Assessing components of the TB care cascade in Ghana

Ohene, S.A.

Publication date
2022
Document Version
Final published version

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SALLY-ANN OHENE

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Sally-Ann Ohene

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PhD Thesis: Amsterdam Institute for Global Health and Development, University of Amsterdam, The Netherlands

Layout and design by: Mahogany Row Limited (info@mahogany-row.com)
Printed by: Ipskamp
Cover Page Photography by Sally-Ann Ohene

The thesis made use of programmatic data from the National Tuberculosis Control Program (NTP) of the Ghana Health Service / Ministry of Health. The research was conducted in collaboration with different colleagues from multiple institutions including the Ghana NTP, Ghana Health Service, KIT Health, Royal Tropical Institute (KIT), Amsterdam, Global TB Programme, WHO, Geneva, Department of Global Health, Academic Medical Centre, Amsterdam Institute of Global Health and Development, Amsterdam.
The authors take full ownership and responsibility of content and the views expressed in the thesis which may not necessarily represent the decisions or policies of institutions mentioned above. The authors wish to thank the staff, patients, participants, collaborating institutions and facilities for the tremendous support and great work being done and the contribution in making the thesis a reality.

Assessing components of the TB care cascade in Ghana

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Universiteit van Amsterdam
op gezag van de
Rector Magnificus

Prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties
ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel op

vrijdag 29 april 2022, te 10.00 uur

door

Sally-Ann Ohene
geboren te Accra

Promotiecommissie

Promotor:	prof. dr. P.R. Klatser	AMC-UvA
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Faculteit der Geneeskunde

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Chapter 1

Introduction

Tuberculosis

Tuberculosis (TB), primarily a lung disease which dates back many years, is caused by the bacteria *Mycobacterium tuberculosis*.[1] It is spread through the air from an infected person to others through coughing and sneezing.[2] A person may be infected with TB but may not develop active TB disease due to the ability of the immune system to render the TB bacteria inactive.[3] An estimated 25% of people globally have such latent TB infection.[4] There is a 5 to 10% lifetime risk of a person with latent TB infection progressing to TB disease if the immune system becomes compromised.[2] Risk factors for developing TB include HIV infection, conditions impairing the immune system, undernutrition, alcohol use disorder and tobacco smoking.[2] Symptoms of pulmonary TB disease include cough, production of sputum which may be bloody, chest pain, weight loss, fever and night sweats.[2] Findings from TB prevalence surveys have however highlighted that a considerable proportion of people may have TB without showing any symptoms.[5] Consequently the usefulness of x-ray as a screening tool for pulmonary TB has gained acceptance. Extrapulmonary TB (EPTB) in which TB affects organs and tissues such as lymph nodes, bones, central nervous system may occur in up to 25% of TB cases and is due to spread of the TB bacteria through the blood and lymphatic fluid. [6]

The cascade of TB care spans identification of presumed TB cases for diagnostic workup and confirmation, enrolment into treatment, achieving treatment success or survival free of recurrence.[7] There are however constraints that could potentially contribute to patient losses along the continuum of care including inadequate access to TB tests, low sensitivity of available TB tests, loss to follow up before initiation of treatment and sub-optimal treatment record keeping. [7] People presumed to have TB may be identified passively as in people on their own seeking care for symptoms suggestive of TB and actively by systematic or provider-initiated screening for TB among targeted groups.[8] Rapid molecular diagnostic tests such as GeneXpert MTB/RIF are recommended by WHO as the first line diagnostic test for persons with symptoms suggestive of TB. [2] This is due to the ability and sensitivity of these tests to facilitate early detection of TB including drug-resistant strains.[2] Samples for TB

testing include sputum and in the case of EPTB, samples/fluids obtained from affected tissues and organs.[9] First line treatment for patients with drug-susceptible consists of a 6-month course that is rifampicin based regimen that also includes isoniazid, ethambutol and pyrazinamide.[10] Multi-drug resistant TB which refers to TB for which isoniazid and rifampicin, the backbone of the short course regimen is no longer effective require longer regimens that are potentially more toxic to patients and relatively more expensive.[2] Persons living with HIV have a much higher risk of contracting TB than their HIV negative counterparts requiring synergy between HIV and TB programs to enhance prevention and optimum care for those who are co-infected.[2]

The END and STOP TB strategies build on the landmark Directly Observed Therapy Short Course (DOTS) expansion strategy DOTS strategy which outlined the framework for effective TB control activities. [11-14] Key elements underpinning these strategies include early case detection, diagnosis of TB and standardized treatment for people with TB inclusive of drug resistant TB, political commitment and supportive systems for TB care and uptake of new tools and innovation.[1]

Clearly, early case detection coupled with a high treatment success leads to a cure of infectious TB cases and cuts the risk of transmission ultimately reducing the burden of TB. To this end and in line with the Millennium Development Goals, the targets of 70% case detection rate (CDR) and 85% treatment success were set for countries.[13] Over the years there was a steady improvement in CDR with an estimated global level of 65% in 2010 up from 54–60% in 2005 and 40–45% in 1995.[15] This has involved several countries adopting various strategies to improve the TB case finding and management. The END TB strategy now urges countries to reach a target of 90% of estimated TB incident cases being notified and treated and 90% treatment success rate for notified TB cases. [14]

The Global TB Burden

Despite the various control strategies implemented over time, TB continues to be a disease of public health concern in the twenty first century and is listed among the

top 10 causes of death across the globe. [1] It is estimated that there were 10 million incident cases of TB globally in 2019, with a mortality of 1.2 million among HIV-negative cases and an additional 208,000 deaths among people who were HIV-positive.[1] A major factor of TB incidence in Africa has been the HIV pandemic which drove up TB cases in many African countries in previous decades.[15] However improvement in HIV care has contributed to a decrease in TB incidence in Africa.[15] Notwithstanding, about 25% of those who developed TB in 2019, an estimated 2.4 million incident cases, were in the WHO region of Africa.[1] Considering that Africa has less than 17% of the world's population, the TB cases reported highlights the disproportionate burden of TB on this continent.[16] In Ghana, like many African countries, TB is a disease of public health importance. More than 13, 800 cases of TB were reported in 2019 in this West African country which was designated as having a high TB/HIV burden.[1] At country level, the Ghana National TB Program (NTP) is addressing TB by implementing programs driven by global strategies.[17] Insights into such local level TB prevention and control activities highlight the efforts that contribute to combating TB, a global disease which is not only treatable but preventable.

The Ghana TB Program

TB was recognized as a public health concern in Ghana as far back as the colonial era.[17] TB prevention and control were however not streamlined and suffered from unpredictable funding.[18] With the formal set up of the National TB Control Program in 1994 and more dedicated funding from the government, Global Fund and other partner funding mechanisms, multiple TB control interventions have been implemented across various levels of the health sector.[18-23] Since inception, NTP activities have been under the direction of four strategic plans which have sought to address quality gaps in TB care, scale up private sector involvement in TB care, prioritize HIV/TB and drug resistant TB, strengthen case detection, surveillance and monitoring and evaluation systems. [18-23] TB control is integrated into the primary health care making use of health staff at sub-national levels.[18] Directly Observed

Treatment Short Course (TB DOTS) is available through 1,600 facilities across the country, 75 of which are private.[18] There are about 325 TB diagnostic laboratories across the country giving an estimated ratio of 1 microscopy center to 90,000 population.[18,20] GeneXpert has now been made the first line diagnostic tool for new presumed TB cases facilitating the identification and treatment of multi-drug resistant TB.[21] From 2013 to 2018, treatment success has been above 84% with the highest over the period being 87.4% in 2017.[21] TB mortality has been in the range of 6 to 9% with higher mortality rates recorded among prisoners (32.6%) and persons living with HIV (20%).[22]

The NTP had in place the Enabler's Package, an incentive program which made available support such as food and transport vouchers to patients to reduce the cost burden of seeking TB diagnosis and treatment.[20] This patient support program was one of the successful strategies to enhance TB case holding but due to limited funding had to be scaled back.[20,21] TB in Ghana is managed according to WHO treatment guidelines using quality assured drugs accessed through the Global Drug Facility.[20] TB medicines including those for drug resistant TB, are procured and distributed in accordance with the country's procurement and supply chain management plan.[20,21] A joint TB/HIV coordinating body oversees TB/HIV collaborative services in line with the country's TB/HIV policy and guidelines for collaborative activities and clinical management for TB/HIV co-infection.[20]

The District Health Information Management System 2 (DHIMS2) software which is the web-based data entry platform has served as the repository for TB data from across the country since 2014.[18] TB data generated from facilities within a district is usually entered into DHIMS2 by facility or district level staff with data validation undertaken regularly at the district. Data access is controlled by user rights. Staff at various levels of the health system can access and analyze TB to monitor trends and other information that is relevant to guide program implementation.

The Burden of TB in Ghana

Two TB prevalence surveys have been held in Ghana.[23,24] In the first survey conducted in 1957, the point TB prevalence was reported in the range of 0.2 % to 0.9% in the general population while in gold mining communities, rates of 0.4% to 3% were reported.[23] From about 3,000 TB cases reported in 1986, the highest number of cases reported in any given year was 15,849 in 2011.[20,21,23] Over the period 2013-2019, Ghana on the average reported 14,500 TB cases annually. [21]

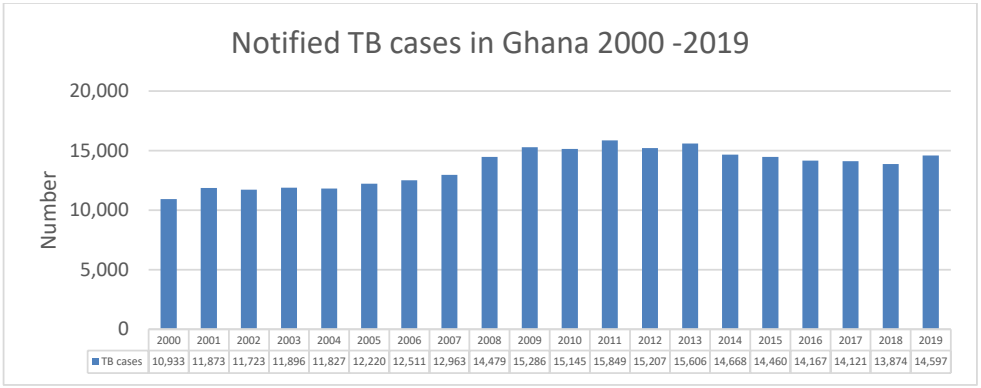

Figure 1. Notified TB cases in Ghana 2000-2019 [18,20,21]

TB case notification rate peaked at 64.4 per 100,000 in 2009.[18,21] The 2013 TB prevalence survey conducted in Ghana however revealed that the prevalence of bacteriologically confirmed TB was 356 per 100,000 population highlighting a gross under-detection of TB burden in the years preceding the survey.[24] Estimates put the number of people with TB in 2019 as 44,000 with 1,200 of them being drug resistant TB.[21, 25]Among TB cases, coinfection with HIV is approximately 21%.[25] Men constitute about 65% while children below 15 years account for less than 6%.[18]

Knowledge gaps informing the research in this thesis

In many countries across the world, there is a significant gap between estimated incident TB cases and reported cases. Ghana is not an exception. The 2007 comprehensive review of the Ghana National TB Program highlighted low TB case

detection as a challenge to TB control (28% for all TB cases and 37% for smear-positive cases).[17] Consequently the National Tuberculosis Health Sector Strategic Plan for Ghana (2009-2013) clearly identified TB case detection as one of the areas for intervention.[18] Despite this recognition, several years down the line, only just about a third of estimated incident cases is detected.[25]

Some of the reasons accounting for these gaps include limited access to TB diagnostic tests and for some of those who are able to get tested, failure to receive the results of the positive test for TB.[7] Beyond the person being tested with TB, there is a sequential decrease in the numbers of people diagnosed with TB, being registered for treatment, accessing medicines for the full period of treatment and achieving treatment success and recurrence free survival at each stage in the TB care cascade.[7] In Ghana several studies have identified a myriad of patient and health system factors affecting access to and delivery of TB prevention and control services contributing to the stepwise reduction in numbers in the TB care pathway.[26-35] Limited knowledge, myths and misconceptions about TB transmission, low perceptions of vulnerability to TB infection, stigma and financial barriers limit demand for and access to TB diagnostic services, enrolment in care and follow through for successful treatment.[26-32] In a qualitative study of TB patients in Ghana, participants failed to reveal they had been coughing for prolonged periods but rather reported non-specific symptoms which ultimately led to delay in the TB diagnosis.[26] Health system factors that contribute to the gaps in the TB care pathway in Ghana include limited access to TB diagnostic tests, inadequate funding of TB services, low interest of some health care providers in TB prevention and control, discriminatory attitude of health facility staff.[21, 31-35] It is estimated that about half of out-patient attendants seek care in health facilities that do not have TB diagnostic tests on-site.[21] Findings from these studies have informed some of the NTP's flagship programs such as the flagship Enabler's package which significantly augmented treatment success.[18]

Several of the studies highlighted above on TB in Ghana have focused a quite a bit on the challenges and gaps and relatively less on solutions. There are however several under-researched areas in TB control which would benefit immensely from evidence-

based data to shape policy and inform program implementation. Though one of the weak links in Ghana's fight against TB is case detection, there is a clear knowledge gap on what effective approaches to improve case finding are. The traditional passive case finding is limited partly due to some of the barriers listed such as poor access to diagnostic tests, missed opportunities for identifying presumed TB cases at health facilities. Consequently, several outstanding gnawing questions include what innovative active case finding approaches can be explored in the resource constrained Ghana setting to improve case finding people with TB? Given that, people presenting to health facilities for whatever reason could potentially have TB, could an intensified case finding approach through out-patient screening for TB symptoms identify presumed TB patients for diagnostic testing? Another question is how feasible and how successful would active case finding interventions implemented under programmatic conditions be among higher risk TB populations such as and persons living with HIV and diabetes attending their review clinic? Drawing from other studies conducted among persons with HIV, would symptom screening conducted by facility health staff using shorter duration of cough and other symptoms such as fever, night sweats and weight loss be more effective in TB case finding than the use of the more traditional approach of prolonged cough?[36] For those vulnerable populations at high risk TB who have limited access to facility-based TB services, could community screening for TB using mobile teams be a worthwhile enhanced case-finding strategy?

Going back to the TB care cascade, even though some literature has shed light on some of the factors contributing to the gaps in the pathway, much of what is known has however come from studies on pulmonary TB in the adult population. On the other hand, there is relatively little known about outcomes of persons diagnosed with extrapulmonary TB and childhood TB. EPTB should be of critical interest to TB control programs as it may account for up to a quarter of all TB cases while among children and those with compromised immune systems, the proportion of EPTB could be even higher.[6] Likewise, childhood TB also serves as a marker for recent TB transmission which has implication for TB control activities.[37] The varying nature of

extrapulmonary TB disease presentation, the different sites affected and limitations in the availability of sensitive tests make the diagnosis of EPTB challenging.[6] Similar challenges including the atypical nature of presentation and availability of sensitive tests confront the diagnosis of TB in children. [5]Whether these challenges have played a role in the knowledge gap on EPTB on childhood TB is speculative but there is clear need to address the outstanding research questions on these two areas in Ghana such as what is the scope of those affected and how do they fare on the TB care pathway including potential for being diagnosed and the treatment outcomes? How does treatment outcome in EPTB compare to pulmonary TB patients and what factors are associated with mortality among EPTB? In a country of limited resources, it is imperative to bridge this significant knowledge gap to provide vital evidence-based data to drive targeted interventions, shape policy and inform rational planning while providing lessons for other programs to learn from. The research in this thesis comes on the heels of this knowledge gap.

Objectives of research and structure of thesis

The overarching objective of the research was to assess outcomes of case finding interventions implemented, as well as investigate aspects of the pathways of TB care focusing on under-researched topics in Ghana namely extrapulmonary tuberculosis and childhood TB.

Overarching research questions:

1. What innovative TB case detection approaches can be deployed to intensify and enhance TB case finding in health facilities and in the community respectively?
2. What are the treatment outcomes and the factors that are associated with the worst outcome, death along the TB care cascade for EPTB and Childhood TB?

Routine data collected by the National Tuberculosis Control Program (NTP) were the primary data source for the analyses performed in this research. The routine NTP data had been submitted by institutional TB coordinators in facilities implementing case find interventions or collected by outreach teams conducting enhanced case finding activities among vulnerable communities with high risk of TB in hard-to-reach areas. Routine data collected by the national TB program is largely an underutilized but exceptionally valuable resource of data. The programmatic database can be harnessed to answer a variety of gaping questions and address the research needs of TB programs to guide tailored adjustments and improvement in program implementation. Key among the advantages of leveraging routine data for analyses include its ready availability, the wide scope of demographic and clinical variables which enable analyses of different dimensions of TB prevention and control such as gender sensitive aspects and a variety of subject that enable exploration of the various stages of the TB case pathway.

Chapter 2: Provider initiated tuberculosis case finding in outpatient departments of health care facilities in Ghana: yield by screening strategy and target group

BMC Infectious Diseases (2017) 17:739
https://doi.org/10.1186/s12879-017-2843-5

Research question: Does a shorter duration symptom screening increase case notification or only earlier case finding?

Synopsis: It is estimated that about two-thirds of TB cases in Ghana are not detected and yet there are limited studies on assessing TB case finding strategies and the ability to improve the low yield of TB. We assess whether using symptom screening based on shorter duration of cough in combination with other symptoms has an advantage over the traditional 2 weeks cough in increasing the yield of TB cases. In the 1st approach, patients with a cough of 2 weeks or more and in the 2nd approach, patients with a cough of 24 hours as well a history of fever or weight loss were asked to provide sputum for smear testing. This study compares the yield of the 2 approaches

and the results between OPD groups. Case notification trends in Accra are compared to those of a control area.

Chapter 3: Yield of tuberculosis among household contacts of tuberculosis patients in Accra, Ghana.
Infectious Diseases of Poverty (2018) 7:14
https://doi.org/10.1186/s40249-018-0396-5

Research question: What is the feasibility and yield of implementing contact investigation activities under programmatic conditions in Ghana?
Synopsis: Even though contacts of individuals diagnosed with TB are identified among risk groups to be screened for TB, contact investigation is not usually routinely in Ghana and little is known about the feasibility of implementing TB contact investigations and what the yield could be. This study therefore seeks to examine the outcomes and feasibility of implementing contact investigation activities under programmatic conditions in Ghana and identify barriers for successful implementation to inform NTP programming. The study assesses various proportions and yield from number of contacts needed to screen (NNS) and number needed to test (NNT) to detect a TB case.

Chapter 4: Case finding of tuberculosis among mining communities in Ghana
PLoS ONE (2019) 16(3): e0248718.
https://doi.org/10.1371/journal.pone.0248718

Research question: What is the yield of TB cases from TB screening activities among artisanal mining communities (AMC) in Ghana?
Synopsis: Miners are among risk groups that are recommended for targeted TB screening. Artisanal miners are not only vulnerable to TB, they may operate in hard to reach areas with potentially limited access to health care services. The NTP has a keen interest to conduct TB case finding among miners given their high risk for TB with. Evidence-based data to guide these case identification activities among artisanal

gold mining communities (AMC) is however sparse not only in Ghana but Africa as well. Against this knowledge gap, the study assesses the conduct of TB screening activities as well as screening methods including the use of chest x-ray among AMC in 3 regions of Ghana. We also evaluate the number needed to screen (NNS) and the number needed to test (NNT) to detect a TB case, the factors associated with TB in these communities and the performance of the screening methods chest X-ray and symptoms in the detection of TB cases.

Chapter 5: Childhood tuberculosis and treatment outcomes in Accra: a retrospective analysis

BMC Infectious Diseases (2019) 19:749
https://doi.org/10.1186/s12879-019-4392-6

Research question: What are the treatment outcomes of children with TB from multiple health facilities in Accra, Ghana?

Synopsis: Tuberculosis (TB) is a leading cause of death in children and adults. Unlike for adults, there's a paucity of data on the TB care pathway for children in several countries in Africa including Ghana. TB in children is a marker for recent TB infection necessitating documented studies to shape programs targeted at childhood TB for optimum outcomes. In Chapter 5, the study assesses the demographic and clinical characteristics and treatment outcomes of children less than 15 years with TB from multiple health facilities in Accra, Ghana and also determines predictors of mortality.

Chapter 6: Extra-pulmonary tuberculosis: A retrospective study of patients in Accra, Ghana

PLoS ONE (2019) 14(1): e0209650 https://doi.org/10.1371/journal.pone.0209650

Research question: What are the treatment outcomes of patients with extra-pulmonary TB and the risk factors for mortality?

Synopsis: There is limited data on the TB care cascade for extrapulmonary TB (EPTB) in sub-Sahara Africa and Ghana is no exception. Data on patients with all

types of TB from diagnosis to treatment retention and outcomes are necessary to facilitate a wholistic approach to TB control. This warrants studies that will explore the characteristics of those contracting EPTB and their outcomes to understand how to address the gaps in diagnosis and management. To this end, this study explores the dimensions and treatment outcomes of EPTB among patients from different types of health facilities including comparison between EPTB and pulmonary TB (PTB) and factors associated with death among EPTB patients.

In summary, chapters 2, 3 and 4 address the question on the TB case detection approaches that can be deployed to intensify and enhance TB case finding in health facilities and in the community respectively.
Chapters 5 and 6 delve into the questions on the TB care cascade for childhood TB and EPTB highlighting treatment outcomes and the factors that are associated with the worst outcome, death.

Chapter 7: Discussion

The seventh chapter ties in the results of the different studies and highlights the key findings, recommendations for policy makers, study limitations and conclusions.

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Chapter 2

Provider initiated tuberculosis case finding in outpatient departments of health care facilities in Ghana: yield by screening strategy and target group

Sally-Ann Ohene, Frank Bonsu, Nii Nortey Hansen-Nortey, Ardon Toonstra
Adelaide Sackey, Knut Lonnroth, Mukund Uplekar, Samuel Danso
George Mensah, Felix Afutu, Paul Klatser, Mirjam Bakker

BMC Infectious Diseases (2017) 17:739
https://doi.org/10.1186/s12879-017-2843-5

Abstract

Background: Meticulous identification and investigation of patients presenting with tuberculosis (TB) suggestive symptoms rarely happen in crowded outpatient departments (OPDs). Making health providers in OPDs diligently follow screening procedures may help increase TB case detection. From July 2010 to December 2013, two symptom-based TB screening approaches of varying cough duration were used to screen and test for TB among general outpatients, PLHIV, diabetics and contacts in Accra, Ghana.

Methods: This study was a retrospective analysis comparing the yield of TB cases using two different screening approaches allocated to selected public health facilities. In the first approach, the conventional 2 weeks cough duration with or without other TB suggestive symptoms was the criterion to test for TB in attendants of 7 general OPDs. In the second approach the screening criteria cough of >24 hours, as well as a history of at least one of the following symptoms: fever, weight loss and drenching night sweats were used to screen and test for TB among attendants of 3 general OPDs, 7 HIV clinics and 2 diabetes clinics. Contact investigation was initiated for index TB patients. The facilities documented the number of patients verbally screened, with presumptive TB, tested using smear microscopy and those diagnosed with TB in order to calculate the yield and number needed to screen (NNS) to find one TB case. Case notification trends in Accra were compared to those of a control area.

Results: In the approach using >24-hour cough, significantly more presumptive TB cases were identified among outpatients (0.82% versus 0.63%), more were tested (90.1% versus 86.7%), but less smear positive patients were identified among those tested (8.0% versus 9.4%). Overall, all forms of TB cases identified per 100,000 screened were significantly higher in the >24-hour cough approach at OPDs (92.7 for cough >24 hour compared to 82.7 for cough >2 weeks), and even higher in diabetics (364), among contacts (693) and PLHIV (995). NNS (95% Confidence Interval) varied from 100 (93-109) for PLHIV, 144 (112-202) for contacts, 275 (197-451) for diabetics and 1144 (1101-1190) for OPD attendants. About 80% of the TB cases were

detected in general OPDs. Despite the intervention, notifications trends were similar in the intervention and control areas.

Conclusion: The >24-hour cough approach yielded more TB cases though required TB testing for a larger number of patients. The yield of TB cases per 100,000 population screened was highest among PLHIV, contacts, and diabetics, but the majority of cases were detected in general OPDs. The intervention had no discernible impact on general case notification.

Keywords: tuberculosis, screening, case finding, Ghana

Background

Ensuring early detection of tuberculosis (TB) cases is one of the key components of the End TB Strategy [1]. It is estimated by the World Health Organization (WHO) that there were 10.4 million incident cases of TB globally in 2015, and 1.8 million deaths due to TB [2]. Undetected active TB cases, as well as the pool of persons with latent TB infection which consists of a third of the human population, serve as an infectious reservoir for potential new cases, thereby posing a challenge to TB elimination [3]. Identification of TB cases usually depends on symptomatic patients voluntarily reporting to the health facility for diagnosis. Usually, a history of cough for 2 or more weeks, with or without other TB suggestive symptoms, is the criterion used to identify people to be tested for TB. However, using this method may be limited by factors such as patient health seeking behaviour, health worker alertness and low sensitivity. Some individuals may not have TB suggestive symptoms at all or may have less prominent symptoms that fail to elicit attention for testing for TB. Therefore, diagnosis of these cases is potentially missed or delayed with the risk of sub-optimal treatment outcomes, health sequelae and continued transmission of TB in health facilities and the general population [4, 5].

Diagnostic delays and low TB case notification pose important challenges, prompting the need to explore interventions that increase TB case detection. In implementing these interventions, however, it is pertinent that they are cost effective and targeted at selected risk groups. Additionally, it is necessary to take into consideration the potential yield of TB cases, benefits, and harms, as well as the feasibility and costs [4].

HIV clinics rank high among the settings for increased yield of TB cases due to the high risk of TB among people with HIV [6, 7]. Similarly, studies among diabetics have shown that the risk of developing TB is higher among persons with diabetes compared to non-diabetics [8, 9]. Contacts of TB cases are another risk group; data from multiple studies from low- and middle-income countries showed pooled prevalence of 3.1% active TB in all contacts [10].

Outpatient departments (OPD) of health facilities are feasible settings for TB symptoms screening [6, 11]. Patients presenting themselves at the health facility, although not constituting a specific TB risk group, constitute a "captive audience" requiring limited logistic arrangements compared to the labour-intensive case finding methods employed in non-facility-based settings.

The 2007 comprehensive review of the Ghana National TB Program (NTP) highlighted low TB case detection as a challenge to TB control in Ghana [12]. With case detection estimated at 27% for all TB cases and 37% for smear-positive cases in 2008, the National Tuberculosis Health Sector Strategic Plan for Ghana (2009-2013) clearly identified TB case detection as one of the areas for intervention [13]. With support from WHO and Canadian International Development Agency (CIDA), the Ghana NTP subsequently implemented a provider-initiated enhanced TB case finding strategy in the capital Accra. The selection of Accra for the initiative was because of proximity to facilitate oversight and monitoring of activities by the national office of the NTP which is located in Accra. This was done under programmatic settings among attendants of general outpatient departments (OPD), HIV clinics, diabetes clinics and contacts of identified TB cases to augment TB case detection [14]. Two approaches which used different durations of cough and other TB suggestive symptoms were used to identify patients for sputum smear testing for TB.

While multiple studies have been published on screening for TB cases in different settings and countries, there is very little in the literature on enhanced TB case detection efforts in Ghana [15, 16]. The first objective of this paper was to compare the yield of the two different approaches used in two sets of general OPD clinics in Accra, with one of the screening approaches using a shorter duration of cough as well as other TB suggestive symptoms. The second objective was to compare the yield from the four groups; namely general outpatients, PLHIV, diabetics and contacts, using the approach with the shorter duration of cough and other TB suggestive symptoms. Finally, as a third objective, case notification trends in Accra were compared to those of a control area.

Methods

This study is a retrospective analysis comparing the yield of TB cases using two different approaches to identify people eligible for TB testing from July of 2010 to December 2013. The approaches were implemented as part of an enhanced TB case finding intervention in Accra Metropolis, the largest city and capital of Ghana, located in the Greater Accra Region (GAR). The following criteria were used to select public health facilities to participate in the intervention: availability of TB microscopy services and functioning DOTS centres, large OPD clientele and capacity to implement the intervention under programmatic settings which translated into the facility management indicating ability to implement the intervention activities in the existing setting using the existing staff. Eleven major public health facilities in Accra, some having and others not having separate independently-ran HIV and diabetic clinics in addition to the general OPD services, fulfilled the criteria and were selected to participate in the intervention. OPD attendance ranged from 100 per day in the smallest facility to 500 per day in the largest facility. The intervention was implemented in the outpatient departments in ten facilities as well as HIV clinics and diabetic clinics that were operating in these facilities, but in the eleventh facility, the intervention was implemented in only the HIV clinic. These 11 facilities made up 24% of the 46 TB diagnostic facilities in Accra, but accounted for approximately 70% of cases reported in Accra city and 53% of TB cases reported in Greater Accra Region in 2009. Accra residents as well as the residents of the neighbouring districts in GAR, who flock into the city during the day to transact various activities including work and educational pursuits, patronize these facilities. To facilitate ownership and buy-in, management and all health care staff of the facilities were sensitized about the modalities of intervention. Standard operating procedures (SOPs) were developed to guide operations at the facilities and health care staff in the OPD, consulting rooms, laboratory and TB DOTS centres who were directly involved in the implementation of the initiative were trained in their use. Tools that were produced to track data included registers for contact tracing, presumptive TB patients, PLHIV screened for

TB and presumptive TB referral forms and screening tool for the two screening approaches.

Screening methods

In the first approach, assigned to 7 general OPDs, the history of cough of two or more weeks with or without other TB suggestive symptoms was elicited from all patients, regardless of the presenting symptoms, by the attending OPD nurse responsible for taking vital signs. If the patient affirmed a cough of 2 weeks or more, this was indicated on the patient's folder/OPD treatment card to alert the clinician. The OPD nurse then filled a sputum request form for the patient, who was then sent to the laboratory for the first collection of sputum specimen. It was ensured that such patients kept their place in the queue to see the clinician. Subsequently, during the consultation, the clinician would conduct a thorough clinical examination to assess for extra-pulmonary TB in addition to making a diagnosis for the patient's presenting symptoms. The clinician would then refer the patient to the laboratory for the second sputum smear examination, even when extra-pulmonary TB was presumed.

The second approach was assigned to 3 general OPDs, 7 HIV clinics - one of which was in a tertiary hospital - and 2 diabetes clinics, using a similar process. The difference in the second approach was that the patients were asked for a history of cough of >24 hours, as well as a history of any of the following symptoms: fever, weight loss, and drenching night sweats. See Fig. 1 for the diagnostic algorithm. The assignment of approaches among the clinics was purposely done in such a way that all the HIV and diabetes clinics used the second approach, hereafter referred to as >24-hour cough approach. This was in consideration of improving identification of TB in those patients who may not have the typical prolonged cough associated with TB [17]. The main reason for the selection of the three facilities to implement the >24 hour-cough approach in their OPD was because they had a relatively larger OPD clientele and it was expected that their laboratories would be able to handle the potentially larger volume of samples for sputum examination expected given the criteria of >24 hours of cough and other TB suggestive symptoms. While the patient population in the two sets of facilities was likely similar, it is important to note that

the intervention was not implemented as a trial. Therefore, consideration was not given to baseline characteristics of the patient population at the facilities that could pose as potential confounding factors. We compared the yield from the two different approaches used in two sets of general OPD clinics in Accra and also compared the yield between the four groups, namely general outpatients, PLHIV, diabetics and contacts using the >24-hour cough approach.

Contact investigation for TB was not a routine practice of the facility staff. It was therefore implemented as one of the case finding interventions with the pool of people screened being contacts of TB cases, in contrast to patients attending the respective clinics for the other groups. Index TB patients from all facilities, with the exception of one that cited inadequate logistics to carry out contact investigations, were invited to list their contacts. Depending on the preference of the index patient, contacts identified were either screened during home verification of the index patient before treatment initiation, or at the health facility while accompanying the index patient.

The screening approach in use at the facility of the index patient was employed for the screening of contacts. Contacts presumed to be TB cases followed the standard diagnostic algorithm. At the time of the intervention, Ziehl Nielsen staining method was used in the diagnosis of TB. A diagnosis of sputum smear positive TB (SS+ve) was made when at least one acid-fast bacilli (AFB) was detected in 100 fields in one out of two slides. A diagnosis of smear negative pulmonary TB was made only after the smear negative sputum result had been followed up with clinician assessment and chest x-ray with findings consistent with TB coupled with the clinician decision to treat with a full course of TB treatment.

The data was cross-checked during periodic monitoring and supervisory support visits to the facilities by the Accra Metropolis Health Directorate TB team and NTP staff. The quarterly figures from the two different screening approaches used in the OPDs were plotted to show the trend of those screened, identified with TB suggestive symptoms, tested, and the yield of TB cases over the period of the intervention.

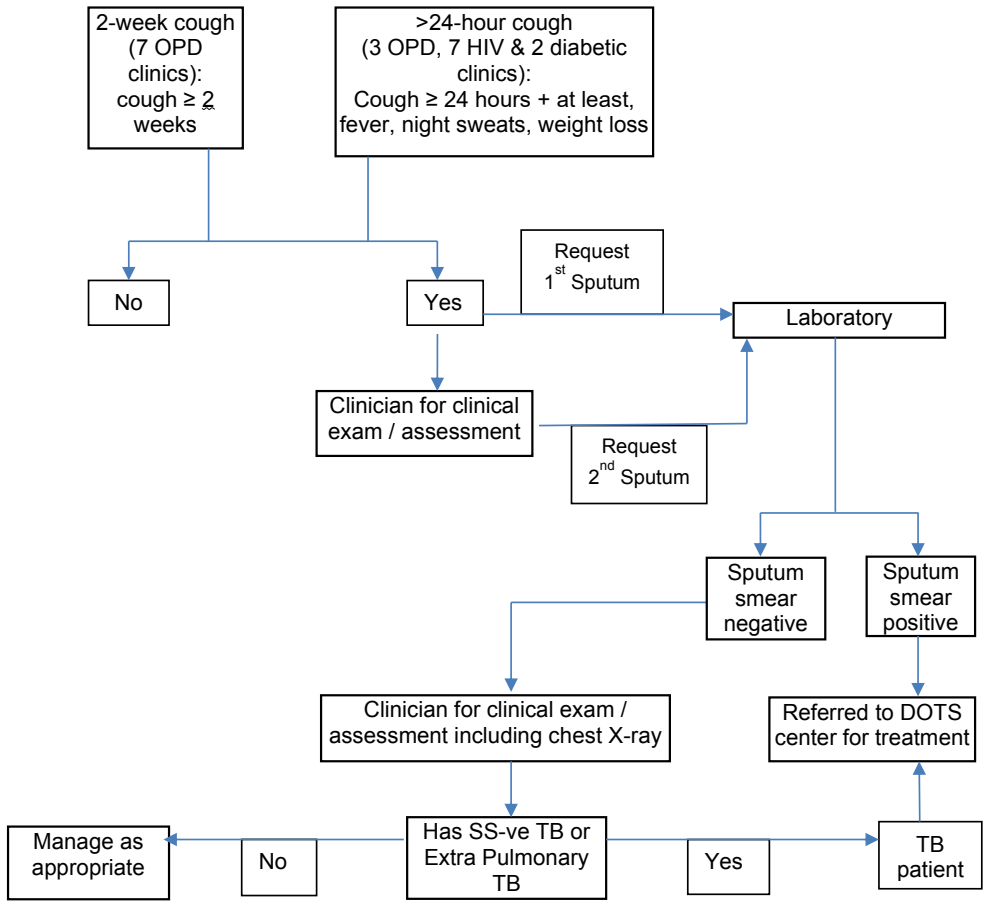

Fig. 1 Algorithm for diagnosing TB among out-patient attendees in 11 health facilities in Accra

The proportion of all forms of TB and SS+ve cases among the numbers screened, the presumptive TB cases and those tested for TB and the number needed to screen (NNS) to identify one SS+ve case, as well as all forms of TB for the two different approaches used in the two sets of general OPD clinics, HIV clinics, diabetes clinics and contact investigations were calculated. Two-sample tests of proportion were used to determine the 95% confidence intervals for these proportions to enable comparison

between the two approaches used in the two sets of general OPD clinics in Accra and across the four groups, namely general outpatients, PLHIV, diabetics and contacts, to identify significant differences. STATA Data Analysis and Statistical Software version 12 was used for the analysis. For the third objective of the paper, the comparison of TB case notification trends at the population level, Greater Accra Region (GAR), in which Accra is located, was assessed as the evaluation population [18]. Like many major cities, the city of Accra is a congregating hub for residents in surrounding districts who come into the city daily for a myriad of activities including accessing health care in the city's facilities. A series of re-demarcation of the districts in GAR has resulted in some residents originally in the geographic region of Accra being assigned to new or other districts in Greater Accra Region, and in some instances residents from the districts bordering Accra have been reassigned to the Accra population [19]. The potential of a spill over effect from the fluid population and the changes in population figures from the re-demarcation exercise necessitated the use of a larger evaluation population and geographic area in order to avoid distortions in the measurements of intervention effects [18]. Ashanti Region, with similar characteristics to GAR, was selected as the control population to compare with GAR. Kumasi, the second largest city in Ghana, is located in Ashanti Region and shares a similar profile with Accra city in population, human resource for health capacity, health infrastructure and economic activities. It also has residents commuting daily from neighbouring districts to the city for various endeavours, creating the potential for similar spill over effects [20]. In the same vain, a demarcation exercise in Ashanti Region resulted in changes in Kumasi's population and geographic spread. In summary, because of the risk of distortion from the demarcation exercises in Accra and Kumasi and spillover effect from fluid populations, we decided to compare notification data from Greater Accra Region and Ashanti Region instead of comparing notification data from Accra and Kumasi. Quarterly notification rates (for all forms of TB and smear positive TB) per 100,000 population were plotted using Microsoft Excel 2010, using figures obtained from the NTP and Ghana Statistical Service for the period 2008 to 2013 for the 2 regions. A linear-trend line was drawn through the quarterly historical TB notification data

during the baseline (the first quarter of 2008 up to the second quarter of 2010) to project TB notification expected during the intervention period for Greater Accra Region and for Ashanti Region. A linear-trend line was also drawn through the actual TB notification data during the intervention period (third quarter 2010 to fourth quarter 2013) for each region. The graphs showed how the two linear-trend lines compared to each other in the intervention area Greater Accra and in the control area Ashanti Region.

Ethical consideration

Ethical clearance for the study was obtained from the Ghana Ministry of Health Research Division Ethical Review Board. Permission was also sought from the NTP and the participating facilities to use the data for the study. The data used in the analyses did not involve personal identifiers, but confidentiality was nevertheless maintained.

Results

During the implementation period, out of the reported 2,954,057 persons screened in the various clinics in participating facilities, approximately 1 out of 100 (24,562) were identified as having symptoms suggestive of TB (Table 1). About 90% (21,890) of these presumptive TB cases were tested for TB. Among these 21,890 presumed TB cases tested, 84.3% were from OPD, 11.9% from the HIV clinic, 2.0% from the diabetes clinic and 1.7% from contacts investigation. Overall, 3,162 TB patients (all forms) were identified, with 79.7% from the OPD, 18% from the HIV clinic, 0.8% from the diabetic clinic, and 1.5% from the contact investigation. Among the TB patients, 57.9% (1,833) were sputum smear positive.

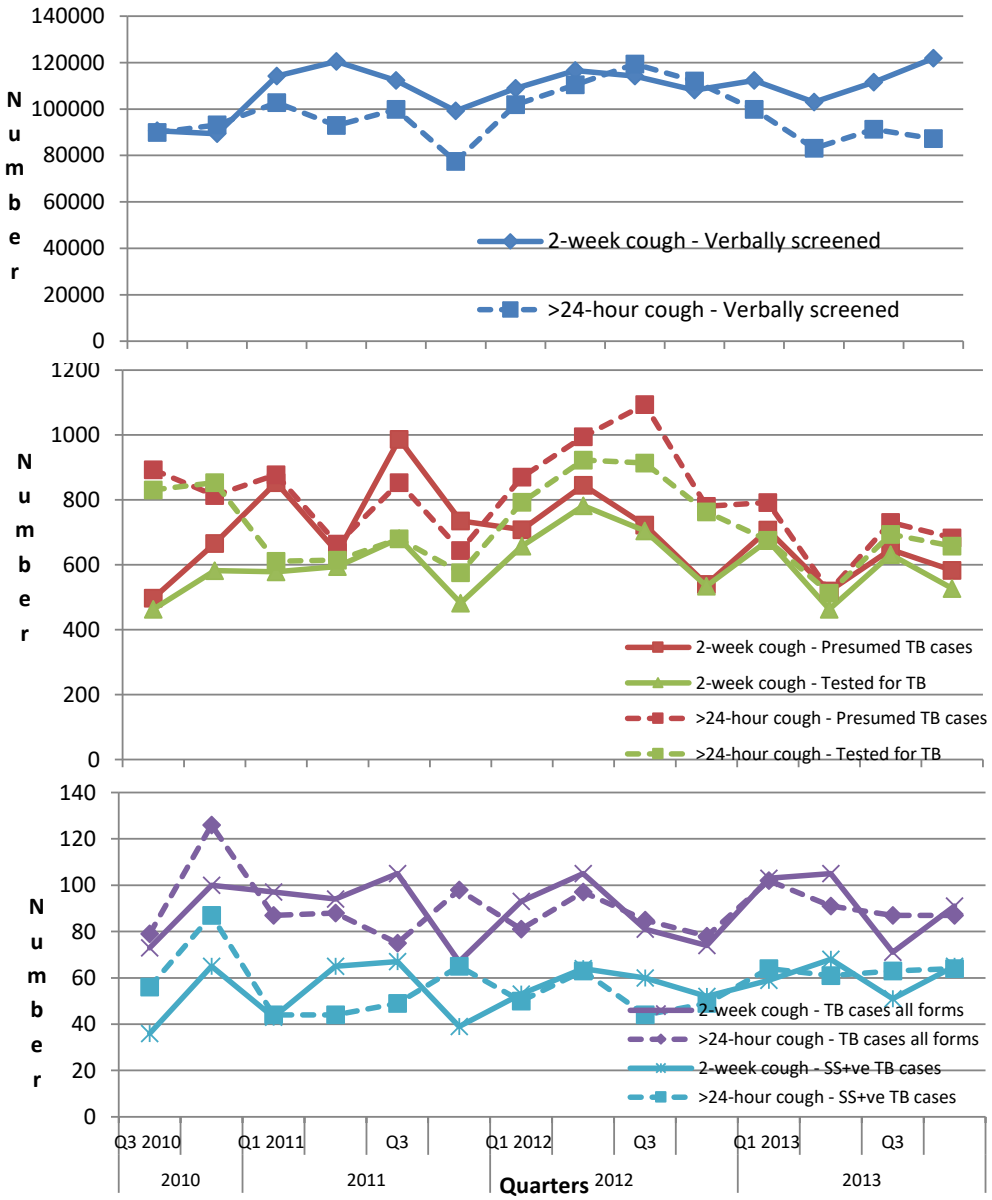

Fig. 2 Number of people verbally screened for TB, identified as presumptive TB, tested for TB, diagnosed with all forms of TB and diagnosed with sputum positive TB identified by the quarter from third quarter 2010 to fourth quarter 2013 for 2-week cough and >24-hour cough approaches in Accra Metropolis facilities

Quarterly variations

The TB cases detected ranged from 170.8 per 100,000 screened in the fourth quarter of 2010 to 73.8 per 100,000 in the fourth quarter of 2012. Figure 2 shows the trend of the number of people verbally screened, identified as presumptive TB, tested for TB, and diagnosed with TB by quarter, from the third quarter of 2010 to the last quarter of 2013 for the two different screening approaches from the OPD clinics.

While fluctuations were observed in these parameters over the period, there was no clear-cut pattern over the course of time. Linear-trends lines for the respective graphs showed that while there was an increasing trend among those verbally screened over the course of the intervention, a decreasing trend was generally identified for the number of presumptive TB cases identified and for numbers tested. Yield from clinics

A comparison of the 2 approaches used in the general OPD setting showed that in the >24 hour-cough approach, significantly more presumptive TB cases were identified among general outpatients (0.82% versus 0.63%; p=0.0000).

Also, more patients were tested (90.1% versus 86.7%; p=0.0000) and fewer smear positive patients were identified among those tested (8.0% versus 9.4%; p<0.007) (Table 1). Overall, the rate of TB cases (all forms) identified among the outpatients screened was higher in the >24 hour-cough approach (92.7 per 100,000 versus 82.7 per 100,000; p=0.004). More patients needed to be screened to identify one TB patient in the 2-week cough approach (NNS=1209, 95% confidence interval (95%CI) 1145 - 1280) compared to the >24 hour-cough approach (NNS=1079, 95%CI 1022 - 1142). The differences between the 2 approaches in all of the above-mentioned indicators were statistically significant. However, the proportion of SS+ve TB diagnosed among all forms of TB did not differ between the two approaches.

Approximately 7% of those verbally screened in the diabetes clinic and contacts of index patients were identified as presumptive TB cases compared to about 5% in the HIV clinic. In the various groups, over 80% of people identified to be presumptive TB cases were tested. However, the HIV clinic had the highest proportion of presumptive TB cases being tested for TB (94.9%), as well as the highest proportion of those tested being diagnosed with TB (21.8%). HIV clinic attendees had the lowest proportion of cases confirmed with sputum smear microscopy (36%). Rates of TB

among those screened were also highest among the HIV patients (995 per 100,000), followed by contact investigation (693 per 100,000). Consequently, the number of people needed to screen (NNS) to identify one TB case was lowest at100 for HIV patients, followed by contacts at 144.

Evaluation versus control area

Both projected TB notification and the actual TB notification for all forms of TB and smear positive TB during the intervention period showed a downward trend in Greater Accra Region (Figs. 3 and 4). However, the actual notification data for smear positive TB cases was less than the projection using the historical data. For Ashanti Region, the control region, projected notification data for all forms of TB and smear positive TB using historical data for the projection also showed a downward trend. However, while actual notification data for smear positive TB during the intervention period was similar to the figures projected from historical data, more TB cases (all forms) were reported in Ashanti Region compared to the projected data. In other words, over the period of the intervention, more TB cases (all forms) were identified among the control population (Ashanti Region), while fewer SS+ve cases were identified in the intervention population (Greater Accra Region) compared to projected figures using historical data.

Table 1 Results from TB case finding activities in clinics in Accra Metropolis from July 2010 to December 2013

	OPD			HIV	Diabetes	Contacts	Total
Indicators	**Option 1**	**Option 2**	**Total**	**Option 2**	**Option 2**	**Total**	**Total**
Number of facilities	7	3	10	7	2	10	29
(A) Number of people screened	1,522,297	1,360,846	2,883,143	57,265	6,866	6,783	2,954,057
(B) Number of presumptive TB patients identified	9,648	11,211	20,859	2,751	495	457	24562
(C) Number of people tested/evaluated for TB disease	8,358	10,100	18,458	2,610	441	381	21890
(D) Number of people diagnosed with all forms of TB	1,259	1,261	2,520	570	25	47	3162
(E) Number of people diagnosed with SS+ TB	787	803	1590	205	14	24	1833
% presumptive TB cases among those screened (B/A)	0.63%	0.82%	0.72%	4.80%	7.21%	6.74%	0.83%
95%CI	(0.62-0.65)	(0.81-0.84)	(0.71-0.73)	(4.63-5.00)	(6.60-7.82)	(6.14-7.33)	
% people tested for TB among presumptive TB patients (C/B)	86.6%	90.1%	88.5%	94.9%	89.1%	83.4%	89.1%
95%CI	(86.0-87.3)	(89.5-90.6)	(88.1-88.9)	(94.1-95.7)	(86.3-91.8)	(80.0-86.8)	
% SS+ TB patients among those tested (E/C)	9.4%	8.0%	8.6%	7.9%	3.2%	6.3%	8.4%
95%CI	(8.8-10.0)	(7.4-8.5)	(8.2-9.0)	(6.8-8.9)	(1.5-4.8)	(3.9-8.7)	
Patients with all forms of TB among those screened (D/A) per 100,000	82.7	92.7	87.4	995.4	364.1	692.9	107.0
95%CI	(78.1-87.3)	(87.6-97.8)	(84.0-90.8)	(914.1-1076.7)	(221.6-506.6)	(495.5-890.3)	
SS+TB patients among those screened (E/A) per 100,000	51.7	59.0	55.1	358.0	203.9	353.8	62.1
95%CI	(48.1-55.3)	(54.9-63.1)	(52.4-57.9)	(309.1-406.9)	(97.2-310.6)	(212.5-495.1)	
% SS+ve TB patients among total number of TB patients (E/D)	62.5%	63.7%	63.1%	36.0%	56.0%	51.1%	58.0%
95%CI	(59.8-65.2)	(61.0-66.3)	(61.2-65.0)	(32.0-40.0)	(36.5-75.5)	(36.8-65.4)	
Number Needed to Screen to find one TB patient all forms (NNS1) (A/D)	1209	1079	1144	100	275	144	934
95%CI	(1145-1280)	(1022-1142)	(1101-1190)	(93-109)	(197-451)	(112-202)	
Number Needed to Screen to find one SS+TB patient (NNS2) (A/E)	1934	1695	1813	279	490	283	1612
95%CI	(1808-2080)	(1584-1821)	(1727-1908)	(246-324)	(322-1029)	(202-471)	

>2-week cough – screening approach using a history of cough of 2 or more weeks with or without other TB symptoms; >24-hour cough – screening approach using a history of cough of >24 hours as well a history of any of the following symptoms fever, weight loss and drenching night sweats. 95% CI – 95% Confidence intervals

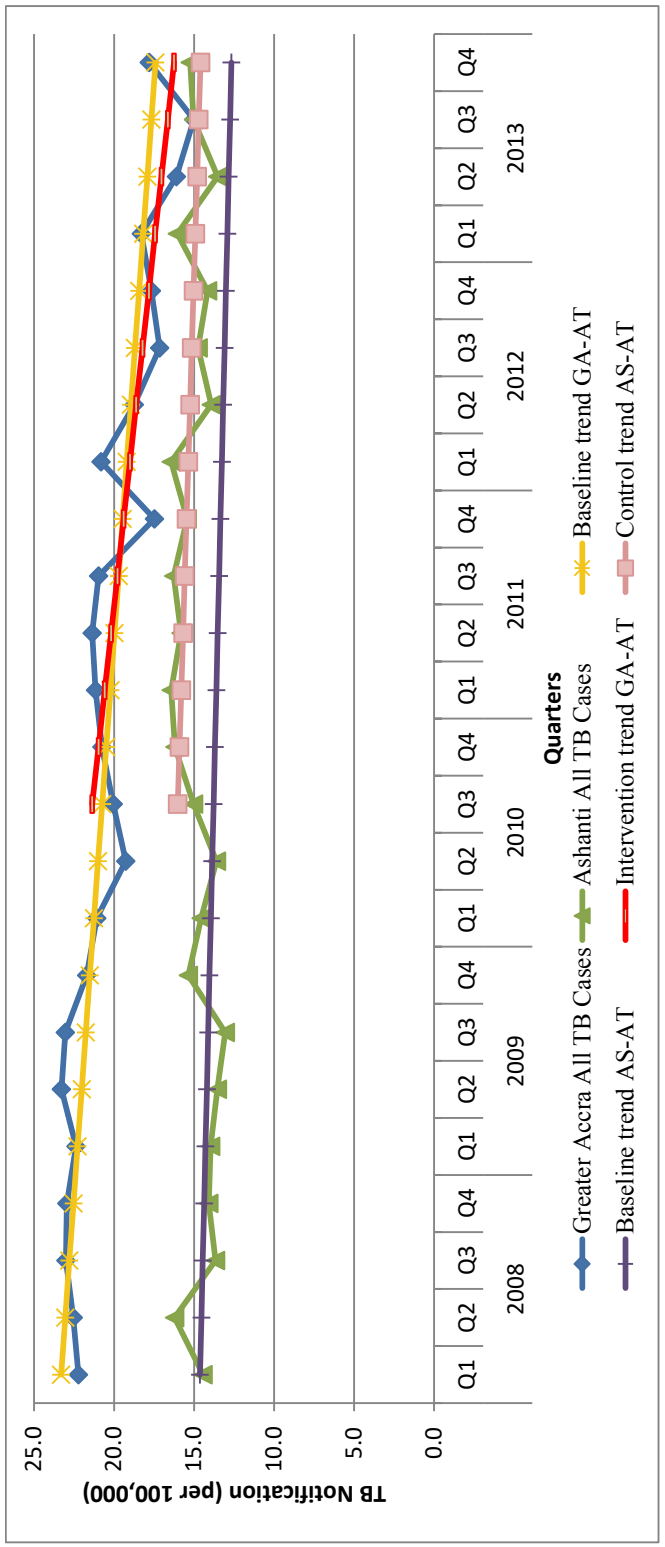

Fig. 3 Quarterly notification rates of all TB cases for Greater Accra (GA) and Ashanti (AS) Regions with linear-trend lines from 2008 to 2013

Q: Quarter, GA-AT: Greater Accra all TB cases, AS-AT: Ashanti all TB cases. Baseline trend – refers to the linear-trend line drawn to project TB notification expected during the intervention period for both regions using quarterly historical TB notification data from Greater Accra and Ashanti Regions during the baseline period (first quarter of 2008 up to the second quarter of 2010) before the intervention started. Intervention trend – refers to the linear-trend line drawn through the actual TB notification data from Greater Accra Region during the intervention period (third quarter 2010 to fourth quarter 2013). Control trend – refers to the linear-trend line drawn through the actual TB notification data from Ashanti Region during the period (third quarter 2010 to fourth quarter 2013).

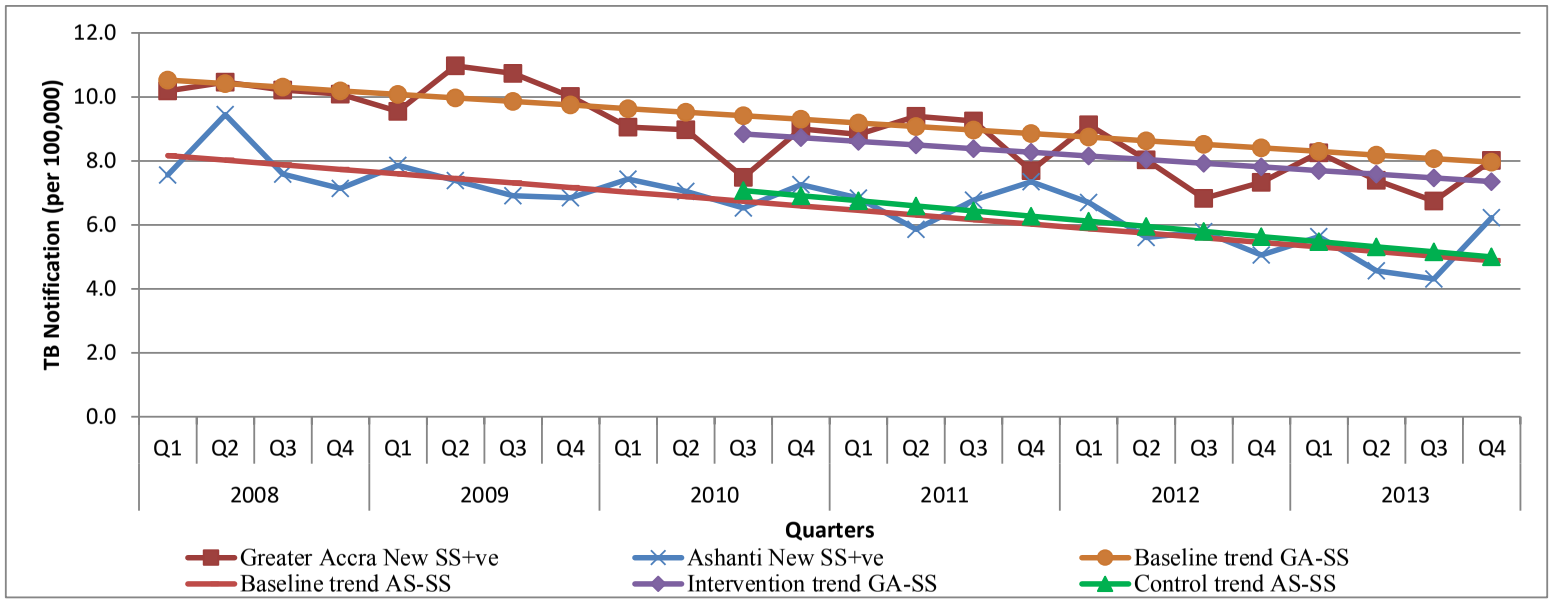

Fig. 4 Quarterly notification rates for sputum smear positive cases for Greater Accra (GA) and Ashanti (AS) Regions with linear-trend lines from 2008 to 2013

Q: Quarter, GA-SS: Greater Accra sputum smear positive cases, AS-SS: Ashanti sputum smear positive cases

Baseline trend – refers to the linear-trend line drawn to project TB notification expected during the intervention period for both regions using quarterly historical TB notification data from Greater Accra and Ashanti Regions during the baseline period (first quarter of 2008 up to the second quarter of 2010) before the intervention started. Intervention trend – refers to the linear-trend line drawn through the actual TB notification data from Greater Accra Region during the intervention period (third quarter 2010 to fourth quarter 2013). Control trend – refers to the linear-trend line drawn through the actual TB notification data from Ashanti Region during the period (third quarter 2010 to fourth quarter 2013).

Discussion

Various TB case finding strategies across different population groups globally have been implemented as a means of diagnosing undetected TB cases that would otherwise be difficult to identify relying only on symptomatic patients reporting to the health facility for diagnosis [21]. The yield of TB cases is affected by several factors including the screening and diagnostic methods, setting and the population being screened, which could range from those considered to be at high risk for TB to the general population. The Ghana NTP implemented a TB case finding intervention across four different groups: OPD attendants, PLHIV, diabetics, and contacts of TB cases. Among the OPD attendants, two screening approaches, which differed on duration of cough, were used. As expected, more people with presumptive TB were identified and tested for TB among the OPD clinics using the >24 hour-cough screening approach, and comparatively fewer numbers of people needed to be screened to detect one TB case (all forms). Across the four groups, the number that needed to be screened to identify a TB case was lowest among PLHIV and highest among the OPD attendants. Despite implementing this initiative, the decreasing trend in the TB notification for all forms of TB noted in the preceding two years before the start of the intervention continued. A similar phenomenon was noted in the control population.

Screening by using more sensitive methods results in an increase in the pool of presumptive TB cases from which actual cases can be identified, because the net is cast wider. This is, however, at the expense of specificity [22]. It was therefore not surprising that our study showed that compared to the OPD attendees with cough of 2 weeks or more, the OPD attendants with a shorter duration of cough yielded a higher proportion of candidates for TB testing but a lower proportion of TB cases among those tested. Yet our overall yield of 0.72% of OPD attendees identified as presumptive TB cases to be tested for TB was quite low when compared to the 2.6% to 3.5% range found in studies on the yield of potential TB cases among OPD attendees in Tanzania and Kenya [23-25]. There could be a number of reasons for this marked difference. For one, different screening criteria were used. For another,

unlike strictly supervised study settings with screening conducted over shorter periods of time our screening occurred over a period of three and a half years and under programmatic settings with inherent challenges. It is therefore possible that the yield could have been higher since under the programmatic conditions, there may have been gaps in following all steps in the algorithm possibly contributing to missed opportunities to screen all patients to ensure that all presumptive cases identified underwent sputum smear microscopy.

Given the higher risk of TB among PLHIV and diabetics and by using the screening criteria of cough of any duration and at least one TB suggestive symptom, we found higher proportions of presumptive TB cases among the attendees in the HIV and DM clinics than in the OPD [7,8]. It was noted that presumptive TB cases among PLHIV had the highest rate of testing for TB. This is indicative of good adherence to the set guidelines, requiring PLHIV with symptoms suggestive of TB to be investigated [26].

In our study the proportion with sputum smear positive results of those tested from the OPD (8.6%) fell within the range of what was found in two studies from Tanzania (6.1%) and Ethiopia (13.5%) [27,28]. The variation could be due to the differences in settings (a tertiary facility in Tanzania and 5 public and private health facilities in Ethiopia) and the different durations of data collection. The rate of sputum smear positive results among PLHIV patients tested for TB was similar to what was found in the study by Seni and colleagues in Tanzania [27].

The proportion of sputum smear positive TB cases among all forms of TB varies in different reports and may be related to the population studied, the setting, the sensitivity of the diagnostic method and microscopy quality assurance issues [29-35]. Consequently, the diverse circumstances and populations studied contribute to the range of 31.6% to 77% found in studies from different parts of the world [29-35]. The proportion of SS+ve TB among the various categories of patients in our study fell within this range. The finding of the PLHIV TB patients having relatively lower prevalence of SS+ve positive is not out of place, since this falls in line with studies reporting higher prevalence of sputum smear negative TB in PLHIV [36-38].

The ranking of the number of TB cases identified per 100,000 populations of the various groups in our study resonates with what others have found, with OPD

attendees having the lowest and PLHIV the highest and more than 10 times the figure for the OPD attendees [9,39]. Overall, slightly more TB cases (all forms) were identified among the outpatients screened in the >24 hour-cough approach (92.7 per 100,000 outpatients versus 82.7/100,000). Although the difference was significant, it is important to consider the implications of the increased burden on the laboratory having to test so many presumptive TB patients. The numbers needed to screen to find one TB patient (NNS) for all the categories of patients was in sync with what one would find in a low to moderate TB incidence country like Ghana [15].

The discovery that the case finding intervention did not demonstrate an increase in TB case notification in the intervention population compared to the comparator and even showed a downward trend compared to historical data was unexpected. It is possible that the number of extra cases was too small to see an effect. Another possibility is that some of the TB patients detected during the program would otherwise also have been detected though perhaps a bit later. It is also important to note that the intervention was facility-based and used symptoms screening to identify potential TB cases for testing, which also limited its ability to identify TB patients not exhibiting these TB suggestive symptoms and those not accessing the facilities for care. Prevalence surveys have demonstrated that 50% or more of those with bacteriologically confirmed TB may not have symptoms commonly used to presume TB [4, 40]. Considering that the 2013 TB prevalence survey in Ghana showed an estimated TB prevalence of 290 cases per 100,000 which was more than quadruple the WHO estimate at the time of the project, a lot more needs to be done to improve case finding among the general population and groups at high risk of contracting TB including miners, PLHIV and diabetics, prisoners and contacts of TB patients [41,42] . Some of these key groups may also not access health care regularly and therefore may not be reached in interventions such as these which are facility based. As reiterated by the End TB Strategy, it is imperative to ensure universal access to early and accurate diagnosis of TB which among others includes education to trigger care seeking among those with symptoms suggestive of TB and screening among high risk groups [42]. In employing these active and enhanced case finding methods, there is a need to scale up the use of more sensitive diagnostic methods beyond sputum smear

microscopy that include new molecular diagnostics and employ additional screening tools beyond symptom screening such as chest X-ray to identify other forms of TB including extra-pulmonary and bacteriologically negative forms as well as TB in children [21,42].

Since the projection from the baseline historical data indicated a downward trend similar to the decreasing TB case notification nationally over the intervention years, it is also possible that there might be some underlying programmatic constraints contributing to fewer cases being detected [41]. This could be a subject for further investigation. Contrary to study settings in which there is meticulous supervision, monitoring and measures put in place to ensure adherence to protocols, this intervention was implemented under programmatic conditions.

There are some limitations to this study. Since it was a retrospective assessment of an intervention that was not implemented under rigorous trial conditions, some elements of bias, such as the assignment of the screening approach to the facilities, could have been introduced in the execution of the intervention. Secondly, validation of the diagnosis of TB cases was not possible. Finally, the study did not explore the possible events and prevailing circumstances that may have affected the outcomes and thrown light on some of the findings, such as suspension of OPD services that occurred as a result of industrial actions by health workers or shortage of diagnostic reagents during the intervention period. Despite these drawbacks, to our knowledge this study is the first in Ghana to assess the yield of TB cases from symptomatic screening of different categories of patients. Further study building on the finding of this paper should explore treatment enrolment and outcomes of the TB cases identified from the different settings.

Conclusion

In this study the screening approach using a shorter duration of cough (>24 hours) had a somewhat better yield of TB cases and appears feasible for implementation. The increased workload on the laboratory, however, warrants further study to assess whether this is outweighed by the higher number of TB cases identified. This study

reiterated that the yield of TB cases was highest among PLHIV, contacts of TB patients and diabetics screened but the vast majority of cases were detected in general OPDs. Though in Ghana screening of PLHIV for TB is being implemented to an appreciable extent in HIV clinics, it is important to ensure that it is being done systematically. Screening of contacts of TB cases and diabetics has been virtually non-existent. Since it is already a policy in Ghana to undertake home verification of TB cases before the initiation of treatment, tagging along screening of the contacts of the TB cases during these home visits could facilitate the identification of potential cases in this high risk group. Greater collaboration between the NTP and the Non-Communicable Disease Control Program could facilitate the introduction of TB screening in all diabetes clinics. When considering a TB screening program, it is essential to simultaneously look at the overall health system functions and enhance capacity to facilitate early detection. This would involve ensuring that more sensitive screening and diagnostic tools such as chest X-rays (CXR) and Gene Xpert (GXP) are available where needed throughout the system. The NTP is rolling out programs to further improve case detection among risk groups and including the deployment of GXPs and the launch of a digital X-ray project in health facilities [41]. Considering that the study could not demonstrate any impact on overall case notification, further research is needed to assess the impact of the introduction of these initiatives which use more sensitive methods for screening and diagnosis of TB on yield and notification.

While the study could not demonstrate any impact on overall case notification, in view of the significant pool of TB cases yet to be diagnosed sole reliance on identifying TB among patients presenting with TB suggestive symptoms or those accessing care at health facilities may limit timely diagnosis creating the conditions for disease transmission and worse outcomes.

Abbreviations

AS, Ashanti; CIDA, Canadian International Development Agency; CXR, chest X-ray; DM, diabetes mellitus; ECF, enhanced case finding; HIV, Human Immuno-deficiency Virus; GA, Greater Accra; GXP, Gene Xpert; NNS, number needed to screen; NTP, National Tuberculosis Control Program; OPD, Out-patient department; PLHIV, persons living with HIV; SS+ve, sputum smear positive; TB, Tuberculosis; WHO World Health Organization.

Acknowledgements

The authors wish to thank the staff and patients of Korle Bu Teaching Hospital, Ridge Hospital, Achimota Hospital, Legon Hospital, Maamobi Hospital, Princess Marie Louie Hospital, La General Hospital, Kaneshie Polyclinic, Mamprobi Polyclinic, Ussher Polyclinic, Dansoman Polyclinic for their wonderful support and cooperation in making this report possible. Thanks also go to Dr. Salah Ottmani and Dr. Jacob Creswell for the tremendous support in facilitating the implementation of the TB case finding initiative in Ghana. Profound appreciation goes to the Canadian International Development Agency for funding the intervention. SAO, KL and MU are WHO staff members. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of WHO.

Ethical approval and consent to participate

Ethical clearance for the study was obtained from the Ghana Ministry of Health Research Division Ethical Review Board. There was no contact with individual patients so consent to participate is not applicable.

Funding

The TB case-finding intervention in the health facilities in Accra Metropolis was funded by Canadian International Development Agency with technical support from WHO. There was, however, no funding allocated to support these analyses.

Availability of data and materials

The data for this study is available at the Ghana National TB Control Program and not accessible online. The data may be made available upon written request to the NTP through the authors, provided the request complies with the Ethical Review Board guidelines.

Authors' contributions

SAO conceptualized and drafted the paper. AS, SD, GM, FA, AT and SAO helped to collect the data. SAO, AT and MB undertook the statistical analysis. FB, NNHN, PK, MB, MU, KL and SAO contributed to the evaluation design and revising drafts of the paper. All authors approved the manuscript.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Author details

1World Health Organization Country Office, 29 Volta Street Airport, Airport Residential Area, P.O. Box MB 142 Accra, Ghana. 2National Tuberculosis Control Program, Accra, Ghana. 3KIT Health, Royal Tropical Institute (KIT), Amsterdam, The Netherlands. 4Global TB Programme, WHO, Geneva, Switzerland. 5Ghana Health Service, Accra, Ghana. 6Department of Global Health, Academic Medical Centre, Amsterdam Institute of Global Health and
Development, Amsterdam, The Netherlands.

Received: 14 August 2016 Accepted: 21 November 2017
Published online: 01 December 2017

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Chapter 3

Yield of tuberculosis among household contacts of tuberculosis patients in Accra, Ghana

Sally-Ann Ohene, Frank Bonsu, Nii Nortey Hanson-Nortey,
Adelaide Sackey, Samuel Danso, Felix Afutu, Paul Klatser, Mirjam Bakker,

Infectious Diseases of Poverty (2018) 7:14
https://doi.org/10.1186/s40249-018-0396-5

Abstract

Background: The End TB Strategy calls for systematic screening of selected high-risk groups including contacts of tuberculosis (TB) cases to facilitate early TB case detection. Contact investigation is not usually routinely practiced in low TB burden countries, such as Ghana, with consequent paucity of data on the yield of TB case detection from such interventions. This study's objective was to document the outcomes and feasibility of implementing contact investigation activities under programmatic conditions in Ghana.

Methods: Retrospective analyses were conducted of abstracted data from the National TB Program, following a contact investigation intervention for TB cases diagnosed in 10 facilities in Accra from June 2010 to December 2014. Various proportions and yield from number of contacts needed to screen (NNS) and number needed to test (NNT) to detect a TB case were assessed.

Results: Overall, out of the 8,519 listed contacts of 3,267 index cases, 8,166 (96%) were screened and 614 (7.5%) were identified as presumptive TB. Out of these, 438 (71%) underwent sputum smear microscopy/evaluation and 53 TB cases were diagnosed. Of these, 56.6% were males, and 49% had sputum smear-positive TB, 38% had sputum smear-negative TB, and 7% had extrapulmonary TB. The NNS and NNT to detect a TB case of all forms were 154 and 8, respectively. The proportion of TB cases with contacts listed and proportion of contacts screened annually were 88 – 96% and 83 – 100%, respectively. The proportion of presumptive TB cases tested and proportion of TB cases diagnosed among contacts tested that were 100% and 36%, respectively, in 2010 dropped to 40% and 14%, respectively, by 2014.

Conclusions: The study demonstrates that contact identification and prioritization components of a contact investigation were feasible, but overall yield of TB cases may have been lower due to the declining rate of clinical evaluation of presumptive TB contacts over time. Addressing barriers to accessing appropriate diagnostic tests may enhance yield from contact investigation in Ghana.

Keywords: Ghana, tuberculosis, tuberculosis contact investigation, screening

Background

Tuberculosis (TB) remains a disease of public health concern globally. The World Health Organization (WHO) Global TB Report 2016 shows that in 2015, there were an estimated 10.4 million new TB cases worldwide [1]. A significant portion of this figure, more than 40% (about 4.3 million), is however not notified. This pool of unidentified TB cases poses a risk for further transmission of TB. Consequently to ensure that this high burden of undiagnosed TB is reduced, it is imperative that strategies that enhance TB case detection with subsequent appropriate treatment are scaled up.

Contact investigation has been proposed as a worthwhile strategy to enhance early detection of TB cases and reduce transmission in high incidence localities [2, 3]. Contacts of TB cases are at a higher risk of acquiring TB than the general population because of their direct exposure to airborne droplets containing *Mycobacterium tuberculosis* [4]. Reviews of studies from low- and middle-income settings looking at contact investigation for TB have reported the prevalence of active TB in all contacts to be in the range of 3.1 – 4.5% and that for microbiologically-proven TB to be 1.2 – 2.3% [2, 4]. While in high-income countries, contact investigation is common practice, the same cannot be said for lower-income settings, where resource constraints and inadequate procedures pose as challenges [3]. Furthermore, given the paucity of data on the yield and contribution of TB case detection from contact investigation in these settings, the ability to assess the contribution of implementing this intervention in reducing transmission in these countries is also limited [3].

One of the challenges identified in the 2009 – 2013 National Tuberculosis Control Program (NTP) Strategic Plan was the low TB case detection rate in Ghana, estimated at 36% of pulmonary smear positive cases [5]. Therefore, improving case detection was targeted as an area for intervention using different innovative strategies. Investigation of contacts of TB cases was among the activities identified to be implemented in the Ghana TB strategic plan, as there was no structured and

systematic way of conducting contact tracing in the country. In 2009, the WHO with funding from the Canadian International Development Agency (CIDA) supported a number of case detection initiatives implemented by the NTP in health facilities in the Accra metropolis in Ghana [6, 7]. Among them was a TB contact investigation component, which was initiated in 2010 and supported until 2013.

Given the dearth of data on the subject in a number of African countries and Ghana in particular, the objective of this paper is to document the outcomes of the contact investigation activities implemented in an urban area, highlighting the feasibility of implementing such an intervention under programmatic conditions.

Methods

Study design and setting

This study is a retrospective analysis of the performance of a contact investigation intervention implemented by the NTP in 10 facilities in Accra, the capital of Ghana, which has a population of 1.5 million.

Tuberculosis control in Accra, as in the rest of the country, is supported by the NTP, which has the mandate of leading the health sector response to TB control [5]. The NTP staff at the national level comprising the program manager and technical officers liaise with TB coordinators and multidisciplinary TB teams at subnational levels to facilitate TB control activities. At community and facility levels, there is a dedicated TB focal person who is supported by community health workers, volunteers, and treatment supporters to implement activities including registration, home verification, management, and follow-up of TB patients. The control of TB is integrated into all levels of care with 100% directly observed treatment, short-course (DOTS) coverage.

In the years preceding the initiative, the TB case notification rate ranged from 57 to 64 per 100,000, with treatment success reaching 85% [6]. Sputum smear microscopy was the mainstay of TB diagnosis, though steps were being taken to make culture services available. GeneXpert had also not been introduced for TB diagnosis

at that time. Case detection was mainly passive with symptomatic patients self-reporting at health facilities.

Before the introduction of the WHO/CIDA supported case finding initiative, there was no structured or systematic way of conducting contact tracing. As a result, systems put in place by the NTP to facilitate this exercise included the development of operating guidelines for conducting contact investigation, a contact investigation register, a questionnaire for screening of contacts, and a monthly contact investigation reporting form that the staff submitted to the NTP. Staff members in the participating facilities were also trained in the contact investigation operating guidelines to undertake the exercise.

Following the identification of an index TB case, defined in the guidelines as a confirmed patient with sputum smear-positive (SS+ve) TB, sputum smear-negative (SS-ve) TB, or extrapulmonary TB (EPTB), the person was requested to list all their contacts. The definition of a contact was derived from what was used in the Ghana Demographic and Health Survey: namely, persons living together in the same house sharing the same housekeeping arrangements and eating together [8]. With the consent of the index patient, the designated contact investigation focal person at the facility, usually a community health officer, visited the home at an agreed time with the list of contacts to do conduct screening for. The index patient also had the option of coming to the health facility with the contacts to be screened. Using a questionnaire that asked for symptoms of cough, fever, drenching night sweats, and weight loss, the contacts were screened and assigned a score depending on the responses given. Those who were suspected to have TB were requested to undergo sputum smear examination at the nearest facility. In these cases, two specimens of sputum were collected, one on the spot and the other at least one hour later or early in the morning within 24 hours, for examination under a microscope for acid fast bacilli (AFB). A diagnosis of SS+ve TB was made if at least one sample was found to be positive for AFB, defined as at least one AFB identified in 100 fields. A clinician diagnosed SS-ve TB after clinical examination and X-ray findings suggestive of TB, following SS-ve microscopy results. Contacts who were subsequently diagnosed with TB were referred for treatment at the nearest TB DOTS facility. In households with contacts

aged under five years, the children were referred to an experienced clinician or a pediatrician for a thorough examination. If active TB disease was confirmed, the child would be put on full-course anti-TB treatment. The guidelines indicated that those children who were not found to have active TB disease were to be put on isoniazid prophylaxis for six months at a dose of 10 mg/kg.

Data collection and analyses

The data repository of the NTP was the key source of data for these analyses. The following data, which each facility conducting contact investigation submitted on a monthly basis to the NTP, were compiled into annual data: the number of index cases identified and those for whom contacts were listed, the number of contacts listed, the number of those listed who were screened, the number identified as presumed TB among those screened, and the number tested and diagnosed with TB. The data analyzed covered the period from June 2010 to 2013, as well as 2014 during which funding for the project officially ceased, but facilities continued contact investigation of index cases.

Among those diagnosed with TB, the sex of the patient and the type of TB were also reported (SS+ve, SS-ve, or EPTB). Children who could not undergo smear microscopy but who were diagnosed clinically as having TB had their type of TB categorized as 'other'. There was no age variable on the reporting form and therefore the ages of the contacts who were diagnosed as TB patients were not available for analyses.

The key outcome of the analyses was the prevalence of TB cases among contacts of index TB patients. The following indicators were assessed: proportion of index cases for whom contacts were listed, proportion of contacts listed screened for TB, proportion of contacts suspected to have TB (also referred to as presumed TB contacts), and proportion of presumed TB contacts who underwent sputum smear microscopy. The number of contacts needed to screen (NNS) to identify a TB case (contacts screened/new cases) overall and per year, and the number of contacts needed to test (NNT) to identify a TB cases (contacts tested/new cases) were also

calculated. Using the chi-square test, the types of TB in terms of sex were analyzed. The level of statistical significance was pegged at a *P*-value of <0.05.

The Ministry of Health Research Division Ethical Review Board gave ethical clearance for the study, while the NTP granted permission for the use of data. Confidentiality was maintained in the conduct of the analyses.

Results

From June 2010 to December 2014, 3,505 index TB patients were identified from the facilities participating in the contact investigation (see Figure 1). Contact listing was undertaken for 3,267 (93%) patients.

On average, 2.5 contacts were listed per index patient. Approximately 96% of the contacts listed (8,166) were screened using the questionnaire and 614 were suspected to have TB (7.5%). Of these, 71% underwent sputum smear microscopy/were evaluated for TB, with 53 cases of TB being diagnosed, representing 12.2% of those evaluated. Overall, the prevalence of TB among the contacts screened was 0.65%. To identify one TB case, the NNS was 154 and the NNT was 8.

Among the contacts diagnosed with TB, 30 (56.6%) were males. Almost half (49%) were SS+ve TB cases, representing 5.9% of the contacts tested/evaluated for TB. Sputum smear was negative in 38% of the contacts diagnosed with TB while 7% had extrapulmonary TB. More males than females had SS+ve TB, while reversely more females than males had SS-ve TB (see Figure 2). The differences across sex, however, were not statistically significant. All four EPTB cases diagnosed were males. Three of the cases (5.7%) were clinically diagnosed TB.

Compared to the other years, there was a relatively smaller number of index TB cases in 2010, as the intervention started mid-year (see Table 1).

The number of contacts suspected to have TB was also comparatively smaller in 2010, however, the yield of TB cases among the contacts screened was the highest. The highest number of contacts listed, screened, and tested for TB was in 2012.

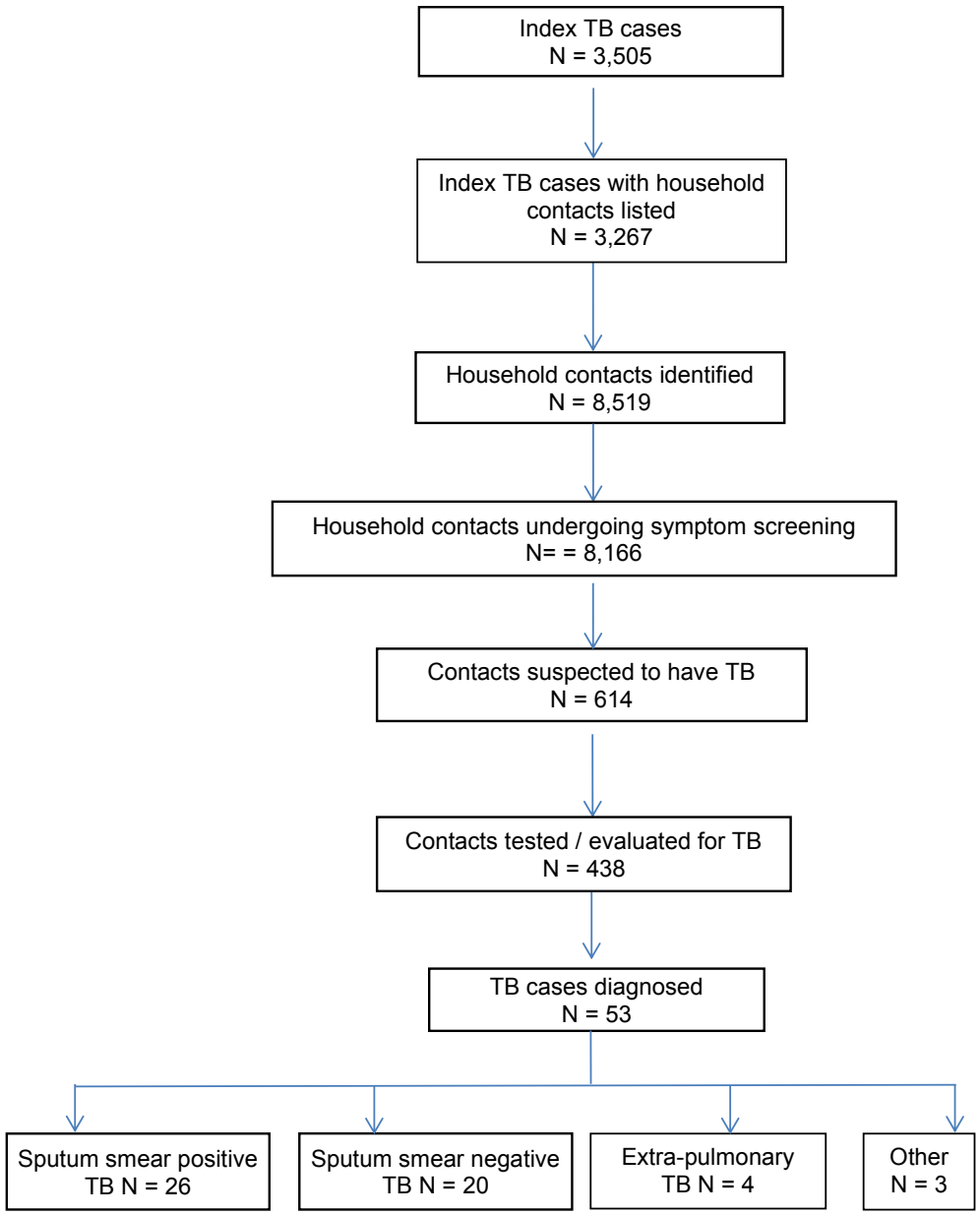

Fig. 1 Flow diagram showing outcome of contact investigation 2010–2014, Accra

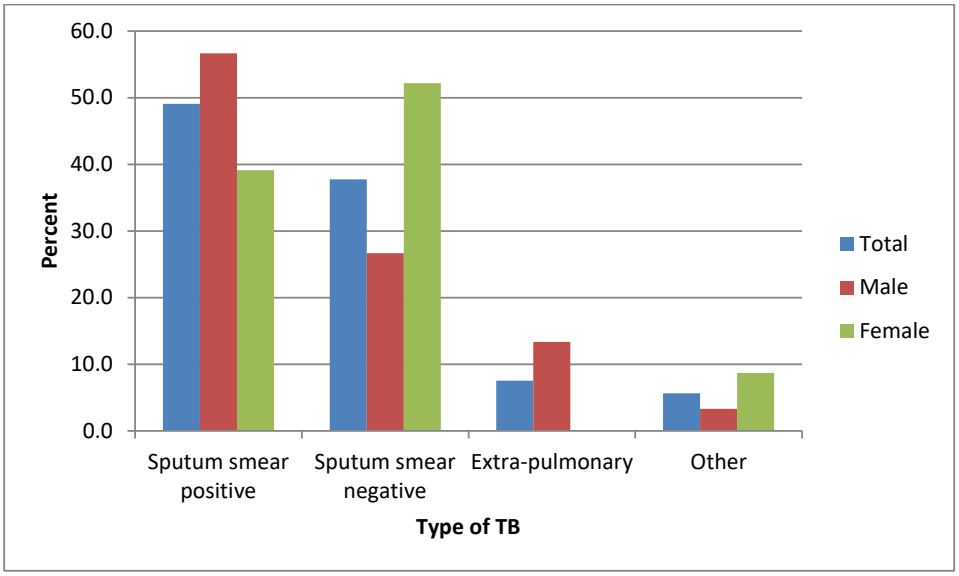

Fig. 2 Type of TB diagnosed among contacts of index TB patients by gender

Table 1: Outcome of TB contact investigation in Accra, 2010–2014

Year	Number of index TB cases registered	Number of index cases with contacts listed	Number of contacts listed	Number of contacts screened	Number of contacts suspected to have TB	Number of contacts suspected with TB who were tested	TB cases identified	Prevalence of TB among contacts screened (%)	NNS	NNT
2010*	359	316	811	679	28	28	10	1.5	68	2.8
2011	873	826	2,051	1,953	136	136	15	0.8	130	9
2012	872	794	2,285	2,219	175	153	11	0.5	202	13.9
2013	797	749	1,930	1,945	139	64	9	0.5	216	7
2014**	604	582	1,442	1,370	136	57	8	0.6	171	7
Total	3,505	3,267	8,519	8,166	614	438	53	0.65	154	8

***The data from 2010 reflects only seven months of that year, from June to December.**
****In 2014, contact investigation activities continued for the entire year up to December 31 even though funding for the project ceased.**

The proportion of TB cases with contacts listed each year was stable over the course of the five years, ranging from 88% to 96% (see Figure 3). Starting from 100%, the proportion of contacts suspected to have TB who were tested dropped by more than half to 40% in 2014. The year 2010 recorded the highest proportion of TB cases diagnosed among the contacts tested (36%).

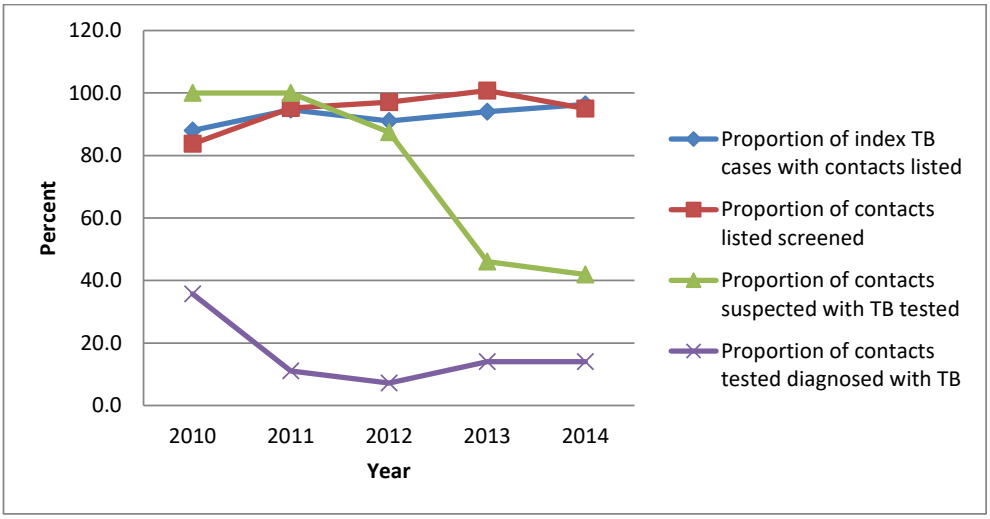

Fig. 3 Performance of contact investigation conducted among index TB patients in Accra from 2010 to 2014

Discussion

This study reviewing a five-year contact investigation intervention conducted in Accra among index TB patients showed that contacts were listed for more than nine out of ten index TB cases. All but 4% of the contacts listed underwent symptomatic screening. Among those screened, seven out of ten of those suspected to have TB underwent sputum smear microscopy, ultimately yielding a TB prevalence of 0.65% among the contacts screened.

The average number of contacts identified per index TB case in our study was consistent with what others have found [4, 9, 10]. While other studies have reported higher figures for contacts identified per index TB case, it is worthwhile to

note that various definitions of index cases and household contacts may account for the discrepancy of figures reported in different studies [3, 4, 11, 12, 13]. In our study, the definition of a household contact did not specify the period that the contact was in close proximity to the index case and it is not known whether this had an effect on the outcome. The consensus definition of household contacts is "a person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before commencement of the current treatment episode" [3]. For standardization and comparability, it is recommended that TB control programs apply this definition to enhance monitoring and evaluation, and contribute to evidence on the impact of contact investigations [3].

Over the course of the contact investigation initiative, the proportion of listed contacts who had symptom screening, identified as presumptive TB and eventually tested for TB, fell within what was found in studies conducted in other countries [10, 14, 15]. Contact investigation of TB patients has been shown to identify significant numbers of TB cases in various contexts and improve TB case detection depending on the diagnostic tools used [9, 15, 16]. Comparative meta-analyses of TB case finding interventions in several low- and middle-resource high burden TB countries using sputum smear microscopy to diagnose TB showed that contact investigation interventions contributed from 0.1% to 14.2% of notified SS+ve TB cases, with a yield of 0.6% to 4.8% of all forms of TB diagnosed through contact investigation [15]. The yield from our study, which also used sputum smear microscopy as the main diagnostic procedure, falls within this range, even though Ghana is a low burden TB country. Blok *et al*. showed that the use of less restrictive criteria for identifying those eligible for sputum examination was associated with a higher yield of TB cases among contacts [15].

Nevertheless, the use of symptom screening and the low sensitivity of sputum smear microscopy in the diagnosis of TB limit the opportunity to detect TB early in high-risk groups, including contacts. This highlights the importance of promoting more sensitive screening tools, such as X-ray, to identify those who need to be further investigated for TB [17, 18]. The use of more sensitive diagnostic methods beyond conventional microscopy further improves the yield of TB cases among those

suspected to have TB. It is therefore possible that the yield observed in our study may also be related to the use of conventional microscopy, which has relatively lower sensitivity than other TB diagnostic methods, yet was the mainstay of TB diagnosis at the time [19].

In consonance with other studies, the proportion of males and females among the contacts identified with TB were similar [16, 20]. While in our study the proportion of SS+ve and SS-ve TB cases were similar, Gashu and colleagues found that SS-ve TB was predominant among contacts diagnosed with TB in Ethiopia [11]. Blok *et al*. found that SS+ve index cases correlated with a higher percentage yield of SS+ve contacts compared to SS-ve index cases [15]. It is therefore plausible that there may have been a relatively higher proportion of SS+ve cases among the index patients in our study and this possibly explains the proportion of SS+ve cases among the contacts. Shapiro *et al*. also found a higher proportion of SS-ve cases in South Africa, but all these patients were found to be culture positive, highlighting the importance of using more sensitive tests such as culture or GeneXpert to improve detection of SS-ve TB, in cases where smear microscopy results are negative [16, 21].

The additional benefit of these tests is the ability to identify drug-resistant TB (DR-TB) [19]. While DR-TB cases had been identified at the time of the study in the country, the prevalence was not known. Given that TB in contacts of DR-TB cases is also likely to be drug resistant, the availability of more sensitive diagnostic tests for TB will enable the detection of drug resistance among contacts diagnosed with TB [19].

In our study, the NNS over the years was within what has been reported from contact investigation studies conducted in low TB incidence countries [22]. The NNT to identify one TB case in the initial year of our study was comparable to what was reported by Jerene *et al*. [14]. The observation that in 2010, the year the initiative started, both NNS and NNT were the lowest and the yield of TB cases among the contacts suspected to have TB was the highest may suggest closer adherence to the protocols following the training that kickstarted the initiative.

It can be said that the first component of contact investigation, which consists of contact identification and prioritization, was satisfactorily carried out in the

intervention reported on in this paper [3]. It demonstrates the feasibility of successfully listing contacts and screening those suspected to have TB and therefore eligible for testing, as these rates remained high in the intervention years and the year afterwards. As home verification of TB before initiation of treatment is routine practice, as instructed by the NTP, adding contact identification and prioritization was practical and thereby contributed to this achievement.

The same, however, cannot be said for the second component of contact investigation, namely contact clinical evaluation across the period of assessment: there was a noticeable drop of more than 50% in the proportion of presumed positive TB contacts tested/evaluated in the final year of the intervention (2013) and in the following year. The decrease, which could have been due to several reasons, suggests challenges with the steps in the referral system as well as functional laboratory diagnostic services, ranging from limited follow up of presumed TB cases, to ensuring arrival at the microscopy center for testing, to shortages of laboratory diagnostic reagents. This raises concerns of missed opportunities to diagnose TB and the overall effect on the yield of TB cases among the contacts, necessitating further investigation to identify the contributory factors to the decrease.

The End TB Strategy calls for the removal of barriers to seeking care so it is imperative that steps are taken to ensure that presumptive TB cases, who have interacted with the healthcare system, benefit from early and appropriate diagnostic tests as soon as possible to reduce the risk of advanced disease and transmission [17]. Apart from identifying active TB cases, contact investigation can also be a means of preventing disease transmission, as the effective treatment of TB diagnosed among contacts will limit the potential of these persons being a source of infection to others.

With the exception of information on the sex of the TB cases identified among the contacts and the type of TB diagnosed, the database from which the analyses for this study were conducted had no disaggregation by sex for the rest of the measures; consequently there was no information on the sex of the index TB cases nor the contacts listed or evaluated. There was also no data on age for any variable. This limitation precluded the ability to conduct demographic or disaggregated analyses by the type of TB of the index case and especially children, considering that

a considerable proportion of childhood TB is diagnosed through household contact investigation [23]. Another limitation of the study is that there was no examination of the possible prevailing factors that accounted for some of the changes in the trends observed in the findings. Despite these limitations, the strength of this paper lies in the documentation of the outcomes of the various components of contact investigation, namely contact identification and prioritization and contact clinical evaluation, over a number of years in a low TB incidence country, where contact investigation has not been routinely practiced.

Conclusions

This study demonstrates that the contact identification and prioritization components of contact investigation were feasible, but the overall yield of TB cases may have been lower than it could have been if the rate of clinical evaluation of presumptive TB contacts had been sustained over time. Contact investigation as a case finding initiative could be enhanced if actively conducted with the adoption of standardized protocols and sensitive screening tools, training of relevant staff in their use, and removal of barriers to contact screening. Where presumptive TB cases have been identified, it is imperative for the NTP to address possible barriers to accessing recommended sensitive diagnostic tests to enable the maximum yield from contact investigation to be achieved. In the event of scaling up contact investigation, it is also recommended that the NTP widens the scope of the variables in the data collection tools to include minimum key variables such as age (especially children aged under five years), sex, type of TB diagnosed, human immunodeficiency virus (HIV) status of contacts diagnosed with TB and children aged under five years, and persons living with HIV initiated on isoniazid preventive treatment. This will facilitate meaningful analyses of outcomes in specific groups, and subsequent monitoring and tracking of program performance indicators, as per the WHO guidelines.

Additional file

Additional file 1: Multilingual abstracts in the six official working languages of the United Nations. (PDF 578 kb)

Abbreviations

AFB: acid fast bacilli; CIDA: Canadian International Development Agency; DOTS: directly observed treatment, short-course; DR-TB: drug-resistant tuberculosis; EPTB: extrapulmonary tuberculosis; HIV: human immunodeficiency virus; NNS: number of contacts needed to screen; NNT: number of contacts needed to test; NTP: National Tuberculosis Control Program; SS+ve: sputum smear-positive; SS-ve: sputum smear-negative; TB: tuberculosis; WHO: World Health Organization

Acknowledgements

The authors wish to thank the staff and patients of the Ridge Hospital, Achimota Hospital, Legon Hospital, Maamobi Hospital, Princess Marie Louise Hospital, La General Hospital, Kaneshie Polyclinic, Mamprobi Polyclinic, Ussher Polyclinic, and Dansoman Polyclinic for their immense contribution to the TB case finding initiative and, ultimately, this study. The authors are also grateful to Dr. Mukund Uplekar, Dr. Knut Lönnroth, Dr. Salah Ottmani, and Dr. Jacob Creswell for their valuable technical assistance in the implementation of the TB case finding initiative in Ghana. The CIDA is duly acknowledged for funding the TB case finding intervention.

Funding

The TB case finding intervention was funded by the CIDA, with technical support from the WHO. Funds were not allocated to support these analyses.

Availability of data and materials

The Ghana National TB Control Program is the custodian of the data for this study. The data are not accessible online, but may be made available upon written request to the NTP through the authors, if in line with the Ethical Review Board guidelines.

Authors' contributions

S-AO conceptualized and drafted the paper. AS, SD, and FA compiled the data. S-AO analyzed the data. FB, NNH-N, PK, MB, and S-AO contributed to the writing of the paper. All authors approved the final paper.

Authors' information

S-AO is a WHO staff member. The contents of this paper are the responsibility of the authors and do not necessarily reflect the decisions or policies of the WHO.

Ethics approval and consent to participate

The Ministry of Health Research Division Ethical Review Board gave ethical approval for the study. The study was a secondary data analysis and did not involve contact with individual patients so consent to participate was not applicable.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

Author details
1World Health Organization Country Office, 29 Volta Street Airport, Airport Residential Area, P.O. Box MB 142, Accra, Ghana. 2National Tuberculosis Control Program, Accra, Ghana. 3Department of Global Health, Academic Medical Centre, Amsterdam Institute of Global Health and Development, Amsterdam, The Netherlands. 4KIT Health, Royal Tropical Institute (KIT), Amsterdam, The Netherlands.

Received: 6 June 2017 Accepted: 12 February 2018
Published online: 27 February 2018

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Chapter 4

Case finding of tuberculosis among mining communities in Ghana

Sally-Ann Ohene, Frank Bonsu, Yaw Adusi-Poku, Francisca Dzata, Mirjam Bakker

PLoS ONE (2019) 16(3): e0248718.
https://doi.org/10.1371/journal.pone.0248718

Abstract

Background: Data on active TB case finding activities among artisanal gold mining communities (AMC) is limited. The study assessed the yield of TB cases from the TB screening activities among AMC in Ghana, the factors associated with TB in these communities and the correlation between the screening methods and a diagnosis of TB.

Methods: We conducted secondary data analyses of NTP program data collected from TB case finding activities using symptom screening and mobile X-ray implemented in hard to reach AMC. Yield of TB cases, number needed to screen (NNS) and the number needed to test (NNT) to detect a TB case were assessed and logistic regression were conducted to assess factors associated with TB. The performance of screening methods chest X-ray and symptoms in the detection of TB cases was also evaluated.

Results: In total 10,441 people from 78 communities in 24 districts were screened, 55% were female and 60% (6,296) were in the aged 25 to 54 years. Ninety-five TB cases were identified, 910 TB cases per 100,000 population screened; 5.6% of the TB cases were rifampicin resistant. Being male (aOR 5.96, 95% CI 3.25–10.92, P < 0.001), a miner (aOR 2.70, 95% CI 1.47–4.96, P = 0.001) and age group 35 to 54 years (aOR 2.27, 95% CI 1.35–3.84, P =0.002) were risk factors for TB. NNS and NNT were 110 and 24 respectively. Cough of any duration had the strongest association with X-ray suggestive of TB with a correlation coefficient of 0.48. Cough was most sensitive for a diagnosis of TB; sensitivity of 86.3% (95% CI 79.4 -93.2) followed by X-ray, sensitivity 81.1% (95% CI 71.7-88.4). The specificities of the symptoms and X-rays ranged from 80.2% (cough) to 97.3% (sputum).

Conclusion: The high risk of TB in the artisanal mining communities and in miners in this study reinforces the need to target these populations with outreach programs particularly in hard to reach areas. The diagnostic value of cough highlights the usefulness of symptom screening in this population that may be harnessed even in the absence of X-ray to identify those suspected to have TB for further evaluation.

Key words: Ghana, tuberculosis, mining communities

Introduction

Tuberculosis (TB) remains the leading cause of death from an infectious agent in the twenty first century despite being curable with antimicrobial drugs [1]. An estimated 10 million people developed TB in 2019, while about 1.4 million deaths occurred as a result of the disease [1]. The WHO African Region has the highest TB incidence rate of 226 per 100,000 population [1]. Ghana classified a high HIV/TB burden, like several countries in the African region, grapples with TB control activities [2]. The TB cases notified annually in Ghana averaged 14, 500 TB cases in the years preceding the national prevalence survey conducted in 2013 and thereafter [2,3]. The prevalence survey findings however suggested that people being detected with TB represent just about 21% of actual cases highlighting the need to adopt different strategies to identify more cases [2]. The END TB Strategy of the World Health Organization emphasizes early diagnosis of TB that involves systematic screening of contacts and high-risk groups, universal drug–susceptibility testing and standardized treatment of TB and drug-resistant TB forms [4]. Early case detection coupled with a high treatment success leads to a cure of infectious TB cases and cuts the risk of transmission ultimately reducing the burden of TB. This has led to several countries adopting various strategies to improve case detection [5-7].

Ghana is one such country in which a 2013 comprehensive review of the Ghana National TB Program highlighted the need to improve access to TB prevention, treatment, care and support services for key affected populations including PLHIV, children, diabetics, and miners or those exposed to silica [8]. Consequently, the National TB Health Sector Strategic Plan for Ghana (2015-2020) clearly identified TB case detection among mining populations as one of these key populations for intervention [2].

High risk populations such as miners especially those engaged in illegal mining activities may however be in hard to reach areas where they may encounter challenges accessing health services including those for diagnosing TB [9,10]. Strategies such as deployment of mobile teams proved to be useful in identifying people with TB in such hard to reach populations and mining communities [10-12]. The implementation

of active case finding (ACF) activities using mobile teams in hard to reach mining communities in Myanmar identified significantly higher TB prevalence in these townships than in the rest of the country [11]. In a study conducted among South African miners, death from TB was more than 2 times higher among those with TB diagnosed through passive case finding than those diagnosed through active screening exercises [13].

The Ghana NTP with funding from the Global Fund supported interventions to improve TB case finding among artisanal gold mining communities in the country [14]. Given the limited data on active TB case finding activities among small scale mining communities in Ghana, the aim of the study was to assess the yield of TB cases from the TB screening activities among artisanal mining communities, the factors associated with TB in these communities and the correlation between the screening methods and a diagnosis of TB.

Methods

Study Design and Setting

The study was cross-sectional consisting of secondary data analyses of routine NTP program data collected from TB case finding activities implemented in selected artisanal mining communities in which mining activities are generally operated without license from authorities. These activities were undertaken from May 2017 to January 2018 as part of NTP's efforts to make available TB screening, testing and treatment to vulnerable populations in these hard to reach artisanal mining areas [2]. The communities were deemed to be at high risk for TB but with limited access to TB services. Having already undertaken passive TB control activities in artisanal mining areas in Ashanti, Brong Ahafo and Western regions (collective estimated population of 11,200,955 in 2017), the NTP in consultation with the respective Regional Health Directorates (RHD) selected 3, 6 and 12 districts respectively from each region with intense artisanal mining activities.

These 21 districts consisted of an estimated total population of 2,120,660 in 2017 with TB notification rates ranging from 37 to 394/100,000 population. In

consultation with the RHD and District Health Directorates (DHD), 78 communities having artisanal mining activities, were selected from these districts for TB screening. In these communities, unlicensed gold extraction using crude mining extraction methods along terraces, mineral deposits in water ways and underground mines are undertaken by small-scale artisanal miners (locally known to as *galamsey)* [15,16]. These unregulated mining activities usually occur in hard to reach areas with limited access to health services. The communities were thus selected on the basis of their vulnerability to TB and being in hard to reach areas.

The conduct of the TB screening exercise was similar in the respective communities in which they were conducted across the three regions. The NTP deployed mobile teams consisting of a team leader to superintend the screening team, field coordinator to coordinate the field activities, radiographer to operate the digital X-ray machine, a physician-assistant to read the digital X-ray information technologist to maintain network connectivity for the transmission and storage of X-ray images and data, engineer to maintain the X –ray equipment and electrical generators, support team members to conduct screening and collect sputum samples and drivers for the digital X-ray van and vehicle to transport the team and other logistics. A week before the arrival of the team to the community, the district TB focal person in collaboration with the community volunteers undertook community mobilization using various methods including house to house sensitization and community radio announcements informing the community member of the upcoming free TB screening exercise, the date and the place where the team will be located.

Study population and data collection

The TB screening exercise was offered purely on voluntary basis to all community members 15 years and above who were willing to participate. Sampling or randomization of the population was therefore not done and neither was enumeration of community members done before the exercise. All community members 15 years and above who voluntarily made themselves available in the designated communities were eligible to be included in the screening exercise though the dataset showed that a handful of children less than 15 years were also screened. On the day of the exercise, community members voluntarily presenting themselves at the location of the mobile

team were registered and their socio-demographic information recorded. A TB symptom screening was administered using a questionnaire inquiring about the presence or absence of cough, fever, sputum production, chest pain, weight loss, night sweats and fever. With the exception of the following; pregnant or possibly pregnant women, those who for one reason or the other could not take or declined taking the chest X-ray, everyone's X-ray was taken using the digital X-ray machine. A physician assistant trained to read digital X-ray images categorized the X-ray finding into 3 groups: normal, abnormal suggestive of TB and abnormal but unlikely to be TB. Those reported to have an abnormal X-ray suggestive of TB, those admitting having a cough of 2 weeks or any duration with at least one other symptom were presumed to have TB and were requested to produce 1 spot sample of sputum. Also included in the presumed TB group and asked to produce sputum for testing were those unable to have an X-ray taken as indicated above and HIV positive individuals. The samples were transported to designated laboratories with a GeneXpert machine for testing. The GeneXpert results were reported as *Mycobacterium tuberculosis* (MTB) not detected, MTB detected rifampicin sensitive and MTB detected rifampicin resistance detected. The field coordinator followed up on the results and arranged for those found to have TB to be registered at the district level to start TB treatment. The analyses of the treatment outcomes of these TB patients were beyond the scope of this paper.

Statistical analyses

The NTP dataset contained data on only the people who volunteered for the screening and did not have data on the total number of people in the communities nor the demographics of the total community population. The analyses for the study was therefore limited to the population that was screened. Descriptive analyses were conducted for the following variables district, age group, sex, occupation, X-ray reading, presence of TB symptoms and GeneXpert results according to region. Due to the lack of census data of the communities targeted, screening coverage, (the proportion of the population screened) could not be assessed; neither was it possible to assess how the study population (the people who showed up for the screening) compared to the demographics of the communities from which they came. Data on

the proportions of age groups and sex by region of persons 15 years and above was however obtained from the 2010 Ghana census data and used as proxy data for the communities to allow for comparison of age group and sex with the study population with the assumption that the community demographics were similar to the census data [17]. Among the population screened, the prevalence of TB was calculated and so were the number needed to screen (NNS) and the number needed to test (NNT) to detect a TB case.

Univariate logistic regression was initially conducted to assess factors associated with TB diagnosis. Given the few characteristics being examined, all variables were then entered into a binomial logistic regression model with the outcome variable being a diagnosis of TB confirmed by GeneXpert. Odds ratio and 95% confidence (95%CI) interval were assessed. The strength of association between symptoms and having X-ray suggestive of TB was also determined by assessing Pearson's phi correlation coefficient as well as multivariable logistics regression controlling for age and sex. Finally, the diagnostic value of the screening methods chest X-ray and symptoms in the detection of TB cases was also evaluated using receiver operating characteristic (ROC) curves. The predictive strengths were determined from the models by calculating the area under the ROC curve (AUC). In the sensitivity analysis, all those not tested for TB were assumed not to have TB. STATA version 13 was used for statistical analyses and $p<0.05$ was set as the level of significance. The Ghana Health Service Ethical Review Committee gave ethical approval for the conduct of the study.

Results

Demographic characteristics and yield of TB among screened population

From among the 3 regions Brong Ahafo, Ashanti and Western, a total of 10,441 people from 78 communities in 21 districts were screened. On the average, 226 people were screened a day. The number of people screened per community ranged from 39 to 202 while for the districts, the numbers screened ranged from 282 to 826. The demographic characteristics of the study population by region and the census data are presented in Table 1.

Table 1. Demographic characteristics and TB screening results of person screened in mining communities in Ashanti, Brong Ahafo And Western Regions, Ghana, May 2017 to January 2018 compared to 2010 regional census statistics

	Ashanti Total= 1896	**Proportions of age groups 15+ from Ashanti census data**	**Brong Ahafo Total=3252 n (%)**	**Proportions of age groups 15+ from Brong Ahafo census data**	**Western Total=5293 n (%)**	**Proportions of age groups 15+ from Western census data**
Districts	3		6		12	
Communities	14		24		40	
	n (%)	(%)	**n (%)**	(%)	**n (%)**	(%)
Age (years)						
<15	0		13 (0.4)		10 (0.2)	
15 – 24	240 (12.7)	33.2	357 (11.0)	33.9	686 (13.0)	33.2
25 – 34	368 (19.4)	25.2	676 (20.8)	24.0	1,225 (23.1)	24.9
35 – 44	351 (18.5)	17.3	653 (20.1)	17.0	1,095 (20.7)	17.9
45 – 54	350 (18.5)	11.3	581 (17.9)	11.5	997 (18.8)	11.8
55 – 64	312 (16.5)	6.1	433 (13.3)	6.1	650 (12.3)	6.1
65+	272 (14.3)	6.9	536 (16.5)	7.5	620 (11.7)	6.2
Missing	3 (0.2)		3 (0.1)		9 (0.2)	
Sex						
Male	882 (47.0)	48.4	1481 (45.5)	49.6	2,268 (42.9)	50.0
Female	995 (52.5)	51.6	1769 (54.4)	50.4	3,018 (57.0)	50.0
Missing	9 (0.5)		2 (0.1)		7 (0.1)	
Occupation						
Agriculture	771 (37.5)		1639 (50.4)		1,911 (36.1)	
Professional	130 (6.9)		242 (7.4)		250 (4.7)	
Miner	103 (5.4)		278 (8.6)		486 (9.2)	
Sales and	497 (26.2)		587 (18.1)		1,496 (28.3)	
services	114 (6.0)		281 (8.6)		447 (8.5)	
Manual labour	319 (16.8)		182 (5.6)		489 (9.2)	
Unemployed	22 (1.2)		43 (1.3)		214 (4.0)	
Missing						
Symptoms						
Cough any	484 (25.5)		575 (17.7)		1,074 (20.3)	
duration	2 (0.1)		232 (7.1)		50 (0.9)	
Sputum	527 (27.8)		336 (10.3)		772 (14.6)	
Chest pain	442 (23.3)		154 (4.7)		644 (12.2)	
Weight loss	309 (16.3)		206 (6.3)		518 (9.8)	
Night sweats	251 (13.2)		57 (1.8)		399 (7.5)	
Fever	1037 (54.7)		2388 (73.4)		3697 (69.8)	
No symptoms						
X-ray Results						
Normal	1,082 (57.1)		2937 (90.3)		3,572 (67.5)	
Abnormal TB	387 (20.4)		213 (6.6)		848 (16.0)	
Abnormal	413 (21.8)		79 (2.4)		798 (15.1)	
Non-TB	14 (0.7)		23 (0.7)		75 (1.4)	
Missing						

Overall among those screened, 45% were male compared to 49% in the census data showing that among those screened, slightly fewer men showed up. While census data showed that among those aged 15 years and above in the general population about 33% were between 15 to 24 years, among those screened about 12% were in

this age group. Those screened in the TB screening exercise consisted of a relatively higher proportion of older people compared to what would be expected in the community using census data as proxy. This general trend was noted across the 3 regions. There were 23 children (0.2%) less than 15 years. About 42% of the people screened were in the agriculture sector while miners comprised 8.5%.

About half of those screened 50.7%, were from Western Region. Ashanti Region had the smallest proportion of miners 5.4% while 50.4% of those screened in Brong Ahafo were in the agriculture sector. The districts in which the TB case finding activities were undertaken are shown in Fig 1.

Fig 2 shows the algorithm of the overall TB screening process and the yield.

Among those who had a chest X-ray done (10,329), almost 14% (1,448) were reported to have findings suggestive of TB. About 23% of those screened were identified as presumed TB cases. The 95 TB cases identified out of the 10,441 people screened was equivalent to 910 TB cases per 100,000 population screened. Out of the 78 communities, thirty-seven (47%) did not have any TB cases detected, fourteen communities had 1 TB case, sixteen had 2, two had 3 TB cases detected. Six communities had 4 TB cases, two had 5 and 1 had 9 TB cases detected. The TB prevalence among the population screened varied between 0 and 6.8%. No TB cases were identified in 3 districts out of the 21 districts undertaking TB case finding activities. Ashanti recorded the highest yield of TB cases among those screened 1.32%, compared to Western 1.11% and Brong Ahafo 0.34%. Table 2 shows the yield of TB cases by regions following TB case finding exercises undertaken in selected mining communities in selected districts.

Western Region accounted for 62% (59) of the TB cases while 26% (25) were from Ashanti Region. Males made up 84% (80) of the total TB cases detected among the population screened, 70% of those with TB were in the age range of 25 to 54 years and miners had the highest prevalence of TB 2.65% compared to 1.41% among those engaged in skilled manual labour and 0.68% among those involved in the agriculture sector.

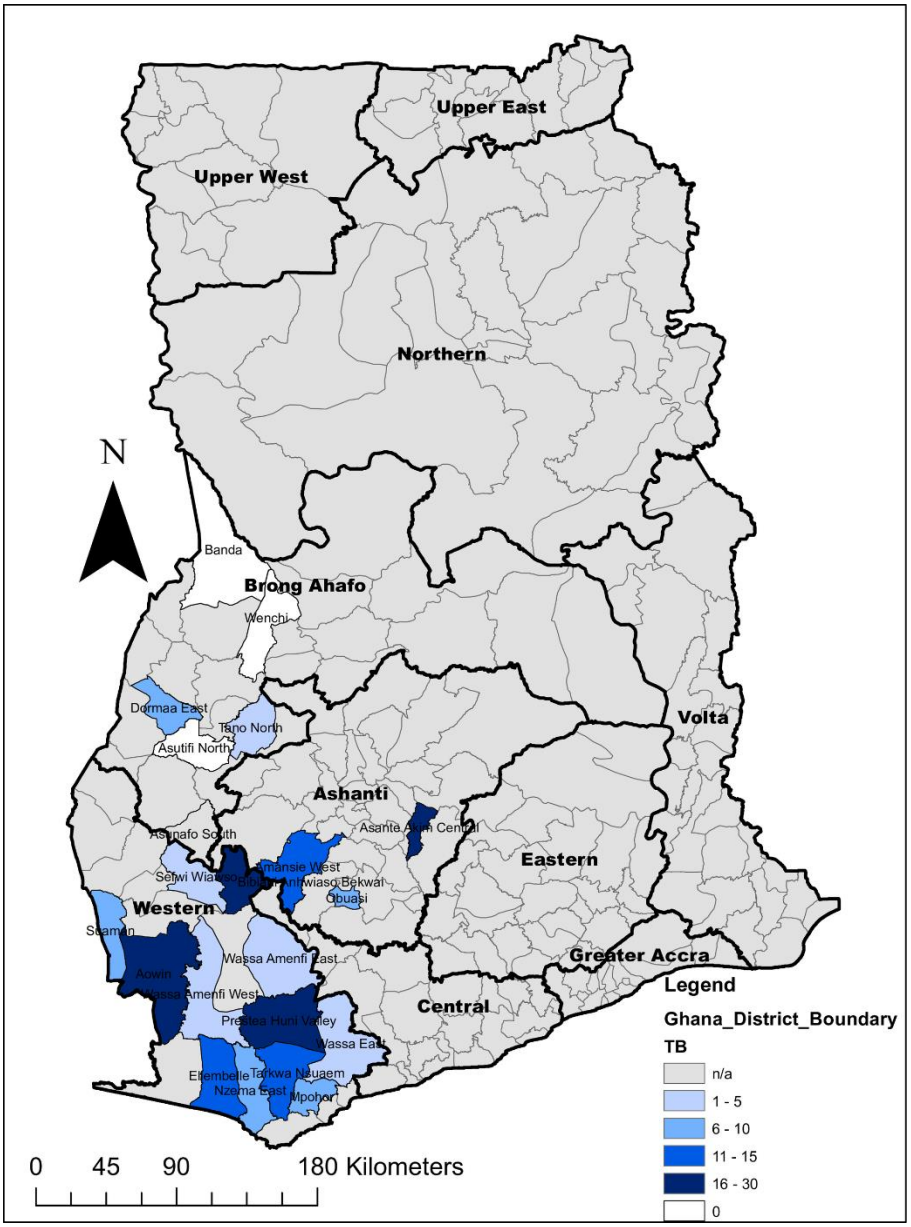

Fig 1. Map of Ghana showing districts in which case finding activities were undertaken in selected mining 2017 to January 2018.

Fig 1 legend shows the range of the number of TB cases detected per 1000 persons screened from the TB case finding exercise in the respective districts.

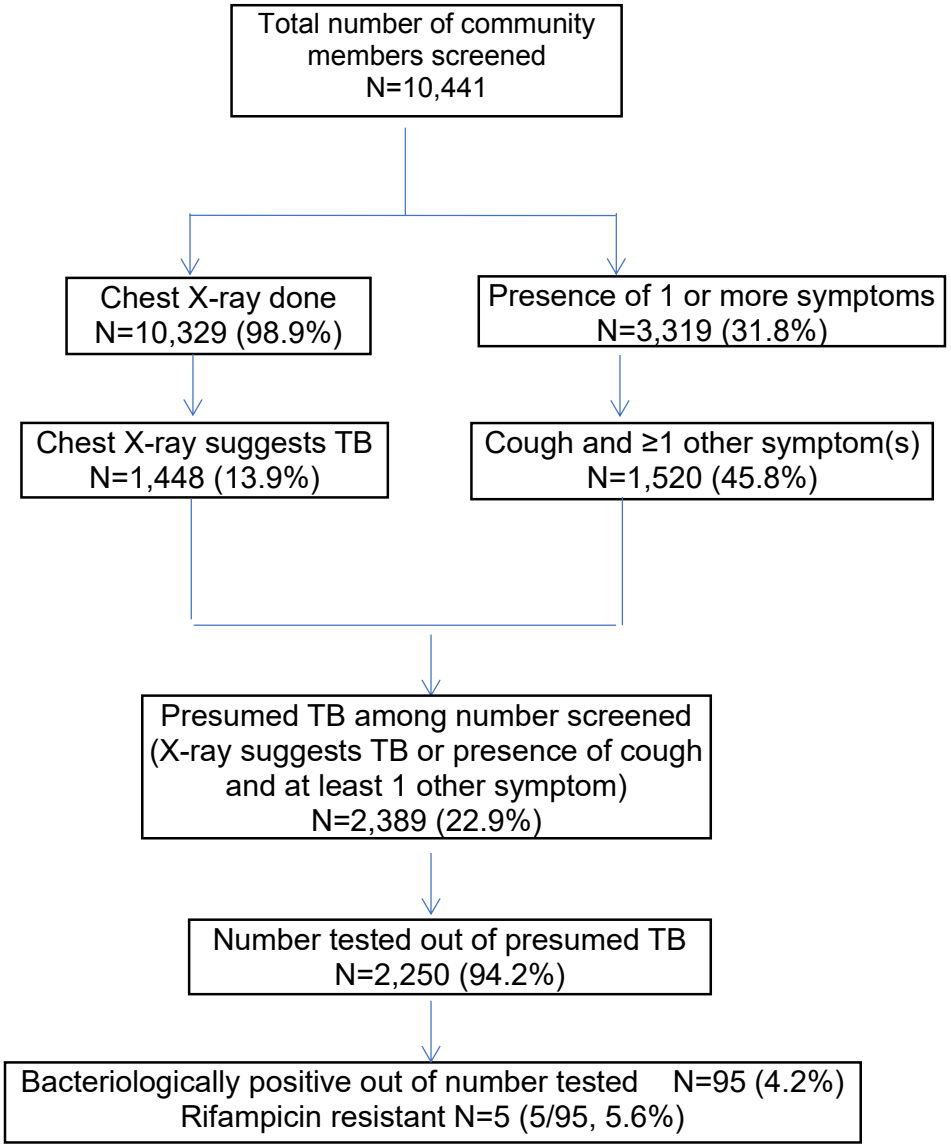

Fig 2. Flow chart of TB case finding screening exercise undertaken in mining communities in 21 districts in Ghana from May 2017 to January 2018

Table 2. Yield of TB cases from TB case finding exercise undertaken in 3 regions in Ghana, May 2017 to January 2018

Regions	Ashanti	Brong Ahafo	Western	Total
Number screened	1896	3252	5293	10441
Presumptive TB (% out of screened)	444 (23.4)	536 (16.5)	1,409 (26.0)	2,389 (22.9)
Number tested (% of presumptive TB)	441 (99.3)	401 (74.8)	1408 (99.9)	2250 (94.2)
Number bacteriologically positive (% out of tested)	25 (5.6%)	11 (2.8%)	59 (4.2)	95 (4.2)
Number rifampicin resistant (% out of TB cases)	1 (4%)	1 (9.1%)	3 (5.1)	5 (5.3)
NNT (Number needed to test)	18	36	24	24
NNS (Number needed to screen)	76	296	90	110

The overall TB prevalence among non-miners in the screened population was 0.64%. Five of the TB cases had rifampicin resistant TB. All 5 were male in the 35 to 44 year age group with 2 of them being miners from Western Region giving a rate of 8.7% rifampicin resistant TB among the miners with TB.

The regional distribution of TB cases across the demographic variables is shown in Table 3.

In the Ashanti Region, all but 1 of the 25 TB case identified were male. Even though miners formed 9.6 % of those screened in the Western Region, 27% of those with TB in the region were miners.

Table 3. Distribution of TB and those without TB across demographic variables among persons screened in selected artisanal mining communities by region in Ghana May 2017 to January 2018

	Ashanti N=1896		Brong Ahafo N=3252		Western N=5293	
	No TB	TB	No TB	TB	No TB	TB
	N=1871	N=25	N=3241	N=11	N=5234	N=59
Age Years)						
<15	0	0	13 (0.4)	0	10 (0.2)	0
15 – 24	240 (12.8)	0	357 (11.0)	0	681 (13.0)	5 (8.5)
25 – 34	361 (19.3)	7 (28.0)	674 (20.8)	2 (18.2)	1212 (23.2)	13 (22.0)
35 – 44	345 (18.4)	6 (24.0)	650 (20.1)	3 (27.3)	1079 (20.6)	16 (27.1)
45 – 54	346(18.5)	4 (16.0)	579 (17.9)	2 (18.2)	983 (18.8)	14 (23.7)
55 – 64	307(16.4)	5 (20.0)	432 (13.3)	1 (9.1)	642 (12.3)	8 (13.6)
65+	269 (14.4)	0	533 (16.4)	3 (27.3)	618 (11.8)	3 (5.1)
Missing	3 (0.2)		3 (0.1)	0	9 (0.2)	0
Sex						
Male	868 (46.4)	24 (96.0)	1472 (45.4)	9 (82.8)	2221 (42.4)	47 (79.7)
Female	994 (53.1)	1 (4.0)	1767 (54.5)	2 (18.2)	3006 (57.4)	12 (20.3)
Missing	9 (0.5)	0	2 (0.1)	0	7 (0.1)	0
Occupation						
Agriculture	700 (37.4)	11 (44.0)	1636 (50.5)	3 (27.3)	1896 (36.2)	15 (25.4)
Professional	130 (7.0)	0	242 (7.5)	0	250 (0.8)	0
Miner	98 (5.0)	5 (20.0)	276 (8.5)	2 (18.2)	470 (9.0)	16 (27.1)
Sales and services	495 (26.5)	2 (8.0)	586 (18.1)	1 (9.1)	1487 (28.4)	9 (15.3)
Manual lab	112 (6.0)	2 (8.0)	278 (8.6)	3 (27.3)	442 (8.4)	5 (8.5)
Unemployed	314 (16.8)	5 (20.0)	182 (5.6)	0	476 (9.1)	13 (22.0)
Missing	22 (1.2)	0	41 (1.3)	2 (18.2)	213 (4.1)	1 (1.7)

Factors associated with TB

In univariate analyses, shown in Table 4, being a male, miner and unemployed were risk factors for having TB as was coming from Western and Ashanti regions. In multivariate analyses also in Table 4, being in the age group 35 to 54 years became a risk factor for TB, (OR [aOR] 2.27, 95% CI 1.35–3.84, P =0.002). Being male, (OR [aOR] 5.96, 95% CI 3.25–10.92, P < 0.001) miners (OR [aOR] 2.70, 95% CI 1.47–4.96, P = 0.001), unemployed (OR [aOR] 3.15, 95% CI 1.66–5.95, P < 0.001) and coming from Ashanti (OR [aOR] 4.12, 95% CI 1.89–8.98, P < 0.001) and Western Regions (OR [aOR] 3.84, 95% CI 1.90–7.80, P < 0.001) were risk factors for having TB.

Table 4. Logistic regression analyses of factors associated with TB diagnosis among persons screened in selected artisanal mining communities in Ghana, May 2017 to January 2018, N=10,441

	Univariate OR (%CI)	p	Multivariate aOR (95CI)	p
Age (years)				
<35	1		1	
35 –54	1.49 (0.92 - 2.40)	0.106	2.27 (1.35 - 3.84)	0.002
≥55	1.08 (0.62 - 1.89)	0.789	1.82 (0.98 - 3.39)	0.055
Sex				
Female	1		1	
Male	6.74 (3.88-11.72)	<0.001	5.96 (3.25-10.92)	<0.001
Occupation				
Agriculture	1		1	
Professional	-		-	
Miner	3.98 (2.29 - 6.91)	<0.001	2.70 (1.47 - 4.96)	0.001
Sales and services	0.68 (0.35 - 1.34)	0.266	1.12 (0.55 - 2.29)	0.751
Manual labour	1.75 (0.85 – 3.61)	0.127	1.08 (0.51 - 2.30)	0.738
Unemployed	2.70 (1.49 - 4.89)	0.001	3.15 (1.66 – 5.95)	<0.001
Region				
Brong Ahafo	1		1	1
Ashanti	3.94 (1.93 - 8.02)	<0.001	4.12 (1.89 – 8.98)	<0.001
Western	3.32 (1.74 - 6.33)	<0.001	3.84 (1.90 – 7.80)	<0.001

OR – Odds ratio, aOR – adjusted odds ratio

Correlation between TB symptoms and X-ray suggestive of TB.

The analysis to assess the correlation between the symptoms and X-ray suggestive of TB is shown in Table 5. Cough of any duration was found to have the strongest correlation with X-ray suggestive of TB with a correlation coefficient of 0.48 pointing to a strong positive relationship while sputum ranked at the bottom.

In the analysis assessing the performance of symptoms and X-ray at screening and a diagnosis of TB confirmed with GeneXpert, cough was also the most sensitive symptom for a diagnosis of TB at a sensitivity of 86.3% (95% CI 79.4 -93.2) followed by weight loss 67.4 % (95% CI 57.0-76.6) and chest pain 63.2% (95% CI 52.6-72.8) with sensitivities that were overlapping Table 6.

Table 5. Correlation between symptoms among persons screened in selected artisanal mining communities in Ghana, May 2017 to January 2018 and X-ray suggestive of TB using Phi Correlation Coefficient

	X-ray suggestive of TB N=1,448	X-ray not suggestive of TB N=8,881	Phi correlation coefficient (r)	p
Cough any duration				
Yes	988 (68.2)	1,122 (12.6)		
No	460 (31.8)	7,759 (87.4)	0. 48	<0.001
Sputum				
Yes	146 (10.1)	135 (1.5)		
No	1,302 (89.9)	8,746 (98.5)	0.18	<0.001
Chest pain				
Yes	686 (47.4)	939 (10.6)		
No	762 (52.6)	7,942 (89.4)	0.35	<0.001
Weight loss				
Yes	612 (42.3)	625 (7.0)		
No	836 (57.7)	8,256 (93.0)	0.38	<0.001
Night sweats				
Yes	488 (33.7)	541 (6.1)		
No	960 (66.3)	8,340 (93.9)	0.32	<0.001
Fever				
Yes	372 (25.7)	334 (3.8)		
No	1,076 (74.3)	8,547 (96.2)	0.30	<0.001

95%CI – 95% Confidence Interval, aOR Adjusted Odds Ratio

Sputum production had the least sensitivity 8.4% (95% CI 3.7-15.9). The sensitivity of X-ray in the diagnosis of TB 81.1% (95% CI 71.7-88.4) ranked after that of cough but was comparable. The combination of cough and chest X-ray had the highest sensitivity 94.7 (95% CI). The specificities of the symptoms and X-rays ranged from 80.2% (cough) to 97.3% (sputum). The positive predictive values of all the symptoms and X-ray suggestive of TB were all low <7%. The diagnostic value of the screening methods, summarized by the AUC, highlighted cough (0.83) and X-ray (0.84) as being at par.

Table 6. Sensitivity and specificity of symptoms and X-ray at screening in the diagnosis of TB

	TB cases	No TB	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	AUC
Cough any duration						
Yes	82	2,051	86.3 (77.7 -92.5)	80.2 (79.4-80.9)	3.8 (3.1-4.8)	0.83 (0.80-0.87)
No	13	8,295				
Sputum						
Yes	8	276	8.4 (3.7-15.9)	97.3 (97.0-97.6)	2.8 (1.2-5.5)	0.53 (0.50-0.56)
No	87	10,070				
Chest pain						
Yes	60	1,575	63.2 (52.6-72.8)	84.8 (84.1-85.5)	3.7 (2.8-4.7)	0.74 (0.69-0.79)
No	35	8,771				
Weight loss						
Yes	64	1,176	67.4 (57.0-76.6)	88.6 (88.0-89.2)	5.2 (4.0-6.5)	0.78 (0.73-0.83)
No	31	9,170				
Night sweats						
Yes	34	999	35.8 (26.2-46.3)	90.3 (89.8-90.9)	3.3 (2.3-4.6)	0.63 (0.58-0.68)
No	61	9,347				
Fever						
Yes	35	672	36.8 (27.2-47.4)	93.5 (93.0-94.0)	4.9 (3.5-6.8)	0.65 (0.60-0.70)
No	60	9,674				
X-ray						
Yes	77	1,371	81.1 (71.7-88.4)	86.6 (85.9-87.3)	5.3 (4.2-6.5)	0.84 (0.80-0.88)
No	18	8,863				
Cough and X-ray Yes	90	2,503	94.7 (88.1-98.3)	75.8 (75.0-76.6)	3.5 (2.8-4.3)	0.85 (0.83-0.88)
No	5	7,843				

95%CI – 95% Confidence Interval, PPV – Positive predictive value, AUC – Area under the curve

Discussion

Miners and the communities in which they live are identified as being at higher risk for TB than the general population [18]. Forging ahead with the End TB Strategy, responsive programs for such key populations require data that will inform and guide stakeholders in the appropriate planning and delivering of services [4,19]. In this study, which is the first to the best of our knowledge to highlight active TB case finding among artisanal mining communities in Ghana using mobile X-ray and symptom screening, the study population consisted of people who volunteered for the screening exercise. The overall rate of TB among the people screened was found to be 910 per 100,000 people screened with 5.3% of the TB cases having rifampicin resistant TB. The NNS and NNT were 110 and 24 respectively. Risk factors for TB were being male,

a miner and location in Ashanti and Western Regions. Cough regardless of duration correlated with X-ray findings suggestive of TB and a diagnosis of TB. It is not straightforward to compare these findings from our study population (in which sampling was not done) to others from TB prevalence and similar studies in which the populations are sampled and the results reasonably reflect the communities in which the surveys are conducted. Given the different methodologies, contexts and the point that it was not possible to tell whether the people screened in our study fairly represented the rest of the community, interpretations of these comparisons should therefore consider the background of our study setting.

Using census data as proxy for the community demographics, it was noted that fewer men and relatively older community members offered themselves for the screening exercise in our study. Some studies conducted among small scale miners in Ghana show that about 70% or more of those surveyed were less than 40 years suggesting one would expect more younger men in such mining communities [20-21]. It may therefore be possible that the screening exercise conducted in the AMC in our study missed relatively younger people. In case, a significant proportion of those missed were miners, given the higher risk of TB among miners, it could be possible that our results may be an underestimation of the TB burden in AMC studied [18]. The prevalence of TB among the people screened in the artisanal mining communities in this study was more than two and half times what was reported for the general population in Ghana in the TB prevalence survey (356 bacteriologically confirmed TB per 100,000), on the face value re-iterating the data on the higher risk of TB among mining communities [9,18,22]. The overall TB prevalence among the community members screened was however lower than that reported in other mining communities such as the copper belt in Zambia (1.2%) and mining communities in Myanmar (2.7%) [11,23]. The TB prevalence among the

miners in our study (2.65%), while also lower than that cited in other studies in South Africa (5.4%) and Zambia (9.5%), was higher than that in miners in Myanmar (1.7%) [11,23,24]. These differences may be related to several factors including varying methods for diagnosing TB in the miners such as sputum microscopy as opposed to GeneXpert, the type of mining, the exposure to silica dust and the duration of exposure to mining conditions [23]. In the Zambia study, study participants were underground miners in copper mines while the miners in our study were likely involved in gold exploration using different mining methods ranging from surface to underground mining [15,16, 23, 25, 26].

The rate of rifampicin resistance found among our study population (5.3%) was slightly higher than the 4.3% drug resistance recorded among South African gold miners and their dependents but much higher than the 1.3% reported from the 2018 national surveillance data from Ghana [27,28]. The setting in the South Africa study was a formal gold mine employment with a well-functioning TB control program that was keeping track of drug resistant TB. In contrast, but for the outreach program to these mining communities, it is not possible to tell how long it would have taken for these drug resistant cases to be detected. This highlights the importance of mainstreaming TB screening services for such high-risk populations [29].

In general males are more at risk for TB in Ghana and other countries and our study findings are in line with this [22,29]. It is reported that in illegal artisanal small-scale mining settings in Ghana, women may constitute up to 50% of the labour force and play various roles [16,30,31]. The men however undertake more hazardous activities including underground mining which may expose them more to silica increasing the risk for TB [23,30-32].

TB prevalence surveys have shown chest X-rays to be more sensitive than symptom screening for TB detection since some people with TB may not have

symptoms [33]. In our study the sensitivity and specificity of chest x-ray as a screening tool for TB fell within the range of what has been reported [34]. Symptom screening, particularly cough of any duration, on the other hand is reported to be less sensitive with pooled sensitivity and specificity in the range of 40 to 74% and 69 to 90% respectively [34]. Several studies on the diagnostic value of x-ray and symptoms screening for TB case detection have been conducted in different populations and among miners but there's a dearth of such studies in artisanal mining communities to compare with [5, 35-39]. Comparing across such studies may however not be straightforward because of the different modalities of symptom definitions, screening criteria and subjectivity in reading of X-rays. [38,40] In our study the sensitivity (86.3%) of cough of any duration as a screening tool for the detection of TB was relatively high and even ranked higher than that of chest X-ray even though it was comparable. The combination of cough and X-ray raised the sensitivity to 95%. This finding is similar to what van't Hoog and colleagues reported in a prevalence study in Kenya even though the cough in their study was 2 weeks or more in duration [38].

In this TB case detection outreach to the artisanal mining communities, those who were eligible to produce sputum for testing consisted of those who had an X-ray suggestive of TB, symptoms suggestive of TB and those who for some reason could not take X-ray totalling about 23% of the population who presented themselves for screening. This is relatively higher compared to the 13% identified during the TB prevalence survey [17]. The difference may be related to the expertise in reading the X-rays (radiologists in the prevalence survey as opposed to physician assistants in our survey), the cough criteria (2 weeks cough in the prevalence survey) the possibility that some of those who had symptoms or were reported as having X-ray suggestive of TB could also have had silicosis which may have symptoms and X-ray findings similar to

that of TB [41,42]. It is also however important to note that, in the TB prevalence survey the population screened were sampled unlike the study population in our study who came voluntarily for screening with the possibility of some selection bias. The yield of TB cases was however much higher and may make the case for the use of this approach of combining symptom and x-ray screening used in the mining communities as opposed to a sequential algorithm of symptom screening following by X-ray [33]. Other studies have explored sequential algorithms in active TB case finding but in settings different from our study which limit comparability with our results [40,43]. The commonality however lies in the benefit of including X-ray to enhance the identification of TB in the case finding exercise. Further studies assessing a cost benefit analyses and factoring in yield of TB cases may shed more light on the more beneficial and cost-effective approach to use in high risk populations in hard to reach communities.

This study has a number of limitations. The NTP dataset used for the analysis did not have data on the number of people in the communities in which screening was conducted nor the demographics of the communities. This limited the ability to assess the size of the community, the proportion of the community population that was screened and whether the demographics of those screened were comparable to those not screened. The diagnosis of TB was based on results from GeneXpert to the exclusion of those who may have had clinically diagnosed TB. Having used routine data already collected, there was no control over standardizing the measurement and reporting of variables to enable further analyses of interest nor was it not possible to apply quality control measures or checks. For example, in the data set the recording cough of any duration without always specifying the duration for each participant limited the ability to assess the sensitivities of the different durations of cough in the diagnosis of TB. It is therefore being recommended to the NTP to have

standardized data collection tools for all teams engaged in outreach programs to enable optimum analyses of data to inform programming. Finally, with this study being conducted in artisanal mining communities the findings may not be generalizable to other communities in the country.

Conclusion

The high risk of TB in the artisanal mining communities and in miners as shown in this study reinforces the need to target these populations with outreach programs particularly given that they may be in hard to reach areas. Even though the combination of cough and chest X-ray had the highest sensitivity, the diagnostic value of cough highlights the usefulness of symptom screening in this population that may be harnessed even in the absence of X-ray to identify those suspected to have TB for TB diagnostic evaluation.

Supporting information

S1 File. Data set for TB case finding activities. (XLSX)

Acknowledgement

The authors acknowledge with much appreciation the staff of the Ghana National Tuberculosis Control Program, regional health directorates of Ashanti, Brong Ahafo and Western Regions, the staff of the district health directorates of the participating districts, the communities that were screened and the various screening teams for the diverse roles played in the TB case finding exercise. Their efforts enabled the generation of the data for this study. Dr Rafiq Okine, Mr Fred Osei-Sarpong and Mr Felix Sorvor are also appreciated for the technical support.

Author Contributions

Sally-Ann Ohene
ROLES Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing
AFFILIATION World Health Organization Country Office, Accra, Ghana

Frank Bonsu
ROLES Conceptualization, Writing – review & editing
AFFILIATION National Tuberculosis Control Program, Ghana Health Service, Accra, Ghana

Yaw Adusi-Poku
ROLES Conceptualization, Writing – review & editing
AFFILIATION National Tuberculosis Control Program, Ghana Health Service, Accra, Ghana

Francisca Dzata
ROLES Conceptualization, Data curation, Writing – review & editing
AFFILIATION National Tuberculosis Control Program, Ghana Health Service, Accra, Ghana

Mirjam Bakker
ROLES Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing
AFFILIATION KIT Royal Tropical Institute, Global Health Amsterdam, Amsterdam, The Netherlands

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Chapter 5

Childhood tuberculosis and treatment outcomes in Accra: a retrospective analysis

Sally-Ann Ohene, Sarah Fordah, Prince Dela Boni

BMC Infectious Diseases (2019) 19:749
https://doi.org/10.1186/s12879-019-4392-6

Abstract

Background: Tuberculosis (TB) is a leading cause of death in children and adults. Unlike for adults, there is paucity of data on childhood TB in several countries in Africa. The study objective was to assess the characteristics and treatment outcomes of children with TB from multiple health facilities in Accra, Ghana.

Methods: A retrospective analyses was conducted using secondary data on children less than 15 years collected from 11 facilities during a TB case finding initiative in Accra from June 2010 to December 2013. Demographic and clinical characteristics as well as treatment outcomes were assessed. Multivariable logistic regression was conducted to assess predictors of mortality.

Results: Out of the total 3,704 TB cases reported, 5.9% (219) consisted of children with a female : male ratio of 1:1.1. Children less than 5 years made up 56.2% of the patients while 44.2% were HIV positive. The distribution of TB type were as follows: smear positive pulmonary TB (SPPTB), 46.5%, clinically diagnosed pulmonary TB 36.4%.%, extra-pulmonary TB 17.4%. Among the 214 children (97.7%) for whom treatment outcome was documented, 194 (90.7%) were successfully treated consisting of 81.3% who completed treatment and 9.4% who were cured. Eighteen children (8.4%) died. Mortality was significantly higher among the 1-4 year group ($p < 0.001$), those with SPPTB ($p < 0.001$) and HIV positive children ($p < 0.001$). In logistic regression, SPPTB and HIV positivity were predictors of mortality.

Conclusion: The proportion of children in Accra successfully treated for TB met the target of END TB Strategy treatment success indicator. HIV positivity was a risk factor for death. Reducing mortality in TB-HIV co-infected children will further improve treatment outcomes of children with TB in Accra.

Keywords: Ghana, TB, Children, Treatment outcomes

Background

It is estimated that there were 1million new cases of tuberculosis (TB) among children less than 15 years globally in 2017 representing 10% of the TB cases worldwide [1]. About 234,000 children were also projected to have died from TB in the same year [1]. This burden highlights the need to surmount the barriers to tackling TB in children which is identified as one of the top causes of death in this age group [2, 3]. There has been a growing interest in childhood TB with the recognition that efforts at TB control are bound to fail if children who serve as potential sources of future infection are ignored [2, 4]. This is in addition to the compelling obligation to diagnose and treat a disease for which drugs are available to effect cure [4]. Considering that TB in childhood also serves as a marker for recent disease transmission and therefore control activities, it is important for national TB control programs to have a good understanding of the burden of childhood TB in the respective settings [4]. This will facilitate the adoption of appropriate strategies to implement the END TB Strategy which among others call for the expansion of services to manage TB among children [5].

Over the years several studies have been carried out in African countries that have thrown light on the burden, diagnosis and treatment outcomes of childhood TB [6-11]. While some studies on TB in adults have been published in Ghana, there is very limited data on childhood TB to inform programming and planning for this age group [12-14]. To address this gap, this study was undertaken with the objective of assessing the demographic and clinical characteristics as well as treatment outcomes and risk factors for mortality among children diagnosed with TB from multiple health facilities in Accra, Ghana.

Methods

Study design, setting and population

The study was retrospective in nature analyzing secondary data from a database of TB patients diagnosed from June 2010 to December 2013 during a TB case finding initiative implemented in 11 health facilities in Accra, the capital of Ghana. The main strategies of the TB case finding initiative involved identification of patients suspected to have TB through symptomatic screening in the OPDs and HIV clinics in these facilities and contact tracing. The presumed TB patients identified through the screening process were investigated for TB and those confirmed to have TB were put on TB treatment as per the NTP guidelines. The 11 public health facilities participating in the initiative included a children's hospital which provided in and outpatient care for children, 3 polyclinics which had only out-patient services for all ages and seven hospitals which consisted of 5 general hospitals, a regional hospital and a teaching hospital all providing both in and outpatient services. For the analyses the regional and teaching hospitals which are referral facilities providing more specialized care were grouped into one category termed "specialized" hospitals to distinguish them from the general hospitals. These facilities which implement the directly observed treatment short course (DOTS) strategy in line with the Ghana National TB Control Program (NTP) guidelines together manage about 70% of TB cases in Accra. Further details of the initiative are described elsewhere [15].

The study population consisted of children less than 15 years identified during the period of the case finding initiative over the stated period. Children below 15 years make up approximately 29% of Accra's population [16]. The NTP guidelines for the diagnosis and management of TB in children made use of a screening tool adapted from Osborne's scoring system. The tool revolved around the identification of clinical features including cough, weight loss or

failure to gain weight and history of contact with a TB patient to detect children suspected to have TB [17-19]. In the event that the child was able to produce sputum or gastric lavage could be performed, 2 samples were sent for smear microscopy for acid fast bacilli. Although culture services were accessible, GeneXpert services were not readily available during the time of the initiative. Children in whom smear results were positive were classified as smear positive TB. Those with smear negative results were designated smear negative TB if after further evaluation by means of a thorough clinical assessment, chest X-ray, tuberculin skin test, the clinician determined the child had TB. Extra-pulmonary TB (EPTB) was also diagnosed after various relevant investigations had been conducted on samples obtained from children with suggestive clinical presentations. Examples of samples included cerebrospinal fluid for TB meningitis and fine needle aspiration of suspected TB adenitis [17, 18]. Children designated as having clinically diagnosed TB were those who may not have been able to produce sputum or for whom gastric lavage could not be done and so did not have sputum microscopy done but had physical signs, chest X-ray suggestive of pulmonary TB, a history of contact with a person infected with TB and were assessed by a clinician to have TB. Children diagnosed with TB were put on a standard 6 months regimen as per the NTP and WHO guidelines consisting of a 2-month intensive phase with 4 drugs (isoniazid, rifampicin, ethambutol and pyrazinamide) followed by 4 months continuation phase with isoniazid and rifampicin [17, 18]. For tuberculous meningitis and osteo-articular TB the continuous phase covered a period of 10 months [18, 19]. TB Treatment in children was directly observed with a care taker identified to be the DOTS provider. At the end of the continuation phase, treatment outcomes were declared as cured, treatment completed, treatment failed, died, lost to follow up and not evaluated defined

in Table 1 [20]. The sum of children with outcomes "cured" and "treatment completed" made up those who were successfully treated.

Table 1 Definition of treatment outcomes

Outcome	Definition
Cured	A smear positive patient who completed treatment with a negative sputum smear in the final month of treatment and on at least one previous occasion
Treatment Completed	A sputum smear negative or extra-pulmonary TB registered patient or one with smear not done who has completed a full course of treatment
Treatment failed	A patient whose sputum smear is positive 5 months of treatment or later
Died	Patient who dies for any reason while on TB treatment
Lost to follow up	A patient with interrupted treatment for 2 or more consecutive months
Not evaluated	A person whose treatment outcome is unknown
Treatment success	A combination of cure and treatment completed

All children who were suspected to have TB were expected to be tested for HIV as per the National AIDS Control Program Guidelines (NACP) and those found to be positive initiated on ART within 2 weeks of starting TB treatment [21].

Data collection and analyses

The data for the study was obtained from the database of patient information compiled from the 11 facilities participating in the case finding initiative over the period June 2010 to December 2013. This case finding initiative database was selected because it was readily available and included data on children less than 15 years, the age group of interest for the study.

The criteria for inclusion into the study sample consisted of all children less than 15 years diagnosed with smear positive and smear negative pulmonary TB, extrapulmonary TB and clinically diagnosed TB. Patients 15 years and older were excluded from the study population. The data were analysed using STATA 12. Descriptive analyses were conducted for demographic and clinical variables including gender, age, TB type, HIV status, facility type and year of TB registration. Those diagnosed with sputum smear negative TB and those clinically diagnosed with TB were combined into one group labelled clinically diagnosed pulmonary TB. The association between the independent variables and treatment outcomes were assessed using Chi-square test and Fisher's exact test as relevant.

By way of definition, those designated as having "treatment success" consisted of patients who were cured and completed treatment while all other patients; those who died, were lost to follow up or failed treatment were classified as having poor treatment outcome. Odds ratio with 95% confidence interval (95%CI) were assessed from univariable (unadjusted) and multivariable (adjusted) logistic regression conducted to identify risk factors for mortality compared to those treated successfully. Given the relatively few variables being assessed, all variables were included in the preliminary multivariable regression model. A backward stepwise elimination process was then employed to account for confounders in the dataset. Significant variables were retained at a p-value of 0.05.

Results

Over the course of the TB-case finding initiative, 219 children less than 15 years were diagnosed with TB representing 5.9% out of the total 3,704 TB cases reported. The female:male ratio was 1:1.1. The median age was 3 years with a range of 3 months to 14 years and children less than 5 years made up 56.2% of the patients. Table 2 shows the characteristics of the study population.

The majority of the children were new TB cases with the exception of 8 (3.8%) 7 of whom were retreatment cases and 1 relapse. Among the smear positive TB cases, 67 (66.3%) were aged less than 5 years and 79 (78.2%) were diagnosed in the children's hospitals. Chest X-ray results were known for 162 (74%) of the children out of whom 159 (98%) were reported to have findings suggestive of TB.

A total of 79 children had clinically diagnosed pulmonary TB. Forty-five of them had a sputum smear negative result. Out of the remaining 34 children who did not have sputum microscopy done, 27 (80%) were less than 5 years and 29 (85%) were diagnosed in general hospitals. Among the 37 children (17%) with extra-pulmonary TB, lymph nodes were most commonly affected as shown in Figure 1. Among the 5 children with EPTB in the bones and joints, the sites affected were femur (2), hip (2) and tibia (1).

Table 2 Demographic clinical and characteristic of children with TB in Accra June 2010 to December 2013

Characteristic	Number (%)
Sex	
Male	113 (52.6)
Female	102 (47.4)
Age (years)	
< 1	31 (14.4)
1 – 4	88 (40.9)
5 – 9	50 (23.3)
10 – 14	46 (21.4)
TB Type	
Clinically diagnosed pulmonary TB	79 (36.4)
Extra-pulmonary	37 (17.1)
Smear positive PTB	101 (46.5)
HIV status	
Negative	117 (54.7)
Positive	97 (45.3)
Facility	
Children's Hospital	102 (46.6)
General Hospitals	66 (30.1)
Specialized Hospitals	36 (16.4)
Polyclinics	15 (6.9)

The HIV status was documented for virtually all the children (97.7%). Forty-four percent of the children were HIV positive. More children (30%) were diagnosed in 2010 from June to December compared to the other years which were full calendar years as shown in Figure 2.

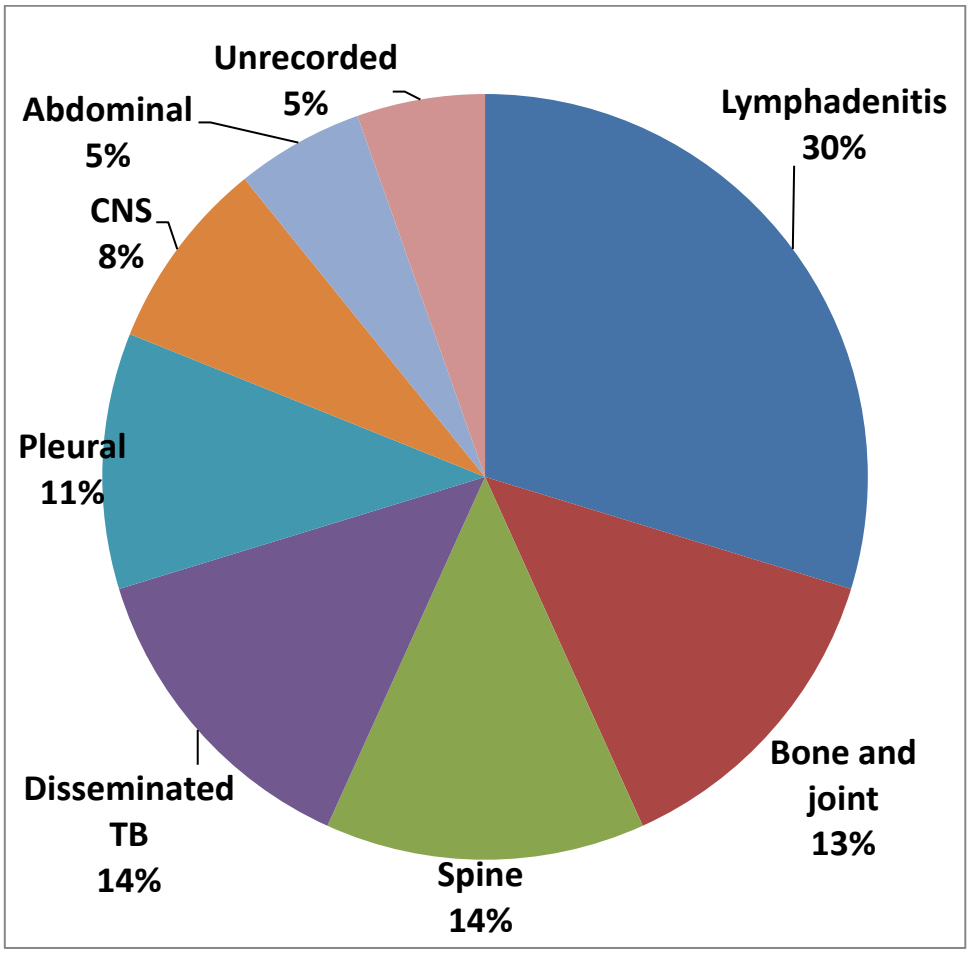

Figure 1 Distribution of extra-pulmonary infection sites among 37 children < 15 years in Accra, June 2010 to December 2013

Almost half of the children (45.6%) were diagnosed in the children's hospital. Less than 10% were diagnosed in the polyclinics. Of the 36 children diagnosed in the specialized hospitals, 4 came from the teaching hospital and the rest were from the regional hospital. There was no significant association between sex and the demographic and clinical variables analyzed.

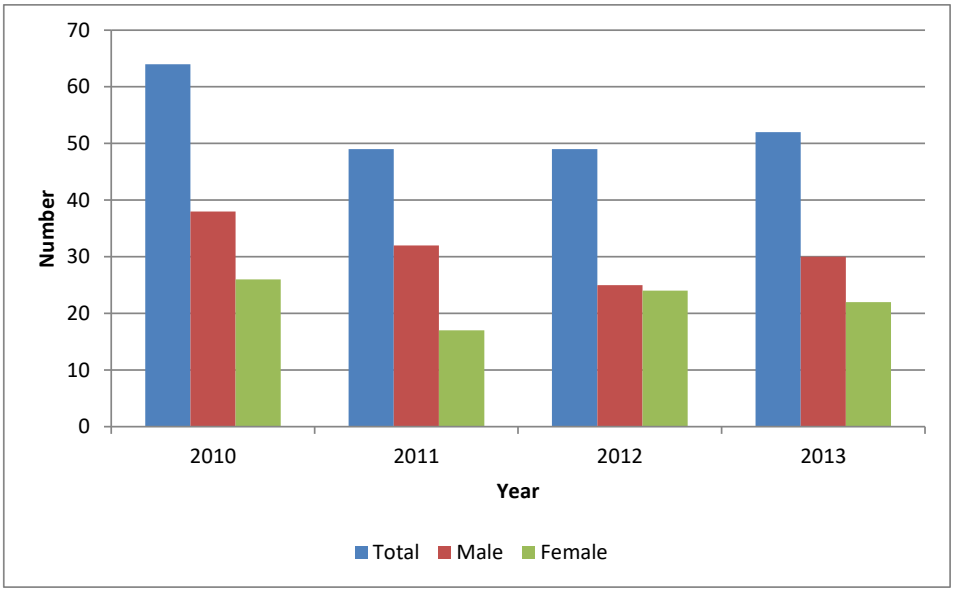

Figure 2 Distribution of children diagnosed with TB during TB case finding initiative by year and sex in Accra, June 2010 to December 2013

Treatment outcome

Treatment outcome was documented for 214 children (97.7%). One hundred and ninety-four of these, 90.7%, were successfully treated consisting of 81.3% who completed treatment and 9.4% who were cured. All the children were successfully treated in 2011. An adverse outcome was recorded for 20 patients; 18 (8.4% of the total with treatment outcome stated) died; 1 was not evaluated and 1 failed treatment. As shown in Table 3, there was significant association between treatment outcome and age, TB type, HIV status, facility attended.

The 10-14 year age group and the polyclinics had the highest proportion of those cured (35.6% and 28.6% respectively. Treatment completion was highest among children with clinically diagnosed pulmonary TB (91.6%). The highest percentage of deaths was recorded among those in the age group 1 to 4 years (13.3%), HIV positive (12.6%), smear positive pulmonary TB (12%) and at the children's hospital (12%). A male HIV positive child who had new smear positive PTB failed treatment while a

female child with EPTB was not evaluated. No child was reported to have been lost to follow up.

Table 3 Treatment outcome of children with TB in Accra June 2010 to December 2013 presented according to demographic and clinical variables

Characteristic	Cured Number (%)	Treatment completed Number (%)	Treatment failed Number (%)	Died Number (%)	Lost to follow up Number (%)	Not evaluated Number (%)	P-value
Sex							
Male	8(7.2)	94(84.7)	1(0.9)	8(7.2)	0	0	**0.426**
Female	11(11.1)	77(77.8)	0	10(10.1)	0	1(1.0)	
Age (years)							
< 1	0	27(93.1)	0	2(6.90)	0	0	
1 – 4	2(2.2)	76(84.4)	0	12(13.3)	0	0	**<0.001**
5 – 9	2(4.0)	46(92.0)	0	1(2.00)	0	1(2.0)	
10 – 14	16(35.6)	25(55.5)	1(2.2)	3(6.7)	0	0	
TB type							
Clinically diagnosed pulmonary TB	0	74(96.10)	0	3(3.90)	0	0	**<0.001**
EPTB	0	33(91.67)	0	2(5.56)	0	1(2.78)	
PTB smear positive	20(20.20)	66(66.67)	0	12(12.12)	0	0	
HIV status							
Negative	18(15.6)	90(78.3)	0	6(5.2)	0	1(0.9)	
Positive	1(1.0)	81(85.3)	1(1.0)	12(12.6)	0	0	**0.001**
Unknown	1(25.0)	3(75.0)	0	0	0	0	
Facility							
Children's Hospital	5(5.0)	83(83.0)	0	12(12.0)	0	0	
General Hospitals	9(13.9)	53(81.5)	0	3(4.6)	0	0	**0.009***
Specialized Hospitals	2 (5.7)	30 (85.7)	1 (2.9)	2 (5.7)	0	0	
Polyclinics	4(28.6)	8(57.1)	0	1(7.1)	0	1(7.1)	

The results of the regression analyses to assess predictors for mortality are shown in Table 4. Smear positive TB was identified as a risk factor for mortality in the univariable regression analyses. The preliminary multivariable logistic regression model showed that children with sputum smear positive TB (SPPTB) had higher odds of mortality compared to those with clinically diagnosed pulmonary TB [AOR = 6.1 (1.04, 35.57), p =0.045]; and HIV positive children had a higher odds of mortality compared to those who were HIV negative [AOR = 3.85 (1.24, 11.4), p =0.020]. In

the final regression model, SPPTB [AOR = 4.21 (1.13, 15.6), p =0.032] and HIV positivity [AOR = 3.24(1.15, 9.14), p =0.026] remained risk factors for mortality.

Table 4 Univariable and multivariable logistic regression analyses showing the risk factors for mortality among children with TB patients in Accra, 2010 to 2013

Characteristic	Died	Successfully treated	Univariable analyses		Multivariable analyses	
	N (%)	N (%)	Unadjusted Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value
Sex						
Male	8 (7.2)	103 (82.7)	Ref		Ref	
Female	10 (10.2)	88 (89.8)	1.42 (0.56, 3.58)	0.461	2.0 (0.71, 5.60)	0.187
Age						
< 1	2 (6.90)	27 (93.1)	Ref		Ref	
1 – 4	12 (13.3)	78 (86.7)	2.1 (0.44, 9.88)	0.358	2.1(0.40, 10.9)	0.386
5 – 9	1 (2.0)	48 (98.0)	0.56 (0.07, 4.22)	0.576	0.74(0.09, 6.11)	0.778
10 – 14	3 (6.8)	41 (93.2)	1.32 (0.22, 7.70)	0.760	1.24(0.16, 9.93)	0.838
TB type						
Clinically diagnosed pulmonary TB	3 (3.9)	74 (96.1)	Ref		Ref	
EPTB	2 (5.7)	33 (94.3)	2.24 (0.43, 11.70)	0.338	2.75(0.45, 16.88)	0.274
Sputum smear PTB	12 (12.2)	86 (87.8)	3.73 (1.02, 13.59)	0.046	6.10(1.04, 35.57)	0.045
HIV status						
Negative	6 (5.3)	108 (94.7)	Ref		Ref	
Positive	12 (12.8)	82 (87.2)	2.45 (0.93, 6.41)	0.069	3.85(1.24, 11.4)	0.020
Facility						
Children's Hospital	12 (12.0)	88 (88.0)	Ref		Ref	
General Hospitals	3 (4.6)	62 (95.4)	0.35 (0.10, 1.31)	0.120	1.30 (0.21, 8.20)	0.778
Specialized Hospitals	2 (5.9)	32 (94.1)	1.22 (0.24, 6.14)	0.807	4.00 (0.45, 35.34)	0.212
Polyclinics	1 (7.7)	12 (92.3)	0.69 (0.18, 2.59)	0.580	1.85 (0.29, 11.7)	0.514

Discussion

Calls for urgent action to protect children from TB and preventable deaths from this disease brings to the fore the increasing attention being paid to the global epidemic of childhood TB [22, 23]. This highlights the need to understand the characteristics and management outcomes of pediatric TB in various settings to inform appropriate planning and use of resources to enhance diagnosis, treatment and reporting in childhood TB services for better results [14]. In this study, the first to characterize

the demographic, clinical and treatment outcomes of children diagnosed with TB in Accra, Ghana, children less than 15 years constituted about 6% of the total TB burden in the participating health facilities. Nine out of ten of the children had a successful treatment outcome. HIV positivity was a risk factor for mortality.

The proportion of childhood TB cases among the total TB cases recorded in this study is similar to figures reported for Ghana [24], and comparable to findings from studies in cities like Lagos (6.3%) and Abidjan (6.6%) which are also in the West African sub-Region [8, 9]. The global TB reports indicate that children less than 15 accounts for 7% of TB cases notified. [1, 25]. Assessing the true burden of childhood TB is fraught with a number of challenges including constraints in bacteriologically confirming TB in children, under-reporting and inadequate TB diagnostic capacity in facilities where children are seen. This is highlighted in our study which showed that most of the children clinically diagnosed with TB were from the general hospitals which may have had limited capacity to adequately investigate and confirm TB in children. At the time of the study smear microscopy was the main stay of TB diagnosis as molecular tests for TB had not yet become widely available. It is expected that with the subsequent Ghana NTP policy to roll out additional screening tools such as digital Chest X-ray and Gene Xpert equipment for testing coupled with appropriate training for health staff, early detection and reliable diagnosis of TB in children will improve [5,24].

Several studies on childhood TB like ours report slightly more males than females with TB; in sync with the ratio of 1.1:1 reported globally [1, 6, 7, 9, 26, 27, 29]. Age wise, more than half of the TB cases in our study were in the younger age group. This is not unusual as younger children are reported to have a higher risk of progression from TB infection to disease [4, 30]. More than two out of five of the children in our study, were diagnosed with sputum smear positive TB similar to a study by Dangisso and colleagues in southern Ethiopia [27]. In contrast, other studies report higher proportions of sputum smear negative TB among children [8, 11, 31]. With TB in children being usually paucibacillary in nature and with the smaller amounts of sputum produced by children being swallowed, bacterial confirmation of TB in children is less common [32, 33]. It is possible that the high percentage of sputum

smear positivity in our study may have been due to under diagnosis of smear negative and clinically diagnosed TB especially among younger children [27, 28]. Kunkel *et al* argue that since children 4 years and below are less likely to be sputum smear positive (0.5%) than older children (14%) and adults (52%), reliance on sputum smear for diagnosis (which was the practice at the time of the case finding initiative) was associated with the risk of under diagnosing and under estimating TB in children.

The proportion of 17% EPTB among the study population was within range reported from studies in Benin [34], Turkey [35] and Cote D'Ivoire [8] while the finding of lymph nodes being the most commonly affected extrapulmonary TB site was also consistent with other studies [6, 36-41]. It is however interesting to note that globally, the proportion of EPTB among children with TB spans a wide range from 6% to 72% depending on the country reporting [8, 9, 26, 29, 31, 40]. A myriad of reasons have been suggested for this observation ranging from under-reporting and missing of EPTB cases, challenges with diagnosis, [29] to over diagnosis of EPTB and HIV infection rates of the population being studied [26, 29, 40]. The diagnosis of TB in children has long been recognized as challenging necessitating the use of multiple strategies including chest X-ray as a screening tool, clinical criteria and more sensitive molecular diagnostic methods [5, 41]. It was good to note that X-ray was being utilized in the TB diagnostic process in our study as three out of four of the children had an X-ray done compared to the 61% recorded in a Congolese study [26].

Unlike other studies in which as much as 75% of the study participants had no HIV status documented, the rate of HIV testing with results known among our study population was quite high [8, 26, 29, 31]. HIV status was not documented in only about 2% . This is commendable and showed that the health facilities were complying with the policy to test and counsel all TB patients for HIV [20].

The HIV infection rate in our children was similar to a study in Uganda [28] but relatively higher than other studies in Togo and Nigeria [9, 10]. In some of these studies, only a proportion of children had HIV status documented highlighting the possibility that the HIV infection rates reported may not have been a true reflection of the actual picture. HIV prevalence among children with TB from different parts of the world ranges from 10 to 60% [42]. Reported HIV-TB co- infection rates reflect

the prevailing national HIV infection rates and other associated factors such as extent of immune suppression [43, 44]. This again reiterates the importance of HIV testing and counselling for all children with TB and TB evaluation for children with symptoms suggestive of TB or history of contact with a person with infectious TB [42].

The treatment success of over 90% in our study is in sync with the trend of treatment success reported for the Greater Accra Region of Ghana where this study was conducted [45]. Our level of treatment success was however generally higher than figures reported from studies conducted in a number of countries Ethiopia (85%), Nigeria (77%), Malawi (77%) in the African Region though lower than the 98% reported from Cote D'Ivoire [6, 8, 9, 46]. In these studies with lower treatment success, the poor outcomes were for the most part due to the patients being lost to follow up or not being evaluated. The treatment success recorded in our study may reflect good case management and the adherence to the DOTS strategy implemented by the NTP in Greater Accra Region in particular and the country as a whole [24]. Amo-Adjei in his paper assessing measures put in place by the NTP in Ghana and the relationship with treatment outcome found that the reduction in TB associated stigma among community members and health workers, the use of treatment supporters and the enablers' package contributed to improved TB treatment outcomes and contributed to a two-fold increase from 44% in 1997 to 87% in 2010 and fewer patients lost to follow up [12]. In our study, mortality accounted for most of the children with poor outcome with the percentage of deaths higher in children with sputum smear positive TB and those co-infected with HIV. The mortality rate of 8.4% was not too far off from the figures reported from Malawi (9.5%), Botswana (10.5%) and Tanzania (10.9%), countries with a relatively higher HIV prevalence than Ghana [6, 47, 48]. In the logistic regression HIV positivity was associated with mortality, a finding corroborated in other studies [50]. Some of the possible reasons include the presence of other comorbidities, poor adherence due to an increase burden of drugs to take and drug resistance in co-infected children [40]. Considering the risk of latent TB developing into disease in persons living with HIV and the contribution of TB to

deaths among those co-infected, implementation of the Three I's for HIV/TB: intensified case-finding of TB (ICF), isoniazid preventive therapy (IPT) and infection control for TB provides opportunity to reduce morbidity and mortality in those without symptoms and signs of TB [49].

A review of the health sector TB program in Ghana indicated that IPT for children was not practiced universally neither was contact tracing conducted routinely [45]. These highlighted missed opportunities to identify children at risk of TB to protect them from developing the disease; and facilitate early diagnosis and initiation of treatment for those already with TB to limit negative outcomes. Subsequently, the NTP included the systemic screening of children as part of contact investigation and the promotion of IPT in its strategic plan [24]. Further studies are needed to assess the progress and outcome of the implementation of these strategies and the effect of preventing TB especially among HIV positive children. It was observed that 2010 recorded more TB cases over the 7-month period compared to the other full calendar years. This may have been due to the staff in the facilities adhering more closely to the case finding protocols in the first year soon after being trained for the new initiative as well as possibly more regular supervision in the starting months of implementation.

This study has some limitations. In making use of secondary data for the analyses, it was not possible to verify the diagnosis of TB in the study population nor distinguish between those that were probable and possible TB cases among those that were clinically diagnosed. It was also not possible to assess the clinical status of the children who were successfully treated especially since the majority was reported to have completed treatment. Another limitation is that there were some missing data in the database. Finally with the study population consisting of children with TB in Accra the findings may not be generalizable to those in other parts of the country. Notwithstanding these limitations, to our knowledge this is the first study to throw light on the treatment outcome of children derived from different categories of health facilities diagnosed and treated for TB in Ghana.

Conclusions

This study highlights the demographic, clinical characteristics and treatment outcomes of children with TB in Accra, Ghana. Strengths identified in the childhood TB management include the high testing and documentation of HIV status in these children and the high treatment success recorded which met the target of END TB Strategy treatment success indicator. This baseline data on childhood TB in Accra throws a challenge to the NTP to at best maintain these standards especially as it rolls out case finding and preventive strategies as well as more sensitive TB diagnostic methods as outlined in the health sector tuberculosis strategic plan. The study also showed that HIV positivity was associated with lower treatment success while death accounted for the majority of those with poor treatment outcome. As the NTP rolls out its interventions, paying close attention to children with smear positive pulmonary TB and those who are HIV positive may reduce mortality among them and improve treatment outcomes.

Abbreviations
AOR: Adjusted Odds ration; DOTS: Directly Observed Treatment Short Course; EPTB: extra-pulmonary TB; GXP: Gene Xpert; HIV: Human Immuno-deficiency Virus; NACP: National AIDS Control Program Guidelines; NTP: National Tuberculosis Control Program; OPD: Outpatient department; PLHIV: Persons living with HIV; PTB: Pulmonary tuberculosis; SPPTB: Sputum smear positive TB; TB: Tuberculosis; WHO: World Health Organization

Acknowledgements
The authors wish to thank the staff and patients of Korle Bu Teaching Hospital, Ridge Hospital, Achimota Hospital, Legon Hospital, Maamobi Hospital, Princess Marie Louie Hospital, La General Hospital, Kaneshie Polyclinic, Mamprobi Polyclinic, Ussher Polyclinic, Dansoman Polyclinic and the National TB Control Program for their part in making the TB case finding initiative possible. Thanks also go to Prof Lorna Renner for reading through the manuscripts and making useful suggestions and Mr John Tetteh and Dr Philip Tabong for the feedback on the data analyses. SAO is a WHO staff member; however the views expressed in this publication do not necessarily represent the decisions or policies of WHO.

Authors' contributions
SAO conceptualized and drafted the paper. SAO, SF, and PB conducted the statistical analysis and interpretation of the data. All authors read and approved the manuscript.

Funding
There was no specific funding support for these analyses.

Availability of data and materials
The dataset supporting the conclusions of this article is available in the Harvard Dataverse repository, https://doi.org/10.7910/DVN/KSTTWY

Ethics approval and consent to participate
Ethical approval was obtained from the Ghana Health Service Ethical Review Committee. The NTP and the participating facilities gave permission to access the data for the study. Consent to participate was waived as it was a retrospective study using secondary data for analyses.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1World Health Organization Country Office, Accra, Ghana. 2Ghana Health Service, Kumasi, Ghana. 3Ghana Institute of Management and Public Administration, Accra, Ghana.

Received: 1 March 2019 Accepted: 19 August 2019
Published online: 28 August 2019

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Chapter 6

Extra-pulmonary tuberculosis: a retrospective study of patients in Accra, Ghana

Sally-Ann Ohene, Mirjam Bakker,John Ojo, Ardon Toonstra, Doris Awudi, Paul Klatser

PLoS ONE (2019) 14(1): e0209650.
https://doi.org/10.1371/journal.pone.0209650

Abstract

Background: Information on extrapulmonary TB (EPTB) patients is limited in many African countries including Ghana. The study objective was to describe the epidemiology of EPTB patients diagnosed from different categories of health facilities in Accra, Ghana compared to pulmonary TB (PTB) patients and identify risk factors for mortality among EPTB patients.

Method: We conducted retrospective analyses of demographic and clinical data accessed from medical records of EPTB and PTB patients from different types of health facilities from June 2010 to December 2013. Factors at diagnosis associated with EPTB compared to pulmonary TB (PTB) and factors associated with treatment outcome death among EPTB patients were assessed using logistic regression.

Results: Out of 3,342 new TB patients ≥15 years diagnosed, 728 (21.8%) had EPTB with a male: female ratio of 1.17. The EPTB sites commonly affected were disseminated 32.8%, pleura 21%, spine 13%, and Central Nervous System (CNS) 11%. Treatment success rate for EPTB was 70.1% compared to 84.2% for PTB ($p<0.001$). In logistic regression, HIV positivity (adjusted Odds Ratio [aOR] 3.19; 95% confidence interval [CI] 2.69 – 3.79) and female gender (aOR 1.59; 95% CI 1.35 – 1.88) were found to be significantly associated with EPTB compared with PTB. Older age, being HIV positive (aOR 3.15; 95% CI 1.20 – 8.25) and having CNS TB (aOR 3.88; 95% CI 1.14 – 13.23) were associated with mortality among EPTB patients. While more EPTB patients were diagnosed in the tertiary hospital, health facility type was not associated with mortality.

Conclusion: EPTB patients in Accra have a worse treatment outcome compared to PTB patients with mortality of EPTB being associated with HIV, older age and CNS TB. Being HIV positive and female gender were found to be significantly associated with EPTB. Increased awareness of these factors may facilitate early case finding and better management outcomes for these patients

Key words: Ghana, extrapulmonary tuberculosis, mortality

Introduction

Despite major strides in prevention, diagnosis and treatment, tuberculosis continues to be a major leading cause of death globally [1]. An estimated 1.67 million people died from TB in 2016 [1]. The causative organism *Mycobacterium tuberculosis,* which is predominantly air-borne, affects the lung causing pulmonary TB. When TB is bacteriologically confirmed or clinically diagnosed in other parts of the body other than the lung such as the abdomen, meninges, genitourinary tract, joints, bones, lymph nodes and skin it is classified as extrapulmonary tuberculosis (EPTB). The prevalence of EPTB among new and relapse TB cases globally in 2016 was 15% [1]. The lowest prevalence (8%) was recorded in the WHO Western Pacific Region while the highest (24%) was recorded in the Eastern Mediterranean. The figure for the African Region was 16% [1].

The African Region, which has 13% of the world's population, accounted for 23% of the 918,011 EPTB cases reported globally in 2016 [1]. There is variation in the proportion of EPTB among TB cases in Africa with 5.2%, 31.7 % and 41.3% reported for Nigeria and Ethiopia and Djibouti respectively [2]. EPTB rates are even higher in the North African countries with Morocco and Algeria reporting 44.4% and 60% respectively [2]. Ghana, a high HIV/TB burden country, with an estimated 28 million population reported 14,675 TB cases in 2016 [3]. The proportion of EPTB patients reported among new TB cases has been in the range of 8 to 10% over the period between 2006 and 2016 [3,4]. Even though data from the Ghana National TB Control Program (NTP) indicate that the prevalence of EPTB among TB patients has remained fairly stable there is concern about the mortality among EPTB patients which almost doubled from 7.8% in 2006 to 14% in 2012 [4,5]. The investigation of contributory factors to this mortality rate was highlighted as an area of interest for research in the NTP 2015 -2020 Strategic Plan [5].

Various risk factors reported to be associated with EPTB include immunosuppression, HIV infection, male gender and younger age [6-13]. On the other hand, other studies have found females and increasing age to more associated with EPTB [14-17]. The sites of EPTB vary by age group and gender across different

populations studied, however lymph nodes and pleura invariably feature among the top reported sites from a myriad of studies [11,13,15,16,18,19]. In view of the peculiarities of EPTB including the atypical nature of presentation, understanding the epidemiology of EPTB in diverse settings is of interest given the relevance of EPTB to TB control [14]. Except for two teaching hospital setting studies on EPTB conducted in Ghana, studies on the EPTB in-country are limited [20,21]. The current study therefore sought to highlight the epidemiology of EPTB patients diagnosed from different categories of health facilities in Accra compared to pulmonary TB (PTB) patients and identify risk factors for mortality among EPTB patients.

Methods

The study was a retrospective secondary data analyses making use of the database of TB patients diagnosed from June 2010 to December 2013 during a TB case finding initiative implemented in 11 health facilities in Accra, the capital of Ghana. The details of the TB finding initiative were described elsewhere [22]. Accra, with a population of 1.7 million in the 2010 census, recorded HIV prevalence of 2.1% among antenatal clinic attendees over the period of 2010 to 2013 [23,24]. The facilities from which the study participants were derived included outpatient departments (OPD), HIV clinics and diabetes clinics in polyclinics, general hospitals, a regional hospital and a teaching hospital. The participants from the teaching hospital were from the HIV clinic only and did not include patients from the OPD or other clinics. These facilities accounted for 70% of TB cases in Accra at the time. From the TB case finding initiative database which consisted of 3,704 records, the participants for this study were selected using the following inclusion criteria: patients 15 years and older newly diagnosed with smear positive pulmonary TB, smear negative pulmonary TB or extra-pulmonary TB. The exclusion criteria were patients less than 15 years and those previously treated for TB. The classification of PTB and EPTB by the National Tuberculosis Control Program (NTP) in Ghana falls in line with WHO guidelines [25]. With the exception of cerebro-spinal fluid (CSF) samples, which were usually quite small in volume, EPTB samples for microscopy and culture were

taken through a decontamination process to get rid of other bacteria using a 4% sodium hydroxide (NaOh) and N-acetyl L-cysteine (NALC) preparation. [26] An equal volume of NaOH-NALC solution was added to the sample for a quarter of an hour followed by neutralization with phosphate buffer solution pH 6.8. The preparation was then subjected to centrifugation for concentration of the specimen and to wash off the sodium hydroxide reagent. The decontaminated concentrated sample was then inoculated for culture and smear preparation. At the time of the case finding initiative, sputum smear samples for examination under light or light emitting diode (LED) microscopy were processed using Ziehl Nielsen staining method. Sputum smear positive PTB was defined as a patient with acid fast bacilli in at least one sample of sputum. A patient was considered to have sputum smear negative PTB if he or she had two sputum smears negative for mycobacteria on microscopy, but Chest X-ray showed evidence consistent with active tuberculosis. EPTB was classified as per organs or systems affected exclusive of the lungs, such as lymphatic comprising of TB in lymph nodes, pleura, spine, TB in bones and joints other than the spine, central nervous systems CNS (TB meningitis, brain), abdominal and other such as genito-urinary tract. EPTB diagnosis was based on having one culture-positive specimen using fine needle aspiration biopsy or organ fluid samples such as ascetic or pleural fluid depending on the suspected site involved, or histological evidence or strong clinical confirmation of active EPTB for which the clinician makes the decision to treat with a full course of TB drugs. Culture methods available included solid culture using Lowenstein-Jensen media and liquid culture by means of Bactec Mycobacteria Growth Indicator Tube (MGIT960, BD, Sparks, USA). These diagnostic methods were available at the teaching hospital laboratory which also performed culture on samples that were delivered from other lower level facilities. In the event that a patient has EPTB in several organs, the patient is classified according to the site that is most severely affected. In NTP registration, patients diagnosed with both PTB and EPTB were registered as pulmonary TB. It is therefore not possible to distinguish which patients had both types of TB. At the time of the case-finding initiative, the same standardized first line TB drugs were used to treat new cases of EPTB and PTB for the duration of 6 months [25]. Classification of treatment

outcomes were cure, treatment completed, default, died, transfer out and treatment failure as per WHO guidelines. The combination of those recorded as having been cured and completed treatment were designated as having a favorable treatment outcome. Data of study participants obtained from their medical records included age, gender, HIV status, type of TB, site of the EPTB, facility of diagnosis, year of diagnosis and treatment outcome.

Data analysis was done by means of STATA version 12. The frequencies and percentages of the respective types of EPTB in totality and then stratified by gender and the age distribution were assessed. Multi-variate logistic regression analysis was conducted to identify factors associated with EPTB relative to PTB and risk factors associated with mortality among EPTB patients. Baseline characteristics including age group, gender, HIV status were included in the first model. In the second model those with who died during treatment were compared to those successfully finishing their treatment. Age group, gender, HIV status, affected site and facility of diagnosis were all included in the second model. Adjusted OR, 95% CI and p-values were calculated for each potential predictor variable with p-value of <0.05 set as the level of significance.

Data collected for the analysis did not have any personal identifying information and was handled with strict confidentiality. Ethics approval for the study was obtained from the Ghana Health Service Ethical Review Committee.

Results

Out of 3,704 TB patients recorded in the TB case finding initiative database, 219 children less than 15 years and 143 patients who were not new TB cases were excluded from the analysis. The study participants consisted of 3,342 new TB patients who were aged 15 years and above. The overall male female ratio was 1.68. A total of 1,443 (42.9%) of these TB patients, were from the polyclinics; 775 (23.2%) were from the general hospital; 775 (23.2%) were from the HIV clinic of the teaching hospital and 359 patients (10.7%) were from the regional hospital. There were 728 patients (21.8%) who had extra-pulmonary TB while 2,614 patients had pulmonary

TB. Out of the 728 EPTB patients, 400 (55%) were diagnosed from the HIV clinic of the teaching hospital. Almost half (48.5%) of the 2,614 pulmonary TB patients, were diagnosed in the general hospitals.

For 646 (88.7%) of the EPTB patients, the site affected was recorded. Two hundred and twelve (32.8%) of the EPTB patients had the classification of disseminated TB, while for 134 patients (18.4%) the site affected was the pleura (Fig 1). Twenty patients (2.9 % of EPTB cases) making up the category of "other" had various sites affected including pericardial, genitourinary, skin, and breast. Significantly more males 25.4% (87/343) reported pleural TB compared to females: 15.6% (47/302) $p<0.01$, while CNS TB was more common among females 15.2% (46/302) than men: 8.2% (28/343) $p<0.01$. For the other categories of EPTB, almost similar proportions of males and females were affected.

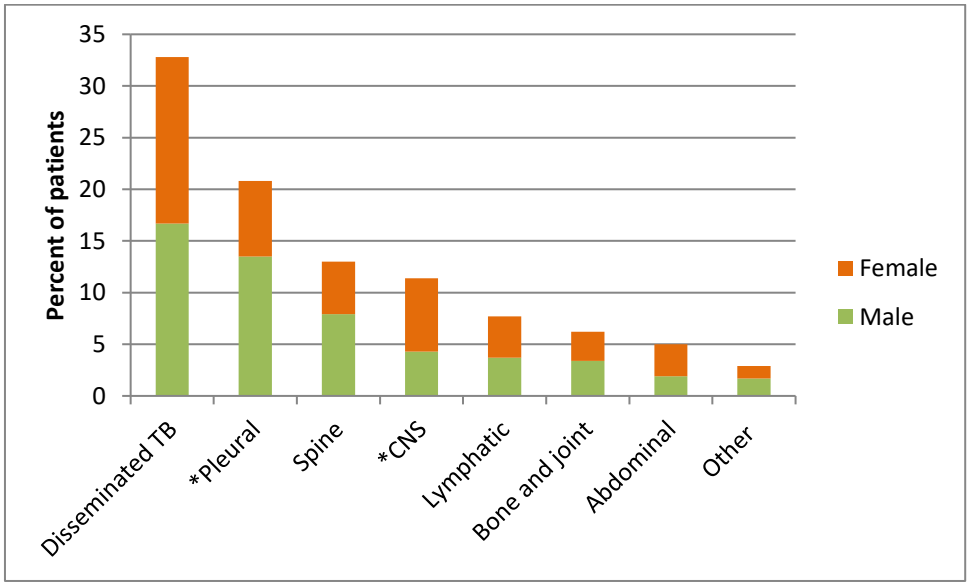

Fig 1. Distribution of 645 extrapulmonary patients by infection site and gender in Accra, 2010-2013.

The figure shows the distribution of EPTB across various sites for males and females. A significantly higher proportion of males had pleural TB while a significantly higher proportion of females had CNS TB compared to males.

Treatment outcome was documented for 665 (91.3%) EPTB patients. The overall treatment success rate was 70.1% for the EPTB patients (Table 1) with 6 patients reported to be cured. Treatment success ranged from 57.9% to 74.6% with 2012 being the year that treatment success rate was highest. The lowest treatment success rate was documented for 2013, possibly related to the low proportion of EPTB patients for which the treatment outcome was known (68%). Among EPTB patients, the overall mortality rate was 28.7%. The mortality rate was highest among those with CNS EPTB (52%) and disseminated EPTB (47%). Death rate among those with pericardial EPTB was also very high, but the number was very small (3/5 patients). Among PTB patients, the overall treatment success rate was 84.2% while the mortality rate was 12.6%.

Table 1. Treatment outcome of 665 EPTB patients with documented treatment outcomes out of 728 diagnosed EPTB patients in Accra from 2010 to 2013.

Year of diagnosis	Total number of EPTB patients diagnosed (% with treatment outcome documented)	Cured n (%)	Treatment completed n (%)	Treatment failed n (%)	Died n (%)	Lost to follow up n (%)	Not evaluated n (%)	Treatment success n (%)
2010	175 (98.9)	5 (2.9)	116 (67.1)	0	49 (28.3)	3 (1.7)	0	121 (69.9)
2011	215 (98.6)	0	154 (72.6)	0	57 (26.9)	0	1 (0.5)	154 (72.6)
2012	182 (95.1)	1 (0.6)	128 (74.0)	0	43 (24.9)	1 (0.6)	0	129 (74.6)
2013	156 (68.6)	0	62 (58.0)	0	42 (39.3)	0	3 (2.8)	62 (57.9)
Total	728	6 (0.9)	460 (69.2)	0	191 (28.7)	4 (0.6)	4 (0.6)	466 (70.1)

There was male predominance for both EPTB and PTB. For EPTB, the male: female ratio was 1.17:1 while for PTB, the male: female ratio was 1.87:1. The proportion of females with EPTB was significantly more than the proportion of females with PTB ($p < 0.001$) Table 2.

Table 2 Comparison of EPTB and PTB across demographic and clinical variables among TB patients in Accra 2010 to 2013

Characteristic	EPTB n (%)	PTB n (%)	p-value
Gender			
Male	392 (54.0)	1,698 (65.1)	
Female	334 (46.0)	909 (34.9)	<0.0001
Age (years)			
Median	38	39	
Mean	40.4 (13.5)	40.6 (14.3)	
15 – 34	270 (37.1)	950 (36.4)	0.722
35 – 54	342 (47.0)	1232 (47.2)	0.928
≥55	116 (15.9)	430 (16.5)	0.601
HIV status			
Positive	454 (62.4)	895 (32.4)	
Negative	268 (36.8)	1,686 (64.5)	<0.0001
Facility			
Polyclinic	72 (9.9)	703 (26.9)	<0.002
General Hospital	165 (22.7)	1,268 (48.5)	<0.0001
Regional Hospital	91 (12.5)	268 (10.2)	0.5411
Teaching Hospital	400 (55.0)	375 (14.3)	<0.0001
Treatment Outcome			
Treatment success	466 (70.1)	2118 (84.2)	<0.0001

The age distribution for both EPTB and PTB by gender is shown in Fig 2. Treatment success was significantly higher among PTB patients than EPTB patients.
The HIV status was known for almost all the TB patients (98.8%). Among these patients for whom the HIV status was known, about two fifths (40.8%) were HIV positive. About 62% of EPTB patients were HIV positive compared to 32.4% of the PTB patients. The participants in the study from the teaching hospital came from the HIV clinic and as such all these TB patients were HIV positive. Among these HIV positive patients from the teaching hospital, 52% had EPTB.
Among those who were HIV positive in the regional hospital, 20.5% had EPTB while the general hospitals and polyclinics had 8.3% and 6.3% respectively of the HIV positive patients having EPTB.

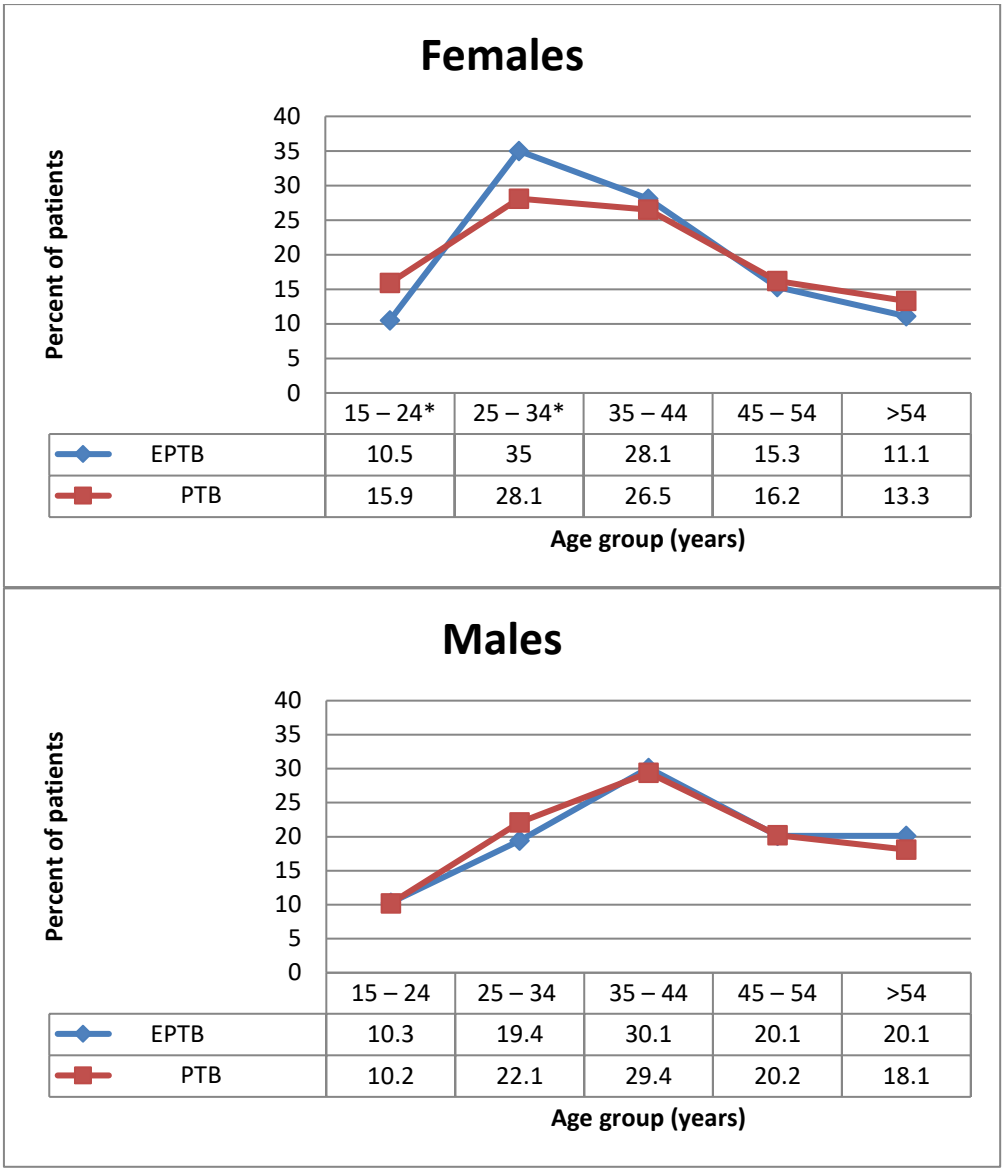

Fig 2. Age distribution of PTB and EPTB by gender among TB patients in Accra, 2010 to 2013. PTB: pulmonary TB EPTB: extrapulmonary TB

The cure rate and treatment success rate for HIV positive EPTB was 1.3% and 51.8% respectively while the figures for HIV positive PTB patients were 26.8% and 66.7% respectively.

The multivariate logistic regression analysis showed that EPTB patients were more often female and HIV positive compared to PTB patients (Table 3). The likelihood of developing EPTB was more than 3 times among those with HIV. On the other hand, the age groups did not show any differential association with EPTB.

Table 3. Multi-variate logistic regression model determining the risk factors for developing extra pulmonary tuberculosis relative to pulmonary tuberculosis among 3,342 TB patients in Accra, 2010 to 2013

Variable	Adjusted odds ratio	95% CI	p-Value
Age (Years)			
15 – 34	1		
35 – 54	0.98	0.81 – 1.17	0.834
≥55	0.95	0.74 – 1.21	0.723
Gender			
Male	1		
Female	1.59	1.35 – 1.88	<0.0001
HIV status			
Negative	1		
Positive	3.19	2.69 – 3.79	<0.0001

Table 4 shows the results of a multivariate logistic regression with mortality as outcome compared to those treated successfully among EPTB patients. Risk factors for death included increasing age, HIV positivity and CNS TB. Going by the cut off for statistical significance, the type of health facility attended by the EPTB patients did not appear to be associated with mortality, however mortality among EPTB patients attending the teaching hospital was worse than for the other facilities with the p value just falling shy of the level of significance at 0.077.

Discussion

This study elaborates on EPTB diagnosed among patients attending different types of facilities and HIV clinics in Accra over a period of three and a half years and

compares demographic and clinical characteristics of these patients with those having pulmonary TB. One fifth of the newly diagnosed tuberculosis had EPTB.

Table 4. Association of clinical factors and facility type with mortality among 657 EPTB patients in Accra 2010 to 2013

Variable	N	% Died	Adjusted odds ratio	95% CI	p-Value
Age (Years)					
15-24	68	8.8%	1		
25-34	176	33.5%	3.79	1.32 – 10.84	0.013
35-44	191	31.4%	2.54	0.88 – 7.23	0.082
45-54	115	31.3%	3.57	1.19 – 10.68	0.023
>54	107	28.0%	5.53	1.77 – 17.19	0.003
Gender					
Female	301	32.6%	1		
Male	354	26.0%	0.96	0.63 – 1.47	0.850
HIV status					
HIV-	249	8.8%	1		
HIV+	402	41.5%	3.15	1.20 – 8.25	0.020
unknown	4	33.3%			
Site affected					
Abdominal	30	13.3%	1		
Bone and joint	37	5.4%	0.56	0.14 – 3.64	0.547
CNS	67	53.7%	3.88	1.14 – 13.23	0.030
Disseminated	188	47.3%	2.85	0.89 – 9.11	0.078
Lymph nodes	47	14.9%	1.04	0.26 – 4.25	0.952
Other	13	15.4%	0.98	0.14 – 6.65	0.982
Pericardial	5	60.0%	4.15	0.49 – 35.30	0.193
Pleural	118	16.1%	0.84	0.24 – 2.89	0.780
Spine	78	12.8%	1.11	0.28 – 4.34	0.880
Facility					
General Hospital	148	11.5%	1		
Teaching Hospital	353	43.6%	2.40	0.91 – 6.31	0.077
Polyclinic	69	8.7%	1.54	0.45 – 5.23	0.489
Regional Hospital	87	16.1%	2.15	0.82 – 5.56	0.116

The most common form of EPTB was disseminated TB followed by pleural TB. A favorable treatment outcome was observed for seven out of ten EPTB patients with documented treatment outcome. Being HIV positive and female gender were found to be significantly associated with EPTB compared with PTB while older age, being HIV positive and having CNS TB was associated with mortality among EPTB

patients. The reported proportion of EPTB among TB patients in our study (21.8%) fell within the range of what has been reported for other countries such as Swaziland (18.4%), Cameroon (19.4%) and Botswana (25%), which like Ghana are also classified as having a high HIV/TB burden [1,4]. In this same category of HIV/TB burden countries, Uganda and Malawi have EPTB prevalence reported of 11% and 41%, respectively, highlighting the wide variation of the EPTB prevalence across countries and the uncertainty of reasons for this observation [4,13]. Interestingly, the prevalence in our study was relatively higher than the countrywide data in the range of 8-10% reported for Ghana [4]. It is worthy to note that our study population was derived from facilities in Accra and also consisted of patients from the country's premier teaching hospital HIV clinic, which has a large clientele. Usually such tertiary facilities have more sensitive diagnostic options for identifying EPTB. Secondly being a referral hospital, it receives a range of patients from other facilities including possibly HIV positive EPTB patients who may have been referred because of difficulties in making a diagnosis. This may explain the preponderance of the EPTB patients from the teaching hospital and the observed prevalence of EPTB [12]. The HIV prevalence of 40% among our patients was also high compared to the 24% reported for Ghana because of the selection of the clinics for the case finding initiative which in the teaching hospital involved only the HIV clinic to the exclusion of the OPD and other clinics [4, 22].

Different studies report the pleura and the lymphatic system as the commonly affected extra pulmonary sites, while in our study disseminated TB topped the list followed by the pleura and other sites similar to what others have reported [12,13, 18, 27,28]. The rate of disseminated TB that we found was similar to what was reported in a study of EPTB patients seen in a referral hospital in the capital of Cameroon [28]. Disseminated TB is a severe form of EPTB usually associated with HIV infection with progression linked to the immuno-suppression and delayed treatment [29]. Given the HIV coinfection in our study population and with disseminated TB presenting with systemic symptoms, it is possible that delayed diagnosis may have contributed to this magnitude of disseminated TB [6,12, 20].

In consonance with other studies, our study found an association between female gender and EPTB [10,13,27,30]. While the reasons for this finding have not been clearly identified, it is suggested that genetic factors, gender differences in exposure to TB and the presence of other risk factors such as smoking could possibly be the linking factors [12,15]. Further studies are needed to clearly delineate the linkages. The distribution of the site affected by EPTB across gender however does not appear to follow a clear pattern as various studies show similar or slightly different gender predominance in one site or the other [11, 12,14,16]. The predominance of males among those with pleural TB found in our study has also been reported by other researchers [10,27,28]. Similar to what was observed in other studies, we found no association between EPTB and age [15,31].

The treatment success rate for EPTB in our study was comparable to what Gomes *et al.* reports for EPTB patients in Brazil but lower than what was reported by studies conducted in Benin, Ethiopia and India [10,15, 32,33]. On the other hand, it is higher than what was reported by other researchers in Nigeria [34,35]. Various systems of DOTS implementation may be contributory factors to the differences. The treatment success rate for Ghana has shown consistent improvement over the years with figures exceeding 85% over the course of the time during which data for our study was recorded [4,36]. This achievement has been attributed to various factors including social and biomedical factors including the enablers package, community involvement in treatment and the used of fixed dose combinations [36]. The EPTB patients in our study had a relatively lower treatment success rate than the national average for the country. Among those with poor outcomes, it was observed that death was responsible for an overwhelming majority. The rate of disseminated TB among our patients may be associated with the mortality observed given that in their study of mortality among Ghanaian TB patients, Nassikas *et al*. and Burton and colleagues showed disseminated TB as one of the highest risk factors for death [20,37]. The HIV co-infection predominance among EPTB patients compared to PTB and the finding of HIV and CNS TB as risk factors for death in our study corroborates findings from different studies and highlights the importance of early initiation of anti-retroviral therapy for the survival of HIV-infected EPTB patients [7, 10,29,37-39]. As pointed

out by Ade *et al.* severe immune-suppression found in HIV patients with EPTB predisposes to these patients succumbing to opportunistic infection and ultimately death especially when anti-retroviral therapy is started late [10]. This re-iterates the importance of vigilance to facilitate early diagnosis of EPTB to improve treatment outcomes and minimize the risk of progression to advanced forms and death [40,41]. TB infection in people is mainly caused by *Mycobacterium tuberculosis* complex [42]. The data on the causative pathogens for EPTB was however not available to this study. Unlike for pulmonary tuberculosis, very little has been studied on the *Mycobacterium tuberculosis* complex species responsible for EPTB in Ghana. One study conducted in Accra however found *M. tuberculosis* to be the predominant organism (eighty-eight percent of the samples) with *M. africanum* being the only other organism accounting for the remainder [26]. In various studies on pulmonary TB in Ghana in which samples were analyzed, *M. tuberculosis* was also the major organism of *M. tuberculosis* complex isolated followed by *M. africanum* accounting for 73% to 97.6% and 2.4% to 23% of samples respectively [42-45]. *M. Bovis* was however isolated in fewer studies and accounted for 0.4 to 3% of the samples [42,44].

EPTB diagnosis in general poses a challenge given the problem of obtaining the appropriate specimen from suspected EPTB sites and the fewer *Mycobacterium* bacilli in EPTB samples limiting the identification of AFP using microscopy [41]. At the time of the TB case finding initiative, microscopy which has low sensitivity but high specificity, was the main stay of TB diagnosis in these lower level facilities though further tests such as cultures on samples could be accessed at the teaching hospital laboratory. Fewer cases of EPTB were diagnosed in general hospitals and clinics in our study and may reflect a lack of appropriate well-defined diagnostic algorithms as available for PTB as well as inadequate facility resources and clinical expertise [30]. Since generally more people access health care at lower level health facilities compared to tertiary hospitals, the cost benefit may be in favour of enabling these non-tertiary facilities using appropriate algorithms to freely access molecular tests and culture, which have higher sensitivity and specificity compared to microscopy [46]. This may improve timely diagnosis of EPTB especially among those living with HIV to ultimately reduce morbidity and mortality [41]. Our study

shows that health facility type was not significantly associated with mortality. Further studies could explore possible factors at play including the association if any between the time to diagnosis and initiation of treatment at the respective facilities and treatment outcomes.

Our study has some limitations. It involved secondary data analyses with the data source being the TB-case finding initiative database. Consequently there could be potential errors in the data since it was not possible to verify the diagnosis of EPTB or assess whether some of the study participants were misdiagnosed as EPTB. Similarly, the clinical improvement of patients who completed treatment could not be verified. Secondly, it was also not possible to distinguish patients who had concurrent EPTB and PTB among the study population as this information was not clearly indicated. This is against the background that in reporting as per Ghana NTP guideline, patients with both EPTB and PTB are recorded as PTB. There was also the challenge of incomplete documentation. The data from the teaching hospital consisted only of patients from the HIV clinic which may have introduced an element of bias in the results showing the association between EPTB and HIV. This result should therefore be interpreted against the light of this potential bias. Finally, with the study population being derived from Accra, the study findings may preclude generalization to the rest of the country. Despite these limitations, a major strength is that, to our knowledge, this is the first study that uses data from different facility types in Ghana to elaborate on EPTB in comparison to PTB, the treatment outcomes of EPTB patients and the risk factors for mortality.

Conclusion

This study in summary showed female gender and HIV co-infection as risk factors for EPTB, and HIV and CNS TB as risk factors for death among EPTB patients. Increased awareness of these factors, provision of and training in country-adapted diagnostic algorithms and making more sensitive diagnostic tools accessible may contribute to earlier case finding and diagnosis of EPTB patients especially at lower

level health facilities for initiation of treatment and possibly better management outcomes [41,47].

Acknowledgement

The authors acknowledge with gratitude the staff and patients of Korle Bu Teaching Hospital, Ridge Hospital, Achimota Hospital, Legon Hospital, Maamobi Hospital, Princess Marie Louie Hospital, La General Hospital, Kaneshie Polyclinic, Mamprobi Polyclinic, Ussher Polyclinic, Dansoman Polyclinic for the various roles played during the TB case finding initiative that ultimately made this study possible. Dr. Mukund Uplekar, Dr. Knut Lönnroth, Dr. Salah Ottmani, and Dr. Jacob Creswell are appreciated for the technical support provided for the successful implementation of the TB case finding initiative in Ghana.

Author Contributions

Conceptualization: Sally-Ann Ohene.

Data curation: Sally-Ann Ohene, Ardon Toonstra, Doris Awudi.

Formal analysis: Sally-Ann Ohene, Mirjam I. Bakker, John Ojo.

Investigation: Sally-Ann Ohene, Mirjam I. Bakker, John Ojo.

Methodology: Sally-Ann Ohene, Mirjam I. Bakker, John Ojo, Paul Klatser.

Project administration: Sally-Ann Ohene.

Resources: Mirjam I. Bakker, John Ojo, Ardon Toonstra, Doris Awudi.

Software: Mirjam I. Bakker, John Ojo, Ardon Toonstra, Doris Awudi.

Supervision: Sally-Ann Ohene, Mirjam I. Bakker, Paul Klatser.

Validation: Sally-Ann Ohene, Mirjam I. Bakker, Paul Klatser.

Visualization: Sally-Ann Ohene, Mirjam I. Bakker.

Writing – original draft: Sally-Ann Ohene.

Writing – review & editing: Mirjam I. Bakker, Ardon Toonstra, Paul Klatser.

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Chapter 7

Discussion

Introduction

The global END TB Strategy stresses that driving the TB epidemic down requires interventions that transcend traditional means of TB diagnosis and treatment to exploring a mix of different proactive strategies that make available the range of TB services to all those who need these services. [1] Among others, this calls for learning from and implementing programs that are adapted to local settings taking into consideration the concepts of universal health coverage. Ghana NTP's goal to early detect and increase TB case identification for prompt enrollment into care ultimately to attain higher treatment success and reduced mortality from TB draws from the vision of the END TB Strategy. [2] Against this backdrop, this thesis presents studies assessing components of the TB care cascade, examining outcomes of case finding interventions, the gateway to accessing TB care and evaluating treatment outcomes the last stage of the pathway, looking at childhood TB and extrapulmonary tuberculosis. The objectives of the studies were to investigate what innovative TB case detection approaches could be deployed to intensify and enhance TB case finding in health facilities and in the community respectively and also, assess treatment outcomes and the factors that are associated with the worst outcome, death for EPTB and Childhood TB to outline priorities to improve treatment success. The study findings highlighted the feasibility of implementing viable TB case-finding strategies such as short duration symptom screening leveraging existing structures, and the need to pay attention to enhancing TB/HIV program collaboration and health system strengthening including deployment of relevant tools to improve treatment outcomes.

These studies were however conducted before the era of the COVID-19 pandemic which begun as a health problem but has subsequently affected almost every sector globally. In 2020, the demands of responding to the COVID outbreak compromised delivery of essential health services and TB services were not left out. [3] In a survey of 105 countries, 42% of the countries reported partial disruption of TB case detection and treatment. [3] The Ghana NTP reported a 15% decline in TB cases notified in 2020 compared to the previous year, attributing this reduction to the impact of the COVID

pandemic.[4] As this concluding Chapter ties in the findings from the studies and highlights promising potentials for implementation, the current COVID context makes an argument to strengthen the health system with the necessary support and make it resilient to stand the shocks of future emergencies to minimize essential service disruption and erosion of gains such as those attained for TB.

TB case finding

Given the long-standing challenge of low TB case finding in Ghana, we sought to address questions on whether innovative TB case detection approaches could be deployed successfully under programmatic conditions to intensify and enhance TB case finding in health facilities and in the community, respectively. This involved comparing a shorter cough duration combined with other symptoms screening approach and the traditional 2-week cough in different clinic settings to assess for superiority (Chapter 2). In view of the hitherto largely untapped high-risk group of TB case contacts, the yield of TB from investigated contacts of known TB cases after symptomatic screening in the community was also assessed (Chapter 3). In the community setting, TB case finding this time among vulnerable populations in hard-to-reach areas was assessed. This involved evaluating the outcomes of TB screening activities undertaken by mobile teams among artisanal mining communities (Chapter 4).

Case finding in health facilities

The implementation of the case finding approaches in the health facilities showed that the symptom cum shorter cough duration (>24-hour) approach significantly yielded more people presumed to have TB (0.82% versus 0.63%) and more TB cases per 100,000 screened compared to the longer duration >2-week cough screening approach. Across the groups, PLHIV, diabetics, OPD attendees and contacts, that were screened using the >24-hour approach, the yield per 100,000 from the HIV clinic (995.4) topped followed by that from the contacts (692.9), diabetes clinic (364.1) and OPD (92.7). The implementation of the intervention was nevertheless not

associated with an increase in TB notification. The assessment of historical NTP TB notification data projected a downward trend over the time frame of the intervention. Actual NTP data corroborated these projections implying there could be some intrinsic programmatic bottlenecks that require further investigation. [4]

The value of TB case search in health facilities particularly among outpatients found in this study has however been buttressed by other studies.[5-7] In the quest to increase the pool of TB cases detected however, the use of cough of any duration and other TB symptoms has the advantage of improving sensitivity though at the expense of specificity and having to deal with a higher demand for TB diagnostic tests.[8-10] The advantage is even more striking for high risk populations such as persons living with HIV, diabetics and contacts of TB cases as shown in our study. This screening approach in OPDs has been adopted by the NTP and complemented by availability of other sensitive screening tools and diagnostic tests such as chest x-ray and GeneXpert. An estimated 126 GeneXpert sites had become available in the country in 2020 compared to 15 in 2014. [4,11] This strengthening of the health system is a boost for improving TB diagnosis and case detection.

TB contact investigation

TB contact investigation is recommended given that contact of TB patients are at high risk for contracting TB and yet this practice was virtually non-existent in Ghana under the NTP. [8,13,14] The findings from our study however highlighted that contact investigation of TB cases to identify presumed TB cases for further investigation was feasible under programmatic conditions. More than 90% of TB index patients had their contacts listed and screened similar to what was reported in Armstrong's study on contact investigation cascade under the NTP in urban Uganda.[15] The overall yield of TB cases among contacts screened (0.65%) was within range of what has been reported in other studies. [16,17] It is however likely that this yield underestimates the real burden of TB among the contacts investigated, because a decline in the number of presumed TB cases among the contacts tested for TB was observed over time and may have been due to challenges following through the referral for testing, while

sputum microscopy was the TB diagnostic test in use at the time. Ayakaka and colleagues' study in Kampala identified stigma, unfriendly clinic services and travel costs among the barriers to successful investigation of contacts, while education and personalized services were found to be facilitators. [18] Through follow up visits and calls, community health volunteers in Kenya were found to play an effective role in referred presumed TB contacts making it to the health facilities for testing in a study by Abongo *et al*. [19] In addition to exploring these measures that affect drop out of contacts being investigated, the deployment of TB diagnostic tools that are more sensitive and the adoption of CXR screening algorithms cannot be underscored as a means of improving the diagnosis of TB among this high risk TB group. [8,20,21] The NTP in 2019 introduced the system of transporting sputum samples from facilities to sites with GenXpert machines testing for testing. [22] This is very laudable as a means of improving access to testing samples from peripheral facilities. Ensuring sample collection from eligible contacts who may not present themselves at the facilities would go a step further to minimize missed opportunities.

Case finding among mining communities

We found that the prevalence of TB among the people screened in the artisanal mining communities in this study was more than two and half times what was reported for the general population in the TB prevalence survey while the rate of rifampicin resistance exceeded four times that from surveillance data. Miners are among the groups of people recommended for TB screening given their risk for TB.[8] Rambiki and colleagues in their study of miners in Malawi found that those in informal mining were even more likely to develop TB compared to those in formal mining. [23] Although artisanal mining communities may be hot spots for TB, they may be found in remote and out of way communities necessitating outreach programs to make TB services accessible to them. [24,25] WHO recommends a chest X-ray (CXR) based screening approach in combination with symptom screening.[8] In our study, CXR was one of the screening tools used but the sensitivity of cough of any duration as a screening tool for the detection of TB was comparable to that of chest X-ray. In

this regard, limited accessibility to CXR should not pose a problem in the quest to leave no one behind when it comes to making available to this group of people TB screening services and enrolment into the TB care pathway.

Treatment outcomes

One of the central components of the END TB Strategy integrated patient-centered TB care pillar is the treatment of all people with TB. [26] To this end, having been diagnosed with TB, successfully registered and initiated on TB, the goal is for the person regardless of age or type of TB to achieve treatment success. Given that in the TB care pathway, much attention has been paid to treatment outcomes in those with pulmonary TB, the searchlight was turned in the direction of children diagnosed with TB and those with extrapulmonary TB. In Chapter 5, an assessment of demographic and clinical characteristics and treatment of children with TB was undertaken with an analysis on the predictors of mortality. In a similar vein, in Chapter 6 the dimensions and treatment outcomes of people with EPTB diagnosed from a range of care facilities were investigated. Factors associated with the worst treatment outcome death were determined.

Treatment outcome in children with TB

Our study findings indicated that children less than 15 years made up 6% of the TB cases reported. Nine out of ten children (90.7%) put on treatment were successfully treated while the mortality rate was 8.4%. Mortality was highest among those in the 1 to 4-year group, those coinfected with HIV and those diagnosed with sputum smear positive TB (SSPT). HIV and SSPT were found to be risk factors for mortality. These findings are in consonance with studies assessing treatment outcomes in children from different countries. [27-29] Persons living with HIV and children less than 5 years who are contacts of persons with TB are considered at risk populations in relation to latent TB infection being reactivated to active TB disease. [26] As such, the value of these children being listed as contacts, investigated and initiation of TB preventive therapy (TPT) as relevant in reducing this risk cannot be underscored. [26] The roll out

of TPT is in the Ghana TB strategic plan and guidelines have been developed. [2,30] With such commitments made, rallying round the necessary stakeholders such as HIV service providers, strengthening the health system requirements and deployment of the required tools such as simplified algorithms may pave the way for implementation. [26] SSPT in children may signal more severe TB disease therefore the deployment of more sensitive diagnostic tools to facilitate earlier diagnosis of TB in children and TB treatment initiation and completion may also improve outcomes. [29,31] Parents are key stakeholders for treatment success in children on TB treatment and a conducive relationship with health care workers augurs well for parents positively supporting their children on treatment. [32,33]

Treatment outcome in EPTB

From our study, being female and HIV positive was associated with EPTB. Seven out of ten persons with extrapulmonary TB were treated successfully but this proportion was significantly lower than that for pulmonary TB. Almost all (>95%) of those with a poor treatment outcome died. Being older, HIV positivity and having CNS TB were associated with death among EPTB patients. Our study findings are similar to what other studies on EPTB have found.[34-37] The importance of paying attention to HIV treatment and early diagnosis and management of CNS TB is therefore paramount if the End TB strategy treatment success rate of 90% is to be achieved among those with EPTB.[26] As Ghana has adopted a treat all strategy, ensuring early initiation and adherence to antiretroviral therapy (ART) for persons living with HIV serves to augment immune-suppression improving survival.[38,39] It is therefore imperative to address the bottlenecks in HIV service delivery which includes reported shortages of ART. [40] Zurcher *et al* reported a lower association with mortality among EPTB patients with bacteriologic confirmation compared to those with negative result with the suggestion of lower immunosuppression in the latter. [34] This reiterates the advantage of making available simple diagnostic algorithms and more sensitive diagnostics tests accessible in lower level health facilities where the majority of people access care to facilitate timely identification of EPTB for

treatment. [31,34] In addition, support to promote adherence to complete treatment may be of particular benefit for those with CNS TB to improve outcomes given the treatment regimen is relatively longer. [31, 36,41]

Policy implications

In these studies investigating TB case find initiatives and treatment outcomes, there are underlying themes cutting across the studies. These are the need for the NTP to facilitate decentralized deployment of simplified active case finding screening algorithms and molecular diagnosis tests at facility and community levels to enhance TB diagnosis across board for timely enrolment into care and initiation on treatment, complemented by collaboration with other programs particularly the HIV program to enhance the continuum of integrated care and optimum treatment outcomes.

For TB care delivery to be a reality as expounded in the END TB Strategy, there's a need to go beyond passive TB case finding which relies on the patient's initiative and several other factors to adopting provider-initiated strategies leveraging already available resources in the health system. [20] People presenting to health facilities with various ailments or those presenting to high risk clinics are a "captive audience". Our studies suggest that, with the help of simple sensitive screening algorithms such as that involving a shorter cough duration with other TB symptoms administered by OPD staff taking vital signs, presumed TB cases can be identified for further investigation among OPD attendants especially among those at high risk for TB at HIV and Diabetes clinics. The identification of more people presumed to have TB however usually leads to a higher demand for TB tests which could turn out to be a bottleneck if the laboratory is not adequately prepared to handle the additional tests. Planning to cope with this demand is therefore imperative in the implementation of active case finding programs. [42]

Implementation of contact investigation was also found to be feasible under programmatic conditions. Given that as part of the protocol for initiation of TB treatment home visitation is undertaken for home verification, contact identification and screening can be added on. Finding ways to address all access to testing barriers

such as sample collection and transport for the presumed TB cases among contacts could improve the yield of TB cases. Continuous supervision of the contact investigation steps is imperative to avoid the yield reducing overtime.

Scaling up access to diagnostic molecular tests either at a physical location or through the sample transport mechanisms is imperative to minimize delays and missed opportunities for early diagnosis and treatment initiation.

The TB screening outreach to case mining communities aligns with the tenets of universal health coverage which is a target in the sustainable development goals. [43] While deployment of X-ray equipped mobile teams into the mining communities may not always be practicable, symptom screening using simplified tools administered by community health workers on outreach within their catchment areas could be the bridge to accessing the TB care cascade.

Our findings showed HIV as a key risk factor for poor treatment outcome for EPTB and childhood TB. Identification of and addressing bottlenecks to the promotion and increased coverage of integrated TB/HIV services including at maternal and child health delivery care points will enhance doorstep management of those coinfected ultimately improving survival. [26]

Study Strengths and Limitations

There are several strengths of the studies in this thesis worthy to be elaborated. For one, these studies objectively assessed innovative program activities to provide evidence-based data on the outcomes of case finding activities and the feasibility of implementing the interventions making use of existing structures. The findings pointed out the strengths of the interventions, the gaps and areas for improvement to maximize yield of TB case detection and treatment outcomes.

The methodology for conducting the studies was rigorous and made use of routine data collected by the national TB program. Data from the NTP, largely an underutilized but exceptionally valuable resource of “real world” data, easily allow the expedient and effective assessment of the TB situation. The programmatic database can be harnessed to answer a variety of gaping questions and address the

research needs of TB programs to guide tailored adjustments and improvement in program implementation. Key among the advantages of leveraging routine data for analyses include its cost effectiveness and ready availability. The wide scope of demographic and clinical variables enables analyses of different dimensions of TB prevention and control such as gender sensitive aspects and a variety of subjects that enable exploration of the various stages of the TB case pathway. Similar conclusions can be drawn with secondary data analysis as is done with primary data analysis. The routine data are the same data that are compiled to track TB trends that are described locally and globally such as in annual WHO TB reports to shape policy and the strategic direction for combatting TB.

Another strength is that the diverse study populations and settings evaluated in these case detection and treatment outcomes studies namely OPD patients, contacts of index TB patients, artisanal mining communities in hard to reach areas, children with TB and extrapulmonary TB patients present a unique opportunity to learn different lessons as the TB care pathway is explored.

Finally, to the best of our knowledge, the study investigating TB case detection among communities involved in artisanal mining using different methods including X-ray is novel and has made available data in the relatively under-researched area of TB in small scale mining communities.

There are a few limitations of the studies in the thesis. Routine programmatic data collected by the National TB Program was the primary data source. Though readily available to answer a variety of questions, the quality may less controlled. Secondly, since the data has already been collected, the parameters are set and cannot be manipulated to explore other variables that may be of interest but have not been captured. The dataset for the contact investigation assessment for example did not have age disaggregated data to explore analyses on children who may have contracted TB through contact with an index TB case. The NTP may therefore want to explore deficient data collecting tools to include elements of age, sex, type of TB diagnosed, HIV status of TB cases and PLHIV initiated on TB preventive treatment.

Unlike interventional studies which may be conducted within strict laid down protocols and criteria, activities implemented by NTPs are usually rolled out under

programmatic settings and may not be free of certain biases. In the health facility-based TB case finding intervention, selection and assignment of facilities to the different screening methods were not randomized. As a result, the potential for biases due to particular factors associated with the implementing facilities could not be ruled out.

Though there was no means of confirming the diagnosis of TB reported, the NTP however reports this same data to WHO for the TB reports and the data are recognized as official for the country and consistent with what is reported globally.

The studies in the thesis utilized data collected in specific locations as opposed to nationwide data. The findings may therefore not be generalizable across board.

Recommendations for future research:

1. As more sensitive diagnostic tools are introduced, it would be useful to conduct operational research to assess the impact of this deployment in terms of yield of TB cases in addressing the TB case finding gap.
2. With the ultimate goal of TB case identification being successful treatment, further research could investigate the remaining steps of the TB care pathway up to treatment outcomes for TB cases identified through intensified and enhanced case finding initiatives to determine the barriers to optimum treatment outcomes if any.
3. An assessment of facilitators and barriers to effective integration of TB/HIV services would unearth useful data that can be used to enhance collaborative services for improved treatment outcomes for TB/HIV coinfected persons.

Conclusion

The TB care pathway spans various steps from the number of people infected with TB in the population accessing a TB test to those achieving successful treatment with patient losses along the way. Narrowing the gap between estimated incident and reported TB cases calls for innovative TB case finding strategies. The studies in the thesis have investigated TB case finding approaches and highlighted that systematic

screening of high risk OPD patients particularly PLHIV and diabetics, using a short duration symptom screening and screening of other targeted specific risk groups in the community (such as the miners and contacts of index TB patients) making use of existing structures can significantly enhance TB case finding if complemented by access to sensitive screening algorithms and diagnostic tests with the relevant capacity built. For those with extrapulmonary and childhood TB, mortality accounted for poor treatment outcome and HIV positivity was the major risk factor. Enhancing TB/HIV collaborative services to minimize barriers to integrated care delivery could improve survival and have a positive impact on treatment outcome.

If an estimated two-thirds of incident TB cases are not being identified to get tested as is the case for Ghana, the goal of ending TB will be a pipe dream even if treatment outcomes are good as TB transmission will continue to pose a challenge. The findings from these studies provide the NTP with evidence of innovative low-hanging fruit interventions for implementation.

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Abbreviations

AFB	Acid Fast Bacilli
AMC	Artisanal Mining Community
AOR	Adjusted Odds Ratio
AS	Ashanti
AUC	Area Under the Curve
CIDA	Canadian International Development Agency
CNS	Central Nervous System
CXR	Chest X-Ray
DM	Diabetes Mellitus
DOTS	Directly Observed Treatment Short Course
DR-TB	Drug-Resistant Tuberculosis
ECF	Enhanced Case Finding
EPTB	Extra-Pulmonary Tuberculosis
GA	Greater Accra
GXP	GeneXpert
HIV	Human Immunodeficiency Virus
MTB	*Mycobacterium Tuberculosis*
NACP	National AIDS Control Program
NNS	Number Needed to Screen
NNT	Number Needed to Test
NTP	National Tuberculosis Control Program
OPD	Outpatient Department
OR	Odds Ratio
PLHIV	Persons Living With HIV
PTB	Pulmonary Tuberculosis
ROC	Receiver Operating Characteristic
SS -ve	Sputum Smear Negative
SS +ve	Sputum Smear Positive
SPPTB	Sputum Smear Positive Tuberculosis
TB	Tuberculosis
WHO	World Health Organization

Samenvatting

In dit proefschrift worden verschillende aspecten van het tuberculose (TBC) zorgtraject in Ghana onderzocht en wordt gewezen op een aantal potentiële gebieden voor het verbeteren van de opsporing van mensen met TBC. Ook zijn behandelingsresultaten beoordeeld van belangrijke patiëntengroepen die vaak buiten beschouwing worden gelaten, namelijk kinderen en mensen met extrapulmonale TBC.

Hoofdstuk 1, de inleiding, legt de basis voor het proefschrift door licht te werpen op TBC, wat het is en de wereldwijde strategie voor de bestrijding van de ziekte. Het beeld van de TBC-epidemiologie wereldwijd en lokaal in Ghana wordt beschreven. De interventies en activiteiten, die door het Nationale TBC Programma worden uitgevoerd om TBC te bestrijden, worden aangestipt. Ook wordt gewezen op de leemten in de kennis van TBC-onderzoek in Ghana en deze vormden de basis voor het onderzoek. Naast de overkoepelende doelstelling van het onderzoek en de onderzoeksvragen worden hier ook de synopsis van de specifieke onderzoeksvraag van elk hoofdstuk gepresenteerd. De kern van het onderzoek in dit proefschrift is het onderzoeken van aspecten van de TBC zorgtrajecten door het beoordelen van de resultaten van TBC opsporingsinterventies en behandelingsresultaten bij kinderen en mensen met extrapulmonale TBC (EPTBC). Daartoe werden de volgende onderzoeksvragen gesteld:

1. Welke innovatieve benaderingen voor het opsporen van mensen met TBC kunnen worden toegepast om het opsporen van TBC-patiënten te intensiveren en te verbeteren, respectievelijk in gezondheidsinstellingen en in de gemeenschap?
2. Wat zijn de behandelingsresultaten en de factoren die geassocieerd zijn met het slechtste resultaat, namelijk overlijden, in het TBC-zorgtraject van EPTBC en kinder-TBC?

In hoofdstuk 2 worden de resultaten van een onderzoek voor het opsporen van mensen met TBC beoordeeld, waarbij de standaard hoestduur van 2 weken en hoest van elke duur in combinatie met andere TBC-symptomen, worden gebruikt als screeningsmethoden voor TBC in de algemene polikliniek, HIV- en diabetesklinieken en bij contacten. Het aantal mensen met TBC per gescreende persoon met de kortere hoestduurmethode was het hoogst bij mensen met HIV, contacten en diabetici, maar er werden meer mensen geïdentificeerd in de algemene polikliniek wegens schaalvoordelen. De invoering van dit screeningsprotocol, aangevuld met de inzet van meer gevoelige diagnostische instrumenten, biedt veelbelovende vooruitzichten voor het verbeteren van de opsporing van mensen met TBC in gezondheidsinstellingen.

Hoofdstuk 3 evalueert een programma voor contactonderzoek op opbrengst en haalbaarheid van implementatie onder programmatische omstandigheden. Het aantal mensen met TBC onder de gescreende contacten was vergelijkbaar met andere studies, maar werd hoogstwaarschijnlijk onderschat doordat niet alle geïdentificeerde contacten met symptomen die wezen op TBC getest werden. Het gebruik van gevoelige screeninginstrumenten door opgeleid personeel en het aanpakken van de knelpunten bij het testen met sensitieve diagnostische tests zullen de voordelen van contactonderzoek als een aanpak voor het opsporen van mensen met TBC maximaliseren.

Het opsporen van TBC bij artisinale mijnwerkersgemeenschappen is onderzocht in hoofdstuk 4. De prevalentie van TBC onder de gescreende bevolking van 910 per 100.000 was aanzienlijk hoger dan de 356 per 100.000 die in de algemene bevolking werd gevonden, hetgeen het belang van het opsporen van mensen met TBC in dergelijke gemeenschappen onderstreept. De diagnostische waarde van hoest bij de screening in deze populatie suggereert dat het mogelijk is vermoedelijke TBC-gevallen in deze populatie te identificeren door middel van symptoomscreening, zelfs bij het ontbreken van de aanbevolen röntgenfoto van de borstkas als screeningsinstrument.

De resultaten van de behandeling en het risico op sterfte bij kinderen met TBC was het onderwerp van onderzoek in hoofdstuk 5. Bijna alle kinderen hadden een gedocumenteerde HIV status en tenminste 90% van de kinderen die onder behandeling waren voor TBC werden succesvol behandeld. Een positieve sputumuitstrijk en HIV-positiviteit waren risicofactoren voor sterfte. Hoewel de doelstelling van de END TB strategie van de World Health Organization (WHO) voor een succesvolle behandeling werd bereikt, kunnen de behandelingsresultaten voor kinderen verder worden verbeterd door meer aandacht te besteden aan kinderen met een TBC/HIV co-infectie en door de samenwerking tussen de TBC en HIV programma's zo te optimaliseren dat geïntegreerde diensten van contactonderzoek en TBC preventieve therapie mogelijk worden.

Hoofdstuk 6 richt zich op extrapulmonale TBC, waarnaar in Ghana relatief weinig onderzoek is gedaan. De resultaten van de behandeling van mensen met EPTBC en de risicofactoren voor sterfte werden geanalyseerd. Het resultaat van de behandeling was slechter voor mensen met EPTBC vergeleken met mensen met pulmonale TBC met respectievelijk 70,1% en 84,2% behandelsucces. Ouderdom, HIV-positiviteit en TBC in het centrale zenuwstelsel bleken significante risicofactoren voor sterfte onder EPTBC-patiënten. Investeren in meer sensitieve tests voor een vroegere diagnose en het versterken van partnerschappen met HIV-diensten in gezondheidsinstellingen, vooral in de lagere niveaus waar de meerderheid van de mensen zorg zoekt, kan helpen om de resultaten van de behandeling van mensen met EPTBC te verbeteren.

In hoofdstuk 7 worden de belangrijkste bevindingen van de studies bediscussieerd in het licht van de overkoepelende doelstelling van het proefschrift om innovatieve benaderingen voor de opsporing van mensen met TBC te onderzoeken en de resultaten van de behandeling bij onvoldoende bestudeerde groepen te beoordelen om prioriteiten te kunnen stellen voor de verbetering van het behandelingssucces. De discussie wordt in een meer actuele context geplaatst, waarbij rekening wordt gehouden met geactualiseerde strategieën om een einde te maken aan TBC die zijn ontwikkeld sinds de uitvoering van sommige van de interventies in de studies. Ook

wordt de COVID-19 pandemie in gedachten gehouden die een bedreiging vormt voor de verlening van essentiële gezondheidsdiensten, waaronder die voor de bestrijding van TBC. Implicaties voor het beleid, de sterke punten en de beperkingen van de studies en aanbevelingen voor toekomstig onderzoek worden ook in dit slothoofdstuk gepresenteerd, evenals de conclusie.

Summary in English

This thesis investigated aspects of the TB care pathway in Ghana and highlighted several potential areas for augmenting TB case finding and assessed treatment outcomes for largely unstudied key groups of people affected by TB namely children and those with extrapulmonary.

Chapter 1, the introduction, laid the foundation for the thesis by throwing light on TB, what it is and the global strategy for addressing the disease. The picture of TB epidemiology globally and locally in Ghana was described. The interventions and activities being implemented by the National TB Program to control TB were touched on. The knowledge gaps in TB research in Ghana that set the stage for undertaking the research in the book and the rational for the studies were also highlighted in the first Chapter.

In Chapter 2, the outcomes of a TB case finding initiative using different durations of cough, the standard 2 weeks cough and cough of any duration with other TB symptoms, as TB screening methods in general OPD, HIV and diabetic clinics and among contacts were assessed. The yield of TB cases per persons screened using the shorter duration method was highest among PLHIV, contacts and diabetic but more people were identified from the general OPD due to economy of scale. Incorporation of this screening protocol complemented by deployment of more sensitive diagnostic tools has promising prospects for augmenting TB case finding in health facility settings.

Chapter 3 evaluated a contact investigation program for yield and feasibility of implementation under programmatic conditions. The yield of TB cases among contacts screened was comparable to other studies but was most likely underestimated due to missed opportunity to test for TB among those identified contacts presumed to have TB. The use of sensitive screening tools by trained staff

and addressing the bottlenecks to testing with sensitive diagnostic tests will maximize the benefits of contact investigation as a TB case finding approach.

TB case finding among artisanal mining communities was investigated in Chapter 4. The prevalence of TB among the population screened 910 per 100,000 was considerably higher than that found in the general population 356 per 100,000, buttressing the importance of TB case finding in such communities. The diagnostic value of cough for screening in this population suggests that even in the absence of the recommended Chest X-ray as a screening tool, it is still possible to identify presumed TB cases in this population using symptom screening for further investigation for TB.

Treatment outcomes and risk for mortality in children with TB was the subject for research in Chapter 5. Almost all the children had documented HIV status and at least 90% of children put on treatment for TB were treated successfully. Smear positive pulmonary TB and HIV positivity were risk factors for mortality. Even though the END TB strategy target for treatment success was achieved, treatment outcomes for children can be improved further by paying closer attention to TB/HIV co-infected children and optimizing collaboration of the TB and HIV programs to facilitate integrated services that enable contact investigation and TB preventive therapy.

Chapter 6 focused on Extrapulmonary TB which is relatively under-researched in Ghana. The outcomes of those with EPTB put on treatment and risk factors for mortality were assessed. Treatment outcome was worse for those with EPTB compared to counterparts with pulmonary TB with 70.1% and 84.2% treatment success respectively. Being older, HIV positivity and Central Nervous System (CNS) TB were identified as significant risk factors for mortality among EPTB patients. Investing in more sensitive tests for earlier diagnosis and strengthening partnerships with HIV services in health facilities especially lower level ones where the majority of people seek care may help to improve treatment outcomes in those with EPTB.

In Chapter 7, the key findings of the respective studies are discussed in the light of the overarching objective of the thesis to investigate innovative TB case detection approaches and assess treatment outcomes in understudied groups to outline priorities to improve treatment success. The discussion is situated in a more current context taking into consideration updated strategies to end TB which have evolved since the implementation of some of the interventions in the studies and bearing in mind the COVID-19 pandemic which threatened delivery of essential health services including TB services. Policy implications, the strengths and limitations of the studies and recommendations for future research are also presented in this final chapter with the conclusion to crown it all.

Acknowledgements

This PhD is a dream come true. When my children were young, I used to say to them that when they start going to college, I would also go and get a PhD. At that time, I had no clue how that was going happen. Now that it has become a reality, I cannot start my acknowledgements without thanking the Almighty God Whom I credit as the originator of this PhD. He opened the doors for me to meet the right people at the right time and arranged the right timing and sequence of events culminating in this ultimate achievement and I am eternally grateful.

The PhD journey has been an interesting one and there are several people that have made it possible that I wish to thank with all sincerity.

Prof Andy Ramsay, my University of Amsterdam (UvA) journey started with you when I mentioned a desire to pursue the PhD at a TB meeting. You told me about your positive experience at UvA and proceeded to introduce me to Prof Paul Klatser. Thank you very much. That was tremendously kind of you.

Prof Paul Klatser, my promoter, thank you for taking me on and introducing me to Mirjam. Along the journey, there were times when it seemed the quest for the PhD had been abandoned but you did not give up on me. Your straight to the point guidance and mentorship made a lot of difference and I sincerely thank you.

Dr Mirjam Bakker, co-promoter and role model researcher. Thank you for keeping me on my toes and for being meticulous in your feedback. You accommodated me in your busy schedule and were always on point with technical guidance. I appreciate the great support.

Dr Frank Bonsu, Dr Nii Nortey Hanson-Nortey, Dr Adusi-Poku, Mr Felix Afutu, Ms Francisca Dzata, Ms Adelaide Sackey, Mr Samuel Danso, Mr Felix Sorvor and all cherished colleagues at the National TB Control Program, thank you for the awesome collaboration on the various TB interventions and the willingness to make available routine programmatic data for the studies in the thesis.

Staff, patients and community members in the facilities and communities in Greater Accra, Brong Ahafo, Ashanti and Western Regions where the respective TB

interventions were implemented, my sincere gratitude for your various roles played. Without you there would have been no data for the studies.

Mr Ardon Toonstra, Ms Doris Awudi, Dr Prince Boni, Ms Sarah Fordah, Dr John Ojo, Dr Rafiq Okine, Mr Fred Osei-Sarpong my able and valued collaborators, thank you for the technical guidance and the support in diverse ways which made the publications possible.

Dr Knut Lonnroth, Dr Jacob Creswell, Dr Mukund Uplekar, Dr Salah-Eddine Ottmani and colleagues who were in the TB program at WHO Headquarters and provided technical support for the implementation of the TB case finding initiative in the country, you are very much appreciated for your role in pushing the TB case finding agenda in Ghana thereby highlighting an area of interest for the thesis.

I would like to thank Prof Robert Wm Blum, friends at the University of Minnesota Adolescent Medicine Fellowship Program and work colleagues at the WHO Ghana Country Office for the tremendous impact you have made in my life.

Prof Frank Cobelens, Ms Linde Nieuwenhuys, Ms Evelyn Lammerse and colleagues at Amsterdam Institute of Global Health and Development, Ms Bettina Batista, Ms Marjanne Meinsma, Mr Jordi Cabanas-Danes of the Doctoral School, the teachers and course mates in the courses I took at the Doctoral School and all others I have encountered in one way or the other during this PhD journey, thank you so much for the mentorship, guidance, prompt response to my questions, peer motivation and all the support that made my PhD journey and learning experience so amazing and fulfilling.

My incredible family, Sammy my husband, the children Selorm, Senyo, Sena, my adopted children Mercy, Doris, Kofi, my mother Emelia and all family members for the love, patience, inspiration through the thick and the thin of this journey thank you from the bottom of my heart.

PhD Portfolio

Name PhD student: Sally-Ann Ohene
PhD period: 2017 - 2021
Name PhD supervisor: Prof Paul Klatser
Dr Mirjam Bakker

1. PhD training

	Year	Work load ECTS
General courses		
- Entrepreneurship in Health and Life Sciences	2021	1.5
- Peer to peer group coaching	2021	0.5
Specific courses		
- Practical Biostatistics	2021	1.4
- Research Data Management	2021	0.7
- Systematic review	2021	0.7
- French	2020 - 2021	3.8
- WHO QualityRights e-training – Foundation in Mental Health, Human Rights and Recovery	2018	0.4
- Specialization Management of Skin Neglected Tropical Diseases	2017	10
Seminars, workshops and master classes		
- 13th International Seminar on Noncommunicable Diseases, Lausane	2019	1.4
- Ghana Field Epidemiology Laboratory Training Program 10th Anniversary International Health Regulations Workshop	2017	0.1
- Training workshop on Malacology and Snail Control	2017	1.4
Presentations		
- "Medical Systems and the Traditional African Responses to COVID in Ghana and Africa" Symposium Speaker at University of Denver School of International Studies Global Intelligence and Security Symposium	2021	
- "Updated WHO Discharge Protocols for Confirmed COVID-19 Cases." Ghana Regional Health Directors Meeting to review roadmap for safe easing of restrictions in Ghana, Kumasi, Ghana	2020	
- "Experience with Joint Evaluation Exercise (JEE) and impact on rabies programmes" 2nd international meeting of the Pan-African Rabies Control Network (PARACON), Johannesburg, South Africa	2018	0.2

- "Implementation of Pandemic Influenza Preparedness (PIP) in the AFRO Region: The Ghana Experience." Regional Coordination Meeting for The Implementation of Pandemic Influenza Preparedness in The AFRO Region, Brazzaville, Congo	2018	
- "Experience of WHO Package of Essential Non-Communicable Disease (PEN) in Ghana." 13th International Seminar on Noncommunicable Diseases, Lausanne, Switzerland	2018	
- "Neglected Tropical Diseases" Symposium Speaker At The 41st Annual General And Scientific Meeting of the West Africa College of Physicians, Dakar, Senegal	2017	

(Inter) national conferences

- 15th, 16th, 17th and 18th Annual Meetings On Surveillance, Preparedness And Response To Meningitis Outbreaks In Africa, Dakar, Yaoundé, Ndjamena, Accra respectively	2018 - 2021	2.1
- Managing 21st Century Epidemics Workshop, Dakar	2017	0.8

Teaching

Lecturing

- Integrated Disease Surveillance and Response (IDSR) Cohorts 1, 2 and 3 - Training of District Health Professionals on the IDSR 3rd Edition	2020 - 2021	0.7
- Ghana Field Epidemiology Laboratory Training Program 10th Anniversary International Health Regulations Workshop	2017	0.1
- WHO Role and Functions and Role of Epidemiologist in WH	2017 –	0.2
- Annual Guest Lecturer, Ghana Field Epidemiology and	2021	
- Laboratory Training Program (GFELTP)		

Tutoring, Mentoring

- Mentored Master's student during her internship	2018	5
- Lessons in Engagement – Interactive engagement with University of Alberta School of Public Health MPH students	2020	

Supervising

- Supervised Master's student as intern and project work	2017	2

Other – Policy Development

- Technical support for development of Ghana One Health Policy and Non-communicable Disease Policy and Strategy	2019	2.8

Curriculum Vitae

Sally-Ann Ohene comes from Ghana and was born in Accra 28th June 1968. After completing her primary school education in Christ the King School, she attended Wesley Girls High School in Cape Coast, Central Region graduating in 1987. She obtained her medical degree from the University of Ghana Medical in 1994. She undertook her internship in the Child Health and Surgery Department of the Korle Bu Teaching Hospital in Accra.

She continued working as a medical officer in the Child Health Department until 1998 when she left to start the 3-year Pediatrics residency program at Woodhull Medical and Mental Health Center in New York. She obtained American Board of Pediatrics Certification in 2001.

Sally-Ann undertook a fellowship in adolescent medicine at the University of Minnesota (UMN) and obtained Master's in Public Health from UMN in 2004 and Board Certification in Adolescent Medicine in 2005 from the American Board of Pediatrics.

Back in Ghana, she taught adolescent health in the University of Ghana School of Public Health on part time basis. She joined the World Health Organization Country Officer (WCO) in Ghana as a technical officer in 2005 on the Treatment Acceleration Program that supported the scale up of anti-retroviral treatment for HIV to health facilities across the country.

She has played various roles at the WCO including HIV/TB officer providing technical support for the implementation of multi-sectoral HIV / TB prevention and care programs such as the TB case detection initiative in health facilities in Accra which informed some of the studies in the thesis. She is the Disease Prevention and Control officer providing technical support in the prevention and control of non-communicable and communicable diseases including neglected tropical diseases and

public health emergencies. Dr Ohene is a Fellow of the Faculty of Public Health, Ghana College of Physicians and Surgeons.

Sally-Ann is married to Sammy Ohene and they are proud parents of Selorm, Senyo and Sena.

Education

2005	Board Certification in Adolescent Medicine	American Board of Pediatrics
2004	MPH, Maternal and Child Health	University of Minnesota School of Public Health, Minneapolis, USA
2001	Board Certification in Pediatrics	American Board of Pediatrics
1994	MBChB, Bachelor of Medicine and Surgery	University of Ghana Medical School, Ghana

Professional Experience

2011 - date	National Professional Officer (NPO) Disease Prevention and Control	World Health Organization
2008 -2013	National Professional Officer (HIV/Tuberculosis)	World Health Organization
2005 - 2008	Technical Officer, Treatment Acceleration Programme (TAP)/ Anti-retroviral Therapy Coordinator	Ghana National AIDS/STI Control Program (NACP) Seconded by WHO
2001 -2004	Fellow in Adolescent Medicine	University of Minnesota, USA
1998-2001	Intern and Resident in Pediatrics	Woodhull Medical and Mental Health C USA
1995-1998	Intern and Medical Officer	Department of Child Health, Korle Bu Teaching Hospital, Ghana

List of Publications

Year

Peer reviewed

1. **Ohene SA,** Bonsu F, Adusi-Poku Y, Dzata F, Bakker M. Case finding of tuberculosis among mining communities in Ghana. PLoS ONE 2021; 16(3): e0248718. https://doi.org/10.1371/journal.pone.0248718 — 2021
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8. **Ohene SA**, Bonsu F, Hanson-Nortey NN, Sackey A, Danso S, Afutu F, Klatser P and Mirjam B. Yield of tuberculosis among household contacts of tuberculosis patients in Accra Ghana Infectious Diseases of Poverty 2018; 7:14 — 2018
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