London School of Hygiene & Tropical Medicine

Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



Observational / Interventions Research Ethics Committee

Ms Joyce Der
LSHTM

4 January 2018

Dear Joyce,

Study Title: Pathways to tuberculosis diagnosis and treatment in Ghana: identifying the gaps and seeking solutions

LSHTM Ethics Ref: 14504

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Investigator CV	FrankBonsuCV_010113	01/01/2013	1.0
Investigator CV	VirginiaBondShortCV_170613	17/06/2013	1.0
Investigator CV	GrantsshortCV_apr17	01/04/2017	1.0
Investigator CV	Daniel Grint CV	14/08/2017	1.0
Investigator CV	JoyceDerCV_25817	25/08/2017	1.0
Protocol / Proposal	CRF_prospective cohort study_v1.0_14sep2017	14/09/2017	1.0
Protocol / Proposal	CRF_cross sectional study_v1.0_14sep2017	14/09/2017	1.0
Protocol / Proposal	CRF_qualitative study_v1.0_14sep2017	14/09/2017	1.0
Protocol / Proposal	TB_CF_HCF_Protocol_v2.0_29sept2017	29/09/2017	2.0
Covering Letter	LSHethics14504_cover letter_v1.0_5.12.17	05/12/2017	1.0
Protocol / Proposal	TB_CF_HCF_Protocol_v3.0_5dec2017	05/12/2017	3.0
Information Sheet	PIS_cross sectional study_v2.0_5dec2017	05/12/2017	2.0
Information Sheet	PIS_HCW interview_v2.0_5dec2017	05/12/2017	2.0
Information Sheet	PIS_prospective cohort study_v3.0_5dec2017	05/12/2017	3.0

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: <http://leo.lshtm.ac.uk>

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,



Professor John DH Porter
Chair

ethics@lshtm.ac.uk
<http://www.lshtm.ac.uk/ethics/>

Improving health worldwide

Appendix 10.1.3 Ghana Health Service Ethics Review Committee

GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

In case of reply the number and date of this Letter should be quoted

*MyRef:ghs/rd/erd/Admin/App/18/033
Your Ref. No.*



Research & Development Division
Ghana Health Service
P. O. Box MB 190
Accra
Tel: +233-0302-681109
Fax + 233-0302-685424
Email: ghserc@gmail.com
24th May, 2018

Joyce Der
London School of Hygiene and Tropical Medicine
Keppel St, Bloomsbury,
London, UK WC1E 7HT

RE: REQUEST FOR PROTOCOL AMENDMENT

Reference is made to your letter dated 7th May, 2018 requesting permission to amend your study protocol.

The Ghana Health Service Ethics Review Committee has reviewed and given approval for the implementation of the amended protocol.

GHS-ERC Number	GHS-ERC: 003/09/17
Project Title	Pathways to tuberculosis diagnosis and treatment in Ghana: identifying the gaps and seeking solutions - Version 4.0, 7 May 2018
Approval Date of Amendment	22 nd May, 2018
GHS-ERC Decision	Amendment Approved

The approval covers the following only:

- Study sites: Inclusion of additional rural facilities that refers patients to other facilities for TB investigation namely: Agbozume, Adina, Avegato and Akame Health Centers to ensure that the TB testing pathway is adequately investigated within the Municipality.
- Methods of recruitment for component A: Inclusion of patients who have been referred to another facility for TB investigation in addition to patients with a request for sputum

The following applies:

- Submission of yearly progress report of the study to the Ethics Review Committee (ERC)
- Renewal of ethical approval if the study lasts for more than 12 months,
- Reporting of all serious adverse events related to this study to the ERC within three days verbally and seven days in writing.
- Submission of a final report **after completion** of the study
- Informing ERC if study is discontinued and reasons why
- Informing the ERC and your sponsor (where applicable) before any publication of the research findings.

Please note that any modification of the study without ERC approval of the amendment is invalid.

The ERC may observe or cause to be observed procedures and records of the study during and after implementation.

Kindly quote the protocol identification number in all future correspondence in relation to this approved protocol.

SIGNED.....
DR. CYNTHIA BANNERMAN
(GHS-ERC CHAIRPERSON)

Cc: The Director, Research & Development Division, Ghana Health Service, Accra

Appendix 10.1.4 London School of Hygiene & Tropical Medicine Ethics Committee

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United Kingdom
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LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



Research Ethics Committee

Ms Joyce Der
LSHTM

14 May 2018

Dear Joyce,

Study Title: Pathways to tuberculosis diagnosis and treatment in Ghana: identifying the gaps and seeking solutions

LSHTM MSc Ethics ref: 14504 - 1

Thank you for submitting your amendment for the above research project.

Your amendment has been assessed by the Research Governance & Integrity Office and has been approved as a non-substantial change. The amendment does not require further ethical approval from the observational ethics committee.

List of documents reviewed:

Document Type	File Name	Date	Version
Other	TB_CF_HCF_Protocol_v4.0_13may2018.	13/05/2018	4.0

Any subsequent changes to the application must be submitted to the Committee via an Amendment form on the ethics online applications website:

<http://leo.lshtm.ac.uk> . Best of luck with your project.

Yours sincerely,



Rebecca Carter

Research Governance Coordinator

Ethics@lshtm.ac.uk
<http://www.lshtm.ac.uk/ethics/>

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Appendix 10.2 Permission Letters

Appendix 10.2.1 Volta Regional Health Directorate

In case of reply the number
and the date of this
letter should be quoted

MyRef No.VRHD/ORD/46

Your Ref. No.....

- OUR GHS CORE VALUES**
- PEOPLE-CENTRED SERVICES
 - PROFESSIONALISM
 - TEAM WORK
 - INNOVATION/EXCELLENCE
 - DISCIPLINE
 - INTEGRITY



Volta Regional Health Directorate
GHANA HEALTH SERVICE
P. O. BOX 72
HO. V/R.
Tel: (036) 2028210
Fax : (036) 2028244

volta-health@4u.com.gh

16th January, 2018

MS. JOYCE DER
SCHOOL OF PUBLIC HEALTH, UHAS
HOHOE

**RE: PERMISSION TO USE HEALTH FACILITIES IN YOUR REGION FOR DATA
COLLECTION**

This serves to acknowledge receipt of your letter dated 11th January, 2018 on the above subject matter.

I wish to inform you that permission has been granted to your request to conduct a study at Klikor Health Centre and Municipal Hospital both in the Ketu South Municipality.

Thank you.

[REDACTED]
[MR. EDWARD KABA]
DEPUTY DIRECTOR [ADMINISTRATION]
FOR: REG. DIRECTOR OF HEALTH SERVICES
VOLTA REGION

In case of reply the number
and the date of this
letter should be quoted

MyRef No. VRHD/ORD/46

Your Ref. No.....

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- PEOPLE-CENTRED SERVICES
- PROFESSIONALISM
- TEAM WORK
- INNOVATION/EXCELLENCE
- DISCIPLINE
- INTEGRITY



Volta Regional Health Directorate
GHANA HEALTH SERVICE
P. O. BOX 72
HO. V/R.
Tel: (036) 2028210
Fax : (036) 2028244

volta-health@4u.com.gh

16th January, 2018

**THE MUNICIPAL DIRECTOR OF HEALTH SERVICES
KETU SOUTH MUNICIPAL HEALTH DIRECTORATE
AFLAO**

INTRODUCTORY LETTER

MS JOYCE DER – PhD Student

**FROM LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE
LECTURER, UHAS (SCH OF PUBLIC HEALTH)**

This is to introduce to you the above-named student from the London School of Hygiene & Tropical Medicine and a Lecturer at the school of Public Health, UHAS who wants to conduct a research on the topic 'Pathways to tuberculosis diagnosis and treatment in Ghana: identifying the gaps and seeking solutions'.

She intends to conduct the study in both the Municipal Hospital and Klikor Health Centre.

It would be appreciated, if you could offer her the necessary support in this regard.

Thank you.

[REDACTED]
**[MR. EDWARD KABA]
DEPUTY DIRECTOR [ADMINISTRATION]
FOR: REG. DIRECTOR OF HEALTH SERVICES
VOLTA REGION**

Appendix 10.2.2

Ketu South Municipal Health Directorate

In case of the reply the number and the date of this letter should be quoted.

My Ref. No. KSDG/GHS/GEN/1/17

Your Ref.



Ketu South Municipal Health Directorate
Ghana Health Service
P. O. BOX 126
Aflao, Volta Region
Ghana, West Africa

Mobile Phone: 0244 975062

May 14, 2018

Our GHS Core Values

- People Centered Services
- Professionalism
- Team work
- Innovation/Excellence
- Discipline
- Integrity

**MS JOYCE DER
LONDON SCHOOL OF OF HYGIENE AND TROPICAL MEDICINE
UK**

**PERMISSION TO COLLECT DATA FROM ANY PUBLIC HEALTH FACILITIES -
KETU SOUTH**

This letter serves to permit you to collect data from any public health facilities within the Ketu South municipality.

This letter also wishes to inform you that, all the facilities have been duly informed about your presence in the municipality to collect data for your research.

Many thanks for your support as we look forward to another successful endeavor together.

Best regards,



DEGLE, JOSEPH KWAMI
MUNICIPAL DIRECTOR OF HEALTH SERVICES - KETU SOUTH

MUNICIPAL DIRECTOR
KETU SOUTH MUN HEALTH DIRECTORATE
GHANA HEALTH SERVICE
P. O. BOX 126, AFLAO

Appendix 10.3 Oxford University Press License

Appendix 10.3.1 Permission to include research paper 1 in thesis

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Institution name	London School of Hygiene & Tropical Medicine
Expected presentation date	Sep 2020
Requestor Location	Ms. Joyce Der 52 Claypole Drive Hounslow, Hounslow TW5 0AN United Kingdom Attn: London School of Hygiene and Tropical Medicine
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Mon 11/16/2020 1:26 PM

To: Joyce Der <joyce.der@lshtm.ac.uk>

Cc: permissions@who.int <permissions@who.int>

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Appendix 10.5 Permission from Ghana National TB Control Program to use prevalence survey reproduce TB care cascade

Re: Permission to reproduce data in thesis

Yaw Adusi-Poku <adusipokuyaw@gmail.com>

Wed 12/23/2020 9:33 AM

To: Joyce Der <joyce.der@lshtm.ac.uk>

Cc: Zeleke Alebachew <zalebachew@gmail.com>; Rita Patricia Frimpong-Mansoh <ritapatriciafrimpongmansoh@gmail.com>; Kwami Afutu <kwami.afutu@ghsmail.org>; Bernard Wadie <nanawadie01@gmail.com>

*** This message originated outside LSHTM ***

Dear Joyce Permission granted! Best wishes
Yaw

From: Yaw Adusi-Poku <adusipokuyaw@gmail.com>

Sent: Monday, November 16, 2020 7:25 PM

To: Joyce Der <joyce.der@lshtm.ac.uk>

Cc: Frank Bonsu <fabonsu@gmail.com>; Kwami Afutu <kwami.afutu@ghsmail.org>; Zeleke Alebachew <zalebachew@gmail.com>; Rita Patricia Frimpong-Mansoh <ritapatriciafrimpongmansoh@gmail.com>; Bernard Wadie <nanawadie01@gmail.com>

Subject: Re: Permission to reproduce data in thesis

*** This message originated outside LSHTM ***

Dear Joyce,
Glad to know that you started working with Dr Bonsu. I've put the rest of the team members in copy.
We will discuss and revert soonest. Kind regards
Yaw

Get [Outlook for Android](#)

From: Joyce Der <joyce.der@lshtm.ac.uk>

Sent: Monday, November 16, 2020 5:33:55 PM

To: adusipokuyaw@gmail.com <adusipokuyaw@gmail.com>

Cc: Frank Bonsu <fabonsu@gmail.com>

Subject: Permission to reproduce data in thesis

Dear Dr. Yaw Adusi-Poku,

My name is Joyce Der, a lecturer at the University of Health and Allied Sciences, Ho but currently a PhD student at the London School of Hygiene and Tropical Medicine, UK. My PhD study is on the pathways to TB diagnosis and treatment in Ghana: identifying the gaps and seeking solutions.

As part of the study, I followed patients who had routinely been given a sputum test request by a health worker in Ketu South Municipality to find out whether they submitted sputum for testing and determine factors associated with non-submission of sputum. I also used exit interviews of patients attending the municipal hospital to find out the TB symptom screening and sputum test requesting practices of health workers. This study was done based on findings of the 2013 national TB prevalence survey where they found among patients with prolonged cough who visited a government health facility and required a sputum test, only about 25% submitted a sputum. I therefore wanted to find out whether it is patients who do not submit sputum or health workers who do not screen for symptoms of TB and request a sputum test if patients are eligible for the test. My local supervisor for the field work was Dr Frank Bonsu (cc in this email).

I generated a cascade of prevalence survey participants who did a sputum test using the findings from the prevalence survey which I intend to include in my thesis as justification for the study.

However, I need permission from the TB Control Program to use the prevalence survey findings for this cascade. I will be grateful if you can grant me permission to use the data in the cascade for inclusion in my thesis. Kindly find attached the cascade I generated.

Thank you

Kind regards

Joyce Der

Appendix 10.6 Information sheets and informed consent forms

Participant Information Sheet: component B (cross-sectional study)

Project Title: Pathways to tuberculosis diagnosis and treatment in Ghana: identifying the gaps and seeking solutions

Investigators:

London School of Hygiene and Tropical Medicine, UK: Joyce Der, Prof Alison Grant, Dr Virginia Bond, Dr Daniel Grint

National TB Control Program, Ghana: Dr Frank Bonsu

[Greetings], my name is [_____]. I am a researcher or part of a research team based at the London School of Hygiene and Tropical Medicine, UK. We would like to invite you to take part in this study. This information sheet explains the study. You are free to decide if you want to take part or not. If you decide to take part, I will ask you to sign on a consent form or give a thumbprint. Signing or thumbprinting the form means that you agree to take part in the study. It also means that you are aware of your right not to take part, or to stop taking part at any time. If you decide not to take part, this will not affect your right to health care at this health facility.

Why are we doing this study? Tuberculosis (TB) remains one of the top 10 causes of death worldwide. A survey in 2013 showed that TB remains an important health problem in Ghana, and that people with TB may experience delays before they are given correct treatment. If we can identify where and why people are delayed, then we can make recommendations for improvement so that people with TB can be identified early and put on treatment.

If you take part in this study, what will happen? If you agree to take part in this study, we will ask you some questions about TB symptoms, the reason you visited the hospital and whether you were asked to do a sputum TB test. If you report a cough of 2 weeks or more, we will ask you to produce a sample of sputum (spit from the chest) which will be sent to the laboratory for testing to find out if you have TB. The study will pay for the cost of the test. If you permit, we will review your hospital folder to see what the doctors have written concerning your sickness. The questions will take 10-15minutes. It will not cost you any money to take part in this study and there is no payment to people who take part.

What are the risks and benefits of taking part in this study? There are no risks to your health if you take part in this study. The potential benefit is that, if you need to have a sputum test done, we will do the test for you and if the result is positive, we will contact you to tell you and refer you to the TB clinic at the municipal hospital for further assessment and appropriate treatment. TB is a treatable and curable condition and treatment is provided free of charge at the municipal hospital. Apart from that, this study will not benefit you directly, but your answers will help us come up with solutions so that people with TB can be treated faster.

What happens if I do not agree to take part in this study? You do not have to take part in this study. If you do not take part, this will not affect the medical care that you receive at this health facility. You can decide to stop taking part in the study at any time, without giving a reason.

How will the information collected during this study be kept confidential? We will do everything we can to keep your personal information private and confidential. This will be done by separating your personal details from your sensitive data. If you are able to give us a sputum sample for testing, we will contact you to let you know the result, either by phone or in a way that we will agree with you. If the result is positive for TB we will help you link to the TB clinic for further assessment and appropriate treatment, so that the TB can be properly treated. If the result shows TB in your sputum and we are unable to contact you after trying several times, we will give the result to the TB clinic and they will try to contact you, so you can start treatment. Also, at the end of the study we would like to make information from this study available for other researchers to use but only after that information has been completely separated from any details which identify the people who took part. This will be done by assigning a unique study number to your data and not using your personal details.

What if I have more questions I wish to ask about this study? If you have any questions about this study, please ask us now. If you have questions later you can ask study staff, or telephone:

Person	Designation	Telephone Number
Joyce Der	Principal Investigator	0244667985
Dr Frank Bonsu	Local Supervisor	0244318134
Madam Hannah Frimpong	Administrator-GHS-ERC	0507041223

Consent form: component B (cross-sectional study)

Project Title: Pathways to tuberculosis diagnosis and treatment in Ghana: identifying the gaps and seeking solutions

London School of Hygiene and Tropical Medicine, UK: Joyce Der, Prof Alison Grant, Dr Virginia Bond, Dr Daniel Grint

National TB Control Program, Ghana: Dr Frank Bonsu

Participant ID: _____/_____/_____

I have read the information sheet about this study (or the information sheet about this study has been read to me) and I understand what will be required of me and what will happen if I take part in the study. My questions concerning this study have been answered.

I understand that I may withdraw from this study at any time without giving a reason and without affecting the services I receive from this health facility.

I willingly agree to take part in the study.

Study participant's name Signature/thumbprint
Date (Literate/illiterate)

If the participant cannot read or write, enter the name of the person who witnessed the consent here and their signature:

I was present when the information sheet for this study was read and explained to the participant in the language he/she understands. His/her questions concerning the study were answered and he/she willingly agreed to take part in the study.

Witness name Signature/thumbprint Date

The participant has read the information sheet about the study (or I read the information sheet to the participant) and answered all questions concerning the study. The participant willingly agreed to take part in the study.

Interviewer's name Signature Date

Participant Information Sheet: component A (prospective cohort study)

Project Title: Pathways to tuberculosis diagnosis and treatment in Ghana: identifying the gaps and seeking solutions

Investigators:

London School of Hygiene and Tropical Medicine, UK: Joyce Der, Prof Alison Grant, Dr Virginia Bond, Dr Daniel Grint

National TB Control Program, Ghana: Dr Frank Bonsu

[Greetings], my name is [_____]. I am a researcher or part of a research team based at the London School of Hygiene and Tropical Medicine, UK. We would like to invite you to take part in this study. This information sheet explains the study. You are free to decide if you want to take part or not. If you decide to take part, I will ask you to sign on a consent form, or give a thumbprint. Signing or thumbprinting the form means that you agree to take part in the study. It also means that you are aware of your right not to take part, or to stop taking part at any time. If you decide not to take part, this will not affect your right to health care at this health facility.

Why are we doing this study? Tuberculosis (TB) remains one of the top 10 causes of death worldwide. A survey in 2013 showed that TB remains an important health problem in Ghana, and that people with TB may experience delays before they are given correct treatment. If we can identify where and why people are delayed, then we can make recommendations for improvement so that people with TB can be identified early and put on treatment.

If you take part in this study, what will happen? If you agree to take part in this study, we will ask you some questions about your illness and the places you sought care before coming to this health facility which will take between 20-30minutes. One of the research team will call you every two weeks for the next two months to verify your contact information and find out how you are doing. If you do not have a phone to be called on then a member of the research team will visit your home after one month and two months of recruitment into the study to find out how you are doing. If you permit, we will review your hospital folder to see what the doctors have written concerning your sickness. We will also use a device to locate where your community/village is and the health facilities you have visited because of your current illness before coming to this health facility.

It will not cost you any money to take part in this study and there is no payment to people who take part.

What are the risks and benefits of taking part in this study? There are no risks to your health if you take part in this study. The potential benefit is that, at the end of the two months, if you are still not feeling well and have not received any medication, we will help you get care at the hospital. Apart from that, this study will not benefit you directly but your answers will help us come up with solutions so that people with TB can be identified faster.

You will be given mobile phone airtime of GHc 2.00 of any network of your choice one month after you have been part of the study and airtime costing GHc 2.00 at the end of the study. This is to enable you to maintain contact with the research team.

What happens if I do not agree to take part in this study? You do not have to take part in this study. If you do not take part, this will not affect the medical care that you receive at this health facility. You can decide to stop taking part in the study at any time, without giving a reason.

How will the information collected during this study be kept confidential? We will do everything we can to keep your personal information private and confidential. This will be done by separating your personal details from your sensitive data. We will ensure that all information is held securely and accessible only to study staff, and all personal details will be removed before data are analysed. Also, at the end of the study we would like to make information from this study available for other researchers to use but only after that information has been completely separated from any details which identify the people who took part. This will be done by assigning a unique study number to your data and not using your personal details.

What if I have more questions I wish to ask about this study? If you have any questions about this study, please ask us now. If you have questions later you can ask study staff, or telephone

Person	Designation	Telephone Number
Joyce Der	Principal Investigator	0244667985
Dr Frank Bonsu	Local Supervisor	0244318134
Madam Hannah Frimpong	Administrator-GHS-ERC	0507041223

Consent form: component A (prospective cohort study)

Project Title: Pathways to tuberculosis diagnosis and treatment in Ghana: identifying the gaps and seeking solutions

London School of Hygiene and Tropical Medicine, UK: Joyce Der, Prof Alison Grant, Dr Virginia Bond, Dr Daniel Grint

National TB Control Program, Ghana: Dr Frank Bonsu

Participant ID: _____/_____/_____

I have read the information sheet about this study (or the information sheet about this study has been read to me) and I understand what will be required of me and what will happen if I take part in the study. My questions concerning this study have been answered.

I understand that I may withdraw from this study at any time without giving a reason and without affecting the services I receive from this health facility.

I willingly agree to take part in the study.

_____	_____	_____
Study participant's name (Literate/illiterate)	Signature/thumbprint	Date

If the participant cannot read or write, enter the name of the person who witnessed the consent here and their signature:

I was present when the information sheet for this study was read and explained to the participant in the language he/she understands. His/her questions concerning the study were answered and he/she willingly agreed to take part in the study.

_____	_____	_____
Witness name	Signature/thumbprint	Date

The participant has read the information sheet about the study (or I read the information sheet to the participant) and answered all questions concerning the study. The participant willingly agreed to take part in the study.

_____	_____	_____
Interviewer's name	Signature	Date

Participant Information Sheet: component C (HCW in-depth interviews)

Project Title: Pathways to tuberculosis diagnosis and treatment in Ghana: identifying the gaps and seeking solutions

Investigators:

London School of Hygiene and Tropical Medicine, UK: Joyce Der, Prof Alison Grant, Dr Virginia Bond, Dr Daniel Grint

National TB Control Program, Ghana: Dr Frank Bonsu

[Greetings], my name is [_____]. I am a researcher or part of a research team based at the London School of Hygiene and Tropical Medicine, UK. We would like to invite you to take part in this study. This information sheet explains the study. You are free to decide if you want to take part or not. If you decide to take part, I will ask you to sign on a consent form, or give a thumbprint. Signing or thumbprinting the form means that you agree to take part in the study. It also means that you are aware of your right not to take part, or to stop taking part at any time. If you decide not to take part, this will not affect your right to health care at this health facility.

Why are we doing this study? Tuberculosis (TB) remains one of the top 10 causes of death worldwide. A survey in 2013 showed that TB remains an important health problem in Ghana, and that people with TB may experience delays before they are given correct treatment. We are interested in your experiences in TB diagnosis among patients with symptoms of TB and the challenges you encounter in this regard. Please note that we are NOT doing this study to blame or find fault with any individual health facility or healthcare worker. Health facilities will not be able to trace the source of information. Reports will not identify healthcare workers.

If you take part in this study, what will happen? If you agree to take part in this study, we will ask you some questions about your awareness of the national guidelines for TB diagnosis and your experiences in diagnosing persons with symptoms of TB. We will ask you questions about the challenges you encounter in diagnosing persons with TB and what you think can be done to improve the situation. We would be very grateful if you would allow us to record the interview on tape so that we don't miss any of the things you say. We will also make notes on your answers during the interview. These questions will take about 45-60 minutes in total.

What will we do with what you say? Sometimes in interviews, people say things that are very useful in understanding the situation being studied. Therefore, if you give permission, we may quote things you say in future reports and we will not include any details that will identify you.

What are the risks and benefits of taking part in this study? There are no risks to your job or direct benefits to participating in this study. This study will help us identify the gaps in the diagnostic pathway and the challenges you encounter in diagnosing TB.

What happens if I do not agree to take part in this study? You do not have to take part in this study. You can decide to stop taking part in the study at any time, without giving a reason.

How will the information collected during this study be kept confidential? The information you will give will be strictly secured. We would like to make the information available for other researchers to use but only after that information has been completely separated from any details which identify you. If you permit us to record the interview, the tapes will be stored with only study numbers. After the study, the tapes will be stored for 10years.

What if I have more questions I wish to ask about this study? If you have any questions about this study, please ask us now. If you have questions later you can ask study staff, or telephone

Person	Designation	Telephone Number
Joyce Der	Principal Investigator	0244667985
Dr Frank Bonsu	Local Supervisor	0244318134
Madam Hannah Frimpong	Administrator-GHS-ERC	0507041223

Consent form: component C (qualitative study)

Project Title: Pathways to tuberculosis diagnosis and treatment in Ghana: identifying the gaps and seeking solutions

London School of Hygiene and Tropical Medicine, UK: Joyce Der, Prof Alison Grant, Dr Virginia Bond, Dr Daniel Grint

National TB Control Program, Ghana: Dr Frank Bonsu

Participant ID: ____/____/____

I have read the information sheet about this study (or the information sheet about this study has been read to me) and I understand what will be required of me and what will happen if I take part in the study. My questions concerning this study have been answered.

I understand that I may withdraw from this study at any time without giving a reason and without affecting the services I receive from this health facility.

I agree that things that I say might be quoted in future reports: Yes No _____
Participant's initials

I willingly agree to take part in the study.

Study participant's name Signature Date

The participant has read the information sheet about the study (or I read the information sheet to the participant) and answered all questions concerning the study. The participant willingly agreed to take part in the study.

Interviewer's name Signature Date

Appendix 10.7 Clinic observations checklist



Project Title: Pathways to tuberculosis diagnosis and treatment in Ghana: identifying the gaps and seeking solutions

Observation checklist Health facility observations checklist

Date completed ___/___/___

Time completed ___/___/___

Person completing the form: _____

During the day's health facility observation, complete the checklist below:

No	Key areas	Yes	No	Comment
1	Did you notice any TB related posters in the waiting area?			
2	Did HCWs provide any health talks at the waiting area?			
3	Was TB mentioned in the health talks?			
4	Were clients waiting for a long period before being attended to?			
5	Were HCWs asking clients about cough and related symptoms?			
6.	Were clients who were visibly coughing or reporting a cough separated from other clients at the waiting area?			
7.	Did any client report a cough to a HCW?			
8.	When a client reported a cough, did HCW use a TB symptom questionnaire to screen the client?			
9.	If 'No', did HCW ask about other symptoms of TB (fever, night sweats or weight loss)?			
10.	Did HCW record the reported cough in a cough register?			
11.	Did the HCW request for sputum test for patients who reported cough?			

12.	Did the health care worker provide any education on cough etiquettes and how to produce sputum for testing?			
13.	Was a client who has been asked to do a sputum test escorted to the laboratory by HCW?			
14.	Were clients with a request for sputum test asked to go to the laboratory by themselves?			
15.	Did you see any client submitting a sputum to the laboratory?			
16.	Did you see any client who had come for a follow up visit with a sputum test result?			
17.	If a test result was positive, was the client directed or escorted to the TB clinic for treatment?			
18.	Was there any significant event happening at the health facility today?			

19. During the period of your observation today, how many people reported a cough? _____

20. How many people were asked about a cough? _____

21. Of those who reported a cough, how many were asked to do a sputum test? _____

22. what is your general impression of the HCW-client interaction? (attitude of HCW or client, communication style)

23. What is the average contact time between a HCW and a client reporting a cough? _____

Appendix 10.8 Healthcare worker in-depth interview guide

Pathways to tuberculosis diagnosis and treatment in Ghana: identifying the gaps and seeking solutions

Health care worker qualitative semi-structured interview guide

General Information

Interviewer Code: _____

Note-taker Code: _____

Date: ____/____/____

Start time: _____

Name of Interviewer: _____

Health facility: _____

Description of place of interview:

A. Participant Identifiers

1. What is your full name? _____
Surname First Name
2. What is your date of birth? ____/____/____
DD MM YYYY
3. What is your age in years?
4. Preferred telephone number: _____
5. Alternative telephone number: _____

B. Demographic Characteristics

1. Sex: Male
Female
2. Profession: _____
3. Health Facility Unit: _____

C. Training in TB Control

1. How long have you been working at this health facility? _____
2. What role(s) do you play at this health facility? _____
3. What type of TB services are provided in your unit? (*probe for: education, diagnosis, laboratory, treatment, referral*) _____
4. How long have you been involved with TB control at this health facility? _____

5. Have you had any training on TB diagnosis and treatment? If yes, how many times have you been trained? _____
6. How long ago was your last training on TB? _____

D. Practices in TB diagnosis and treatment

7. Do you have a cough register and how often are entries made in it?
(look at a cough register with the HCW and discuss the gaps in the register (variables entered, last entry date etc))
8. What do you do with the data entered in the cough register? _____
9. If a patient reports a cough, what do you do? *(Probe: if HCW does not mention the use of a symptom screening questionnaire, then you ask about its use).*
10. How do you identify patients needing a TB test? *(Probe: for use of TB symptom screening questionnaire)*
11. If a patient is identified as requiring a sputum test, what do you do? *(Probe: education on sputum, lab request form, provide sputum container, refer to the TB lab)*
12. What do you do when a patient who has been asked to do a sputum test return with
 - a. a positive test results? *(Probe: counselling, TB treatment)*
 - b. a negative test results? *(Probe: counselling, normal treatment)*
13. Do you provide health education in your unit and does it include TB? *(Probe: how often health education is done (both group and individual education), content of TB it covers)*
14. What infection prevention and control measures do you take in this facility to prevent spread of TB *(Probe: promptly attending to patients with cough, promptly identifying and separating potential infectious TB patient)*
15. What guidelines do you follow in diagnosing TB in this health facility? _____
16. Do you have the guidelines available? _____
(If yes, then look at the guidelines with the HCW and probe reasons for aspects of the guideline that are implemented or not implemented, what is done at the waiting areas, OPD, consulting rooms, wards, laboratory and special clinics (ART, Diabetic, ANC, Hypertension Clinics). But if No, show your guideline and go through the same procedure described above)

E. Experience in TB case finding

17. What will you say has been your experience with TB diagnosis and treatment in this health facility?
 - What has been your experience with different categories/attitudes of patients *(Probe: age, sex, occupation, religion, tribe, location (rural, urban, country: Ghana, Togo))*.
 - What has been your experience with screening for cough among patients visiting the health facility? *(Probe: recognition of symptoms, use of symptom questionnaire, referral from the consulting room)*
 - What has been your experience with requesting for sputum test?
 - How easy is it for patient to do the test, receive results and initiate treatment for

those with a positive test result? (*Probe: duration of sputum production, test duration, informing patient of results, patient initiation of treatment*)

- What are the laboratory related factors that hinder requesting for sputum test? (*Probe: unavailability of sputum container, industrial strikes*)
- If a patient is diagnosed with TB and comes frequently to the facility, do you build a relationship with them (*Probe for the kind of relationship: friendly, cordial etc*)

F. Barriers to TB diagnosis and treatment

18. What in your view will you say are barriers to TB diagnosis and treatment in this health facility?

- In your opinion, what challenges do patients with TB symptoms face being diagnosed with TB and put on treatment in this facility? (*Probe: patient behaviour, human resource capacity at the facility, diagnostic capacity, logistics, infrastructure, program level challenges*)
- Are there any health worker challenges that undermine TB diagnosis? (*Probe: knowledge of TB, commitment/motivation, communication, risk of infection, stigma*)
- Away from the health facility, are people with TB symptoms facing challenges which make it harder for them to present at the facility? (*Probe: financial, social, religion, stigma*). Is there anything that you do as a HCW about this?

G. Suggested Solutions

19. What do you think can be done to improve TB case finding in this facility?

20. Do you have any questions you will like to ask?

Thank you

Interview end time: _____