

Burden of pulmonary tuberculosis and its major determinants: A national prevalence survey in Tanzania

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LIST OF ABBREVIATION

AFB	Acid Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome
BMI	Body Mass Index
CPC	Cetyl pyridinium chloride
CTRL	Central Tuberculosis Reference Laboratory
CXR	Chest X-ray
DMO	District Medical Officer
DOTS	Direct Observed Treatment Short course
DTLC	District Tuberculosis and Leprosy Coordinator
HIV	Human Immunodeficiency Virus
LED	Light-emitting diodes
MoHSW	Ministry of Health and Social Welfare
NIMR	National Institute for Medical Research
NTLP	National Tuberculosis and Leprosy Control Programme
NTP	National Tuberculosis Programme
RMO	Regional Medical Officer
RTLC	Regional Tuberculosis and Leprosy Coordinator
SEP	Socio-economic position
SOP	Standard Operating Procedure
TLCU	Tuberculosis and Leprosy Central Unit
TB	Tuberculosis
WHO	World Health Organization
ZN	Ziehl Nielsen

LIST OF PAPERS

This thesis is based on studies reported in the following research articles, which are included in the text and referred by their roman numerals

Paper I. M. Senkoro, S. Mfinanga, S. Egwaga, R. Mtandu, V. Kamara, B. Doulla, L. Fundikira, A. Kahwa, R. Shirima, N. Range, S. G. Hinderaker, F. van Leth. Prevalence of pulmonary tuberculosis in adult population of Tanzania: A national survey, 2012. *International Journal of Tuberculosis and Lung Disease*. Int J Tuberc Lung Dis e-publication ahead of print 9 June 2016

Paper II. M. Senkoro, S. G. Hinderaker, S. G. Mfinanga, N. Range, D. V. Kamara, S. Egwaga, F. van Leth. Health care-seeking behavior among people with cough in Tanzania: findings from a tuberculosis prevalence survey. *Int J Tuberc Lung Dis* 2015; 19: 640-646.

Paper III. M. Senkoro, A.M.V. Kumar, P. Chinnakali, S. G. Mfinanga, S. Egwaga, V. Kamara, F. van Leth, S.G. Hinderaker. Population impact of factors associated with prevalent pulmonary tuberculosis in Tanzania. *International Journal of Tuberculosis and Lung Disease*. Accepted for publication

SUMMARY

Tuberculosis is a major public health problem in Tanzania. The burden of tuberculosis in the country is monitored through a routine notification system. Although the routine tuberculosis surveillance data have been consistent over the years, there are still areas of uncertainty, which make the data not easily translated into exact estimation of tuberculosis disease burden. The lack of information on the true burden of tuberculosis disease in Tanzania stimulated a decision to conduct a national tuberculosis prevalence survey to provide the context in which other available data such as tuberculosis notification and mortality can be re-assessed. The prevalence survey also provided us with a unique opportunity to look at other factors which are important in tuberculosis control at the community level. The survey provided us with an opportunity to have add-on studies to study the health care-seeking behaviour of individuals with symptoms of tuberculosis and to assess factors associated with tuberculosis at a community level in a national scale.

Our prevalence survey conducted in 2012 showed that the weighted prevalence for sputum smear-positive was 249 per 100000 adult population and for bacteriologically-confirmed tuberculosis cases it was 293 per 100000 adult population. The bacteriologically-confirmed tuberculosis prevalence was markedly higher in mainland Tanzania (298/100000 adult population) than in Zanzibar (124/100000 adult population). The prevalence was twice as high in men as in women. The highest prevalence was found in the oldest age group of 65 years and older. In addition, low socioeconomic position was associated with higher tuberculosis prevalence. Individuals 45 years or older constituted 55% (71/129) of the identified smear positive cases, but just 28% (6793/24648) of the notified tuberculosis cases. Chest X-ray (CXR) screening identified more tuberculosis cases than symptoms screening. Weighted for the prevalence of HIV in the notified new smear-positive cases, the overall case detection of incident tuberculosis cases in 2012 was between 37% and 48%.

A study using data from the prevalence survey showed that of the 3,388 individuals with presumptive tuberculosis, only 1,053 (31.0%) had sought care for their symptoms at the time of the survey. Compared to persons with only cough and/or hemoptysis, those patients with additional symptoms were more likely to seek care. Care seeking at health facilities with tuberculosis diagnostic capacity was done by 42.3% of the individuals with presumptive tuberculosis. For individuals with presumptive tuberculosis who did not seek any care, lack of money (29.6%) and perceiving symptoms as not serious enough (23.9%) were the main reasons given for not seeking care.

Another study based on data from the survey showed that tuberculosis was more common in persons aged 25-34 years, and 55-64 years compared to persons aged 15-24 years. Tuberculosis was more common among men than women, and also more common among individuals with a low body mass index (BMI) than those with normal BMI. The associations with HIV and diabetes were not statistically significant, but their statistical power was low due to few events/cases. Population attributable fraction was 2% for diabetes and 3% and for HIV.

In conclusion, our results showed that the prevalence of sputum smear-positive and that of bacteriologically-confirmed pulmonary tuberculosis in the adult population were higher than previous WHO estimates. Many presumptive tuberculosis patients had not sought care for their symptoms, and among those who did, the majority went to sites with limited tuberculosis diagnosis capacity. Some factors associated with tuberculosis were identified. On a population level, HIV and diabetes have no major effect on prevalent tuberculosis from which future transmission can derive.

1. INTRODUCTION

1.1 General information about Tuberculosis

1.1.1 Definition

Tuberculosis is a chronic infectious disease caused by bacilli belonging to the genus *Mycobacterium*. These micro-organisms have a characteristic of retaining aniline dye (e.g. carbol fuschin) even after decolourization with acid and alcohol, and this is due to the fact that they have wax and fat in their cell walls, therefore classified as Acid-Fast Bacilli (AFB) [1]. The principal bacterium responsible for causing tuberculosis disease is called *Mycobacterium tuberculosis*. Tuberculosis is also occasionally caused by other bacilli such as *Mycobacterium africanum* which sometimes appears in West Africa and *Mycobacterium bovis* which causes tuberculosis in domestic or wild cattle but can also causes tuberculosis in humans. Another bacillus which has been identified recently in humans, mainly in immunosuppressed subjects, is *Mycobacterium microti* which is a causal agent for tuberculosis in rodent. These four microorganisms, *Mycobacterium tuberculosis*, *Mycobacterium africanum*, *Mycobacterium bovis* and *Mycobacterium microti*, comprise the so called *M. tuberculosis* complex [2, 3].

1.1.2 Types of tuberculosis

Tuberculosis is sorted by how infectious it is and hence there are two forms of tuberculosis: (a) pulmonary tuberculosis, which accounts for 80% of all cases of tuberculosis, and is the infectious form of the disease; and (b) less common, non-infectious, extra-pulmonary tuberculosis which can affect any part of the body other than the lungs, e.g. lymph nodes, spine, pericardium, pleura, joints, genital urinary tract and abdomen [4, 5]. Pulmonary tuberculosis is further classified as either sputum smear-positive or sputum smear-negative. A patient with both pulmonary and extra-pulmonary tuberculosis should be classified as a case of pulmonary tuberculosis because it is infectious [5, 6].

1.1.3 Mode of transmission

Patients with pulmonary tuberculosis are the main reservoir of *Mycobacterium tuberculosis* and are the most infectious cases. The mode of transmission of the bacilli is mainly by aerosol, hence an individual with tuberculosis of the lungs expelling micro-organisms into the air in tiny droplets when talking, coughing, laughing or sneezing is the most important source of infection [5, 7]. In a small proportion of cases, the bacillus (*Mycobacterium bovis*) is transmitted to humans from infected cows through drinking non sterilized milk. The existing control of tuberculosis in livestock and widespread pasteurization of milk has made this second mode of transmission rare in industrialized countries but remains an important problem in developing countries [2, 7, 8].

1.1.4 Pathology and pathogenesis

Primary infection

When a healthy individual comes into contact with the tubercle bacillus for the first time, and becomes infected, the infection is referred to as primary infection [2, 9]. When droplet nuclei are inhaled into the lung, some of them are not captured by the mucociliary defence of the bronchi, and some may lodge in the terminal alveoli of the lungs. Here the tubercle bacilli starts to multiply to form a small sub pleural lesion called Ghon focus [1, 9]. Furthermore, there is a rapid transport of bacilli to the regional lymph nodes called hilar lymph nodes. The Ghon focus and the related hilar lymphadenopathy form the so called primary complex [9, 10].

In one to two months, the primary complex heals spontaneously in about 85 to 90% of cases and the patient develops latent infection, which may just result in radiographic evidence of self-healed tuberculosis or a positive tuberculin skin test [9, 10]. In most cases, the infection of a healthy individual by the tubercle bacillus is asymptomatic and it goes unnoticed. Its presence is indicated by a change from negative to positive Mantoux test (tuberculin conversion) which reflects an immune reaction to the injection indicating that a person has been exposed to the bacteria previously [2, 9]. The Mantoux test is a tuberculin skin test done by exposing the patients to intracutaneous injection of a small amount of “tuberculin”,

a protein derived from *M. tuberculosis*. After 2 days it is measured by the size of the induration over the injection site.

Post primary tuberculosis

Post primary tuberculosis is the development of tuberculosis disease in a patient who had already been infected with the tubercle bacillus in the past [2, 9]. Post primary tuberculosis can develop after a latent period of months or even years following primary infection. This can occur if dormant bacilli persisting in tissues for months or even years start multiplying. It can occur if the patient who was previously infected and neutralised the bacteria is infected again by another person.[1, 5, 9]. The lifetime risk of getting post primary tuberculosis is only about 5% for the HIV negative individuals, but increases to about 50% to 60% in patients with HIV [2, 9].

1.1.5 Etiologic epidemiology

The study of dynamics of tuberculosis epidemic in a society is made less complicated by the following simplified model of the pathogenesis of tuberculosis. From the model, four distinct steps can be identified: exposure, infection, disease, and death [7, 11].

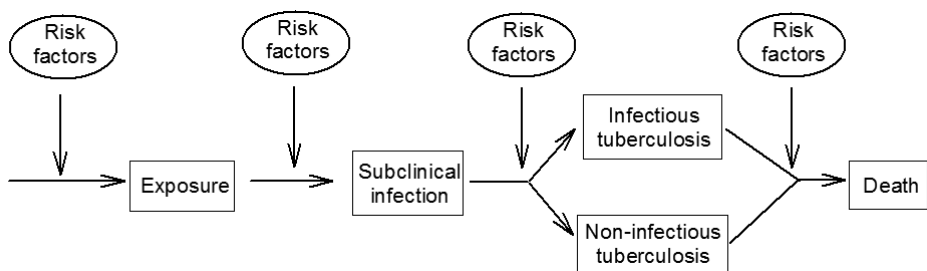


Figure 1: A model of the pathogenesis of tuberculosis and risk factors influencing each step [7, 11].

Risk of exposure

The risk of a susceptible contact becoming exposed to tubercle bacilli depends on three things. First is the number of incident infectious cases in the community, second is for how long these incident infectious cases in the community remain infectious, and third is the number and nature of interactions between a case and a susceptible contact per unit of time of infectiousness. The risk increases with increasing number of incident infectious cases, with increasing duration of their infectiousness, and with increasing number of interactions with the susceptible contact per unit time [7].

Risk of infection

Literature shows that two factors influence the probability of becoming infected with *M. tuberculosis*, these are the concentration of droplets nuclei in the contaminated air and the duration of exposure of the susceptible individual to the infectious droplet nuclei [7]. When the intensity and/or duration of exposure increase, so does the rate of transmission. One good example of such scenario is the transmission which typically occurs within the household of a patient with pulmonary tuberculosis, especially if poorly ventilated and overcrowded. This is often coupled with delays in diagnosis of patients with tuberculosis, therefore increasing the length of time that their families are exposed to the bacilli [12, 13]. It has been shown that risk of tuberculosis infection among household contacts was associated with the intensity of exposure of the household member to the case, to the presence of a cavity on the chest X-ray of the index tuberculosis case, and to the number of zones involved on the X-ray, with the last two reflecting both the capacity for the case to excrete bacilli and the severity of the disease [13, 14]. One paper showed that a duration of exposure of five hours or more per day was a risk factor for tuberculosis [13].

Risk of progression of infection to disease

Development of tuberculosis disease in a person infected with *M. tuberculosis* does not occur frequently. A person who is infected can stay for many years, probably for life, without developing tuberculosis [1]. The integrity of the cellular immune system is what determines the risk of progression of infection to disease [7]. Therefore, factors that are likely to accelerate progression from infection to disease are those factors which reduce the

body's immunity. Examples of such factors are HIV infection, diabetes, long term treatment with immunosuppressive medications, and malnutrition [7, 12]. It has also been shown that individuals with latent tuberculosis had a lower risk of progressive tuberculosis after reinfection than uninfected individuals [15].

Risk of death

The probability of dying from tuberculosis is influenced by several factors including the site in the body where tuberculosis disease is located, type of the disease, and the duration before a diagnosis is made. The risk is much higher in those with pulmonary tuberculosis, those with smear-positive tuberculosis, and those with delayed diagnosis [7]. But in one of a systematic review, smear-positive tuberculosis was found to be a risk factor of dying from tuberculosis in a setting with low tuberculosis incidence, while in setting with high tuberculosis incidence, having a smear-negative tuberculosis meant a higher risk of dying perhaps reflecting a higher rate of co-infection with HIV [16]. Studies have also shown that the risk of dying from tuberculosis is also increased by other factors such as cigarette smoking, diabetes, Multidrug (MDR)-tuberculosis, history of previous tuberculosis and injection drug usage to name a few [17, 18].

1.1.6 Natural history of tuberculosis

The natural history of tuberculosis is the course in which a tuberculosis patient will follow in the absence of treatment. It has been shown that, in the absence of treatment, after a period of one and a half years, approximately a quarter of the patients die, half of those who survive become chronic infected and continue to excrete bacilli for many years, and the remainder are spontaneously cured by the body defence mechanism. By the end of five years, the proportion of patients' dead rises to 50% [19]. In a review carried out in 2011, although with many limitations, it was concluded that in 10 years' time the case fatality estimates were 70% for smear-positive and 20% for smear-negative culture positive tuberculosis [20].

1.2 Measuring burden of Tuberculosis

Assessment of the burden of disease caused by tuberculosis, can be done using three indicators: (1) prevalence (defined as the number of cases of tuberculosis at a given point in time), (2) incidence (defined as the number of cases of tuberculosis arising during a given time period, usually one year), and (3) mortality (defined as the number of deaths caused by tuberculosis in a given time period, usually a year) [21].

Tuberculosis prevalence

The prevalence of bacteriologically-confirmed pulmonary tuberculosis can be directly estimated in national wide population-bases surveys in countries with a relative high burden of tuberculosis (around 100 cases per 100000 population or more). The results from the survey can then be used to produce a national estimate of tuberculosis prevalence that includes all forms of tuberculosis. In order to assess trends in tuberculosis burden, repeated surveys must be conducted, e.g. every 10 years. However, the cost of the surveys and the large sample sizes required in repeated surveys makes this exercise a big challenge in low income countries, the countries which are also most affected with tuberculosis. Without a survey, tuberculosis prevalence can be estimated only indirectly as the product of incidence and the average duration of disease, but with considerable uncertainty [21, 22].

Tuberculosis incidence

Measuring tuberculosis incidence at national level requires long-term studies among large cohorts of people, involving high costs and challenging logistics. For that reason, tuberculosis incidence has never been measured nationally. Tuberculosis incidence can be estimated indirectly using country's notifications of tuberculosis cases and also through multiple prevalence studies if there is rigorous monitoring of the study population to detect new cases that die or migrate out in between prevalence surveys. But this only works in countries that have a good surveillance system and where the quality of and access to health care means that few cases are not diagnosed. These conditions are usually not met in many countries, and for that reason incidence

estimates in these countries are made using notification data combined with experts opinions [21, 23].

Tuberculosis mortality

Data from national vital registration system can be directly used to measure tuberculosis mortality among HIV-negative people. However, this can be done only when causes of death are accurately coded according to the latest revision of the International classification of diseases (ICD-10) and the vital registration systems have high coverage. Tuberculosis mortality among HIV-positive people is hard to measure even when vital registration systems are in place, because deaths among HIV-positive people are coded as HIV deaths and contributory causes (such as tuberculosis) are often not reliably recorded [21]. In countries with good vital registration system we would expect >90% of all tuberculosis deaths to be reported [24]. In the absence of a good vital registration system, verbal autopsy data can be used to estimate tuberculosis mortality, but with considerable variations among and within sites, due in part to the small numbers of deaths covered and the varying diagnostic definitions and algorithms [24].

1.3 Global burden of Tuberculosis

Tuberculosis remains a major health problem globally. In 2014, it was estimated that there were almost 13 million people living with tuberculosis equivalent to 174 cases per 100000 population [21]. In the same period it was also estimated that there were 9.6 million new tuberculosis cases, of whom 12% were HIV positive. Tuberculosis is unequally distributed in the world with the highest incidence rates found in developing countries. The highest estimated incidence was in South-East Asia and Western Pacific regions (56%) and in Africa Region (28%). The 22 high burden countries account for approximately 80% of the estimated number of new tuberculosis cases (all forms) arising worldwide each year [21], and nine of them are in Africa. In 2014, only 6 million of the 9.6 million incident cases (63%) were detected and notified to national tuberculosis programmes (NTPs) or national surveillance systems globally. This leaves an estimated gap of approximately 3.6 million people with tuberculosis who were “missed”, either because they were not diagnosed (or

not yet) or because they were diagnosed but not reported [21]. Those with active pulmonary tuberculosis who do not receive any treatment can infect an average of 10 to 15 people annually [25]. A total of about 1.5 million people died of tuberculosis in 2014, including 0.4 million patients infected with HIV. Approximately 90% of total tuberculosis deaths and 80% of tuberculosis deaths among HIV-negative people occurred in the African and South-East Asia Regions [21].

1.4 Tuberculosis in Tanzania

1.4.1 Tanzania burden of tuberculosis

In 2012, the World Health Organization (WHO) ranked Tanzania 16th highest tuberculosis burden globally, with a prevalence of 176/100000 [26]. In 2002, WHO estimated that in Tanzania tuberculosis ranked 7th as a cause of death among people older than 5 years, and that in 2012, HIV, tuberculosis and malaria accounted for more Disability-adjusted life years (DALYs) and deaths than any other diseases [27, 28]. The HIV / AIDS epidemic has caused the number of tuberculosis cases to increase rapidly from the early 1980s. The sharp annual increase of tuberculosis cases between 5% and 10% experienced in the 1990's reached peak in 2001 and remained more or less steady thereafter with the average annual increase of only 2% between 2000 and 2010 [4, 29]. The notification data show that in 1983 the number of cases notified was 11,753 (57/100000) and in 2004 it has increased to 65,665 [29]. In 2012, the total number of the notified cases was 63,892 (142/100000) and in 2013 it was 65,732 (142/100000). The majority (about 70%) of the notified cases in 2012 and 2013 appeared in young population groups aged 15-44 years, an age group heavily affected by HIV/AIDS. About 71% of all tuberculosis cases reported are from ten regions of Tanzania (Dar es Salaam, Mwanza, Shinyanga, Mbeya, Morogoro, Tanga, Iringa, Arusha, Mara, and Kilimanjaro), with Dar es Salaam being the major contributor of tuberculosis cases notified, with 22% [4, 30, 31].

1.4.2 National Tuberculosis and Leprosy Programme

The National Tuberculosis and Leprosy Programme (NTLP) was launched as a single combined programme in 1977 by the Ministry of Health and Social Welfare (MoHSW).

NTLP is within the department of Preventive Services in the MoHSW under the Epidemiology and Disease Control section[29].

In terms of administration, NTLP works at three levels: national, regional and district level. At the national level there is Tuberculosis and Leprosy Central Unit (TLCU) which is responsible in coordinating all activities relating to tuberculosis and leprosy in the country. Also, the unit is responsible for planning, policy formulation, monitoring, evaluation, resource mobilization and coordination of drugs and supplies procurement and distribution. At the regional level there is Regional Tuberculosis and Leprosy Coordinator (RTL) who works closely with TLCU and the districts. His/her responsibility is to interpret the policy guidelines and monitor their implementation at the district level. RTL is answerable to the Regional Medical Officer (RMO). At the district level there is a District Tuberculosis and Leprosy Coordinator (DTLC) who works under the District Medical Officer (DMO). The DTLC is the main link between TLCU through the region on one hand and health units and community on the other hand[29].

1.4.3 Diagnosis of pulmonary tuberculosis

Diagnosis of tuberculosis in Tanzania relies on passive case finding where patients present themselves to a health facility once they have symptoms. The highest priority in the control of tuberculosis is the identification and cure of all sputum smear-positive pulmonary tuberculosis cases as soon as possible in order to terminate tuberculosis transmission and to prevent emergence of drug-resistant tuberculosis. Therefore, priority is given to the detection of bacilli in sputum samples of all suspected pulmonary tuberculosis cases [4, 5]. Regardless of HIV status, all patients with features suggestive of pulmonary tuberculosis must submit sputum for diagnostic sputum smear microscopy [1, 5]. Symptoms suggestive of pulmonary tuberculosis are persistent cough for two weeks or more, coughing blood, night sweats, loss of weight, and fever [4]. However, some or even all of these symptoms may be absent[3].

Sputum smear microscopy

Acid fast bacilli (AFB) detection in sputum using microscopy is the common method used, especially in developing world, to diagnose tuberculosis, follow up of pulmonary tuberculosis patients as well as to estimate the bacterial load [32]. Two sputum specimens (one spot specimen and one morning specimen when the patient returns to the laboratory) for smear microscopy are collected from every individual with presumptive tuberculosis, and these specimens should be submitted within 24 hours. For patients considered at risk of not returning for investigations, spot-spot sputum collection for microscopy is considered [4, 5]. Bacteriological monitoring is also needed in all tuberculosis-confirmed patients. Routine examination of an early-morning sputum at the end of 2 months and 5 months is required. When properly stained with Ziehl Neelsen (ZN) technique mycobacteria are seen as red rods. When stained using auramine-O, the bacilli appear as bright yellow rods against a dark background [4]. In microscopes, dead bacteria after treatment started are indistinguishable from live bacteria.

Chest X-ray

In many clinical situations, a normal chest X-ray effectively rules out the presence of active pulmonary tuberculosis and may be used to select outpatients who do not need further tuberculosis testing [4]. Also, in most cases of smear-positive pulmonary tuberculosis, a chest X-ray is unnecessary. But a chest X-ray should be done in presumptive tuberculosis patients with smear-negative sputum, and who do not improve after broad spectrum antibiotics. A patient is then diagnosed as having smear-negative pulmonary tuberculosis if the chest X-ray is typical of pulmonary tuberculosis [1, 5]. On the other hand, it is also important to note that in a chest X-ray other chest diseases can produce similar changes as those produced by tuberculosis. This is further complicated with HIV infection, as in late phases often causes atypical pattern on the chest X-ray. As a result, chest X-ray is considered not sufficiently reliable as a single tool in the diagnosis of tuberculosis [5, 29].

Sputum culture

Culture of *M. tuberculosis* from clinical specimens such as sputum is the gold standard for the definitive diagnosis of tuberculosis [1]. Culture is a more sensitive method to detect

mycobacteria than AFB smear microscopy, but it is very expensive and slow. Also the equipment and materials needed for culture are costly and require complex facilities with highly skilled staff [4, 33]. In Tanzania, since Löwenstein Jensen medium is used for sputum culture, it takes from two to eight weeks for the results to be obtained [4]. All these, together with the fact that persons who are positive only on culture are less infectious than those who are also positive in smear microscope, make culture not a priority test for systematic detection of cases[34].

GeneXpert® MTB/RIF assay

GeneXpert® MTB/RIF, a highly sensitive and specific rapid, automated, molecular test for the combined detection of tuberculosis and rifampicin resistance, was endorsed by WHO in December 2010. Although some reservations have been raised with regards to the use of the GeneXpert® MTB/RIF in low income countries [35], Tanzania is in the process of defining where in the laboratory system it will be placed [4]. Recently, the Ministry of Health and Social Welfare has determined that GeneXpert® MTB/RIF testing will be implemented as the initial diagnostic test in all presumptive pulmonary tuberculosis and presumptive MDR-tuberculosis cases in adults and children. This includes; (1) Patients presenting with symptoms suggestive of pulmonary tuberculosis, irrespective of HIV status (2) Presumptive MDR-tuberculosis. The plan is to have one GeneXpert instrument in each district hospital by 2018 [36]. Regular maintenance is a great challenge with this undertaking.

1.4.4 Definitions

In our study the following definitions will be used:

A smear-positive pulmonary tuberculosis (PTB+) case is any person with at least two initial smear examinations positive by direct microscopy for Acid Fast Bacilli (AFB+); OR with one initial smear examination positive by direct microscopy AND positive by culture for mycobacteria; OR with one initial smear examination positive

by direct microscopy for Acid Fast Bacilli (AFB+) AND chest X-ray abnormalities suggestive of active tuberculosis.

A bacteriologically confirmed case is any person with a positive culture for tuberculosis AND / OR smear-positive case

A presumptive tuberculosis patient, also known as “tuberculosis suspect” or “patient for tuberculosis examination”, is a patients presenting at a health facility with symptoms of pulmonary tuberculosis: persistent cough for two weeks or more, coughing blood, night sweats, loss of weight, and fever.

1.4.5 Treatment of tuberculosis

The significance of tuberculosis diagnosis is high if and only if it is complemented by prompt treatment. The Direct Observed Treatment Short Course (DOTS) strategy is a strategy that aims to cure tuberculosis patients, prevent death from active tuberculosis or its late effects, prevent further transmission of tuberculosis to the community, and prevent the development of drug resistance due to inadequate drug therapy. In the DOTS strategy, provision of chemotherapy is an important component and it is the most effective way to ensure rapid sputum conversion of infectious patients. The first short course regimen in Tanzania, which was an eight months course, was introduced in 1987. This was changed in 2006 as a six months regimen was introduced and have been used to date[29]. Tuberculosis treatment and regimens are divided into two phases: initial (intensive) and continuation phases. The initial phase, lasting for two months, is designed for the rapid killing of the bacilli that are actively growing, causing infectious patients to become non-infectious within a couple of weeks. The continuation phase, lasting for four months, is designed to eliminate persisters or semi-dormant bacilli, hiding in tissues or macrophages and thus prevent failures and relapses after the completion of treatment [1, 4, 5]. The regimen requires daily observed treatment by a health care worker or treatment supporter throughout the six months [4]. For the cohort of tuberculosis patients in Tanzania who were notified in

2012, the year which the first national tuberculosis prevalence survey was done, the overall treatment success for new and relapse case was 90% [31].

1.5 Statement of the problem and study rationale

Tanzania was one of the first countries in the world to use the now standard approach of “Directly Observed Treatment Short Course” to treat tuberculosis. The burden of tuberculosis in the country is monitored through a routine notification system.

Although the routine tuberculosis surveillance data have been consistent over the years, there are still areas of uncertainty.

A wealth of information on the prevalence of tuberculosis-infection through repeated national Tuberculin Skin Test (TST; see 1.1.4) surveys in schoolchildren has been collected in Tanzania. The surveys showed a decline in the Annual Risk of Tuberculous infection (ARTI) in both the younger (aged 5-9), and the older children (10-14) [37-40]. However, it is also not possible to accurately estimate the tuberculosis disease burden from these data, because the frequently-used Styblo rule has become less applicable in a situation where interventions that interrupt transmission, such as the tuberculosis-control activities in Tanzania, are available [41, 42].

The Millennium Development Goals had targets formulated by The United Nations to be reached within 2015, and was signed by 189 countries in the year 2000. By 2015, every country was supposed to evaluate the time trend in national incidence and the magnitude of reductions in either tuberculosis prevalence or deaths. As stated earlier, the prevalence of bacteriologically-confirmed pulmonary tuberculosis can be directly measured in nationwide population-based surveys [22, 43]. The lack of information on the true burden of tuberculosis disease in Tanzania stimulated a decision to conduct a national tuberculosis prevalence survey to provide the context to re-assess other available data such as tuberculosis notification and mortality. In addition, the results would contribute information to the evaluation of the Millennium Development Goals. Goal number six referring to tuberculosis aims at as halting and beginning to reverse the incidence of tuberculosis by 2015 [44].

The prevalence survey also provided us with a unique opportunity on the level of community, to look at other factors which are important in tuberculosis control. Early identification and cure of infectious tuberculosis patients in the community is the method used for preventing tuberculosis transmission [4]. The identification of tuberculosis patients in Tanzania is done through passive case findings which, among other things, depend on the individual's health seeking behaviour [4, 45, 46]. Many studies looking at health-seeking behaviour have focused on patients who have already been identified by the formal health system [47]. Hence a community survey provided us with an opportunity to look at the health seeking behaviour of individuals with presumptive tuberculosis before they were identified by the health system. The survey also allowed us to assess factors associated with tuberculosis at a national scale. The information on factors associated with tuberculosis could then be used to identify and prioritize high-risk groups in which targeted efforts can be made for improved case detection, as WHO recommends 'early detection of tuberculosis by systematic screening in selected high-risk groups' to reach missing cases, in its post-2015 'End TB strategy'[48]. Therefore we think this information will be useful for the National Tuberculosis and Leprosy Programme (NTLP) in Tanzania as they begin to adapt the global End TB strategy for the country.

2. STUDY OBJECTIVES

2.1 General objective

To measure the burden of tuberculosis and its major determinants through a national prevalence survey in Tanzania

2.2 Specific Objectives

The specific objectives of the study were the following:

1. To measure the burden of bacteriologically-confirmed pulmonary tuberculosis in Tanzania through a nation-wide prevalence survey
2. To assess health care-seeking behavior among individuals with presumptive tuberculosis in a tuberculosis prevalence study in Tanzania
3. To assess factors associated with tuberculosis present in the general population and estimating population-attributable fractions for selected factors

3. METHODOLOGY

3.1 Study Settings, Design and Population

3.1.1 Study setting

The United Republic of Tanzania is a union of Tanganyika (Tanzania Mainland) and Zanzibar (Tanzania Zanzibar). Tanzania is the largest country in East Africa occupying an area of about 940,000 km² and share borders with eight neighbouring countries: Kenya and Uganda in the north; Burundi, Democratic Republic of Congo and Rwanda in the west; Zambia, Malawi and Mozambique in the south; in the east is the Indian Ocean (figure 2). Administratively, Tanzania has 30 regions (25 in Tanzania Mainland and 5 in Zanzibar), 169 districts and 3644 wards [49]. The study was conducted in 62 wards; in this study they are referred to as clusters.

According to the 2012 census Tanzania had a total population of about 45 million of whom 70% lived in rural areas and 62% depended on agriculture (mainly subsistence agriculture) as their main source of income. The population is relatively young with 44% aged less than 15 years. The annual population growth rate was estimated to be about 3% [49, 50].

3.1.2 Study Design

The main study was a nation-wide population-based survey to assess the burden of tuberculosis (Paper I). A cross sectional and a case-control study were nested within the survey to assess the health care-seeking behaviour of individuals with presumptive tuberculosis (Paper II) and factors associated with tuberculosis (Paper III), respectively.

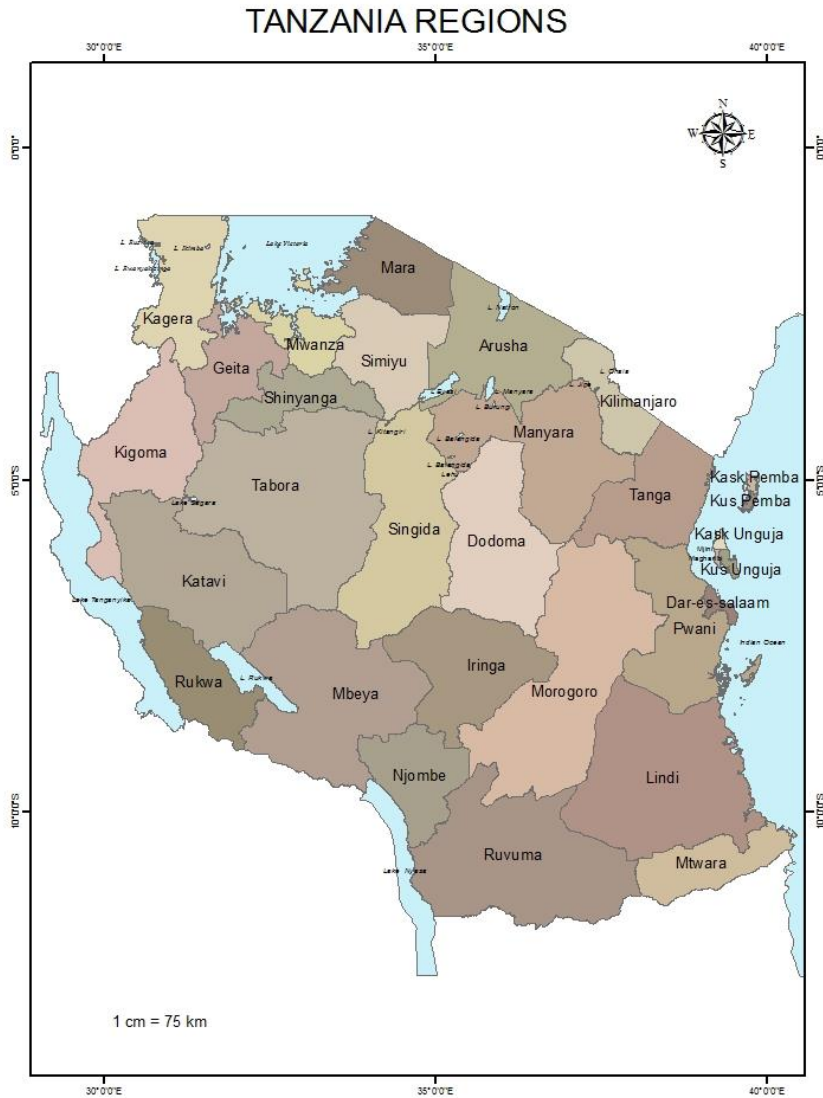


Figure 2: Map of Tanzania (Source: National Bureau of Statistics, Tanzania)

3.1.3 Study population

The target population was the adult population (15 years of age or older) of the United Republic of Tanzania. The study population for the prevalence survey (Paper I) was the adult population of the 62 selected clusters. The study subjects were participants who were visited during the census, judged to be eligible, presented to the field site, and provided informed consent. For the study on health care-seeking behavior (Paper II), the study subjects were those who were presumed to have tuberculosis (after tuberculosis screening) because they had cough for ≥ 2 weeks and/or were coughing blood. For studying factors associated with tuberculosis (Paper III), our study subjects were those presumed to have tuberculosis (by chest X-ray or symptoms) and a sample of individuals without presumptive tuberculosis.

Table: Summary of the studies conducted: the design and subjects

Paper	Topics	Study design	Participants
I	Bacteriologically-confirmed tuberculosis prevalence	Survey	50447 enrolled individuals ≥ 15 y
II	Health care-seeking behaviour	Cross sectional	3388 presumptive tuberculosis patients with cough for ≥ 2 weeks and/or coughing blood
III	Factors associated with tuberculosis	Case-control	6302 presumptive tuberculosis individuals and a sample (861) of individuals without presumptive tuberculosis.

3.2 Sample Size

The sample size of the main study (Paper I) was calculated based on the expected prevalence of smear-positive tuberculosis in the general population, using the following assumptions: (i) a prevalence of smear-positive tuberculosis in the general population of 145/ 100000 in 2010. This number was provided by the WHO Task Force on Impact Measurements at the time of the sampling; (ii) 56% of population is 15 years or older (extrapolated from 2002 national census data); (iii) a 25% relative precision around the estimate (iv) a participation rate of 80%, and (v) a design effect of 1.6. The minimum required sample size based on these assumptions was 46792. With a cluster size of 750 adult individuals, the number of clusters required was 62. We targeted 900 adults in each cluster in an effort to ensure precision.

3.3 Sampling strategy

The sampling frame for the cluster selection was obtained from the National Bureau of Statistics and contained information on age-specific population size of each district and ward in the United Republic of Tanzania as projected for 2010 based on the latest census of 2002. The selection of the clusters followed a stratified proportional-to-population-size approach including four steps.

In step 1, the total number of clusters (62) was divided proportional-to-population-size over four different strata based on setting, being (i) rural, (ii) urban, (iii) semi-urban, and (iv) Zanzibar. The allocated number of clusters was 37, 9, 14, and 2, respectively. In step 2, a separate sampling frame for each stratum was drawn that contained the districts with the total sample size of the population of 15 years and older. From these frames, the districts for the allocated number of clusters for the stratum were selected proportional-to-population-size. In step 3, a single ward within each sampled district was selected by simple random sampling. In step 4, the first household to be included was chosen by chance from an appropriate sampling frame, after which households were added consecutively in a clockwise manner until the required population was reached.

3.4 Inclusion criteria

Individuals were enrolled in the survey if they

- were at least 15 years old
- had slept in the household for at least two weeks before the survey
- provided informed consent.

3.5 Exclusion criteria

Individuals that were excluded from the survey included those who were mentally challenged, those who were in congregate settings e.g. prisoners, refugees, schools, offices, and embassies.

3.6 Data collection

3.6.1 Training of research assistants

A central training workshop was conducted for all staff involved in any of the survey activities. The workshop consisted of plenary sessions (tuberculosis epidemiology, rationale for survey, role of SOPs) as well as specialised sessions for each group of survey staff (interviewers, team leaders, radiologists, laboratory technicians, data entry clerks, data managers, and supporting staff). The specialist sessions were facilitated by experts. All activities were simulated in role plays in which all staff participated. A trial census was conducted using actual households and residents in a community.

The workshop was monitored by the Technical Consultant who also acted as the facilitator for selected sessions. The findings of the training were discussed with the team organizing the survey after which some adjustments of the data capture forms and questionnaires were implemented.

3.6.2 Field activities

Field activities and enrolment started by December 2011 and ended in November 2012.

Pre-survey visit and population listing

The Survey Coordinator together with the district authorities visited the selected ward several weeks prior to the field activities, to assess if the infrastructure was adequate to host the survey team and to conduct the survey. After assessing infrastructure all districts were found adequate to host the survey. During the same visit, local health workers were selected and trained to prepare a list of all residents (population listing) of the selected area of the ward, their age and sex. Information leaflets discussing the purpose of the survey and the activities that would take place were also provided to the residents.

Census

During the first two days of field work, small teams consisting of a local health worker and survey staff carried out house-to-house visits (census). They used information gathered by the local health workers during the population listing and updated it (with deletions or additions) where necessary. Information on history of previous tuberculosis and current tuberculosis treatment was also recorded. The residents were explained the purpose of the survey and the activities that would take place. All eligible residents were provided with an invitation card with an individualized registration number.

During the census, the socio-economic position (SEP) of the household was assessed through the use of an asset list. This approach has been validated to be used for rapid assessment of SEP and is recommended to be used in large-scale surveys [51]. The approach captures information on the presence of certain goods in the household, the construction of the house, and the access to services (water, electricity, etc).

Registration and consents

When reporting to the field site, residents were briefed in small groups on the purpose and activities of the survey, the informed consent form was explained, and all outstanding questions were addressed. Formal individual written informed consent was obtained during the registration of participants.

Symptom screening

All participants were screened for the presence of symptoms suggestive of tuberculosis by using a questionnaire with five questions (cough for 2 weeks or more, haemoptysis, fever for 2 weeks or more, weight loss of more than 3 kg within a month, and excessive sweating for 2 weeks or more). The interviewer was trained to probe for correct answers based on their own observations and judgement. Participants identified with any symptom of tuberculosis were identified as an individual with presumptive tuberculosis. After symptoms screening, participants were measured their height and weight. They were then referred to further examination by X-ray.

X-ray screening

All participants were invited for a chest X-ray which was done using digital X-rays machines mounted in a specifically designed truck. Since the initial assessment was for screening purposes only, a person was presumed to have tuberculosis if there was any abnormality in the lung fields or mediastinum. All X-ray images were digitally stored for future reference and selected re-reading.



Figure 3: X-ray screening during the survey (picture taken during the field activities)

Field laboratory

Individuals with presumptive tuberculosis were requested to produce three sputum specimens. The first spot specimen was requested soon after the identification of a participant being an individual with presumptive tuberculosis. Then the participant was given a pre-labelled sputum container and was asked to bring a morning specimen collected immediately after waking up. Information on the importance of these specimens, the method to collect the specimen, and the need for returning to the survey site for handing in the morning specimen was given. The second spot specimen was requested the following day when the participant returned with the morning specimen. When individuals with presumptive tuberculosis did not return to hand-in the morning specimen (and provide the second spot specimen), they were traced by the local health workers and persuaded to finalize the survey activities. The morning specimens were transported to Central Tuberculosis Reference Laboratory (CTRL) twice a week.

The two spot specimens were examined by light-emitting diodes (LED)-microscopy at the survey site. When a specimen was found to be smear-positive, the participants were referred to the field team leader, who informed the DTLC. The participant was offered further clinical assessment and treatment in the nearest diagnostic centre.



Figure 4: Field laboratory during the survey (picture taken during the field activities)

Transport and logistics

Sputum specimens were transported in Falcon tubes from field sites using public means. Arrangements were made with local buses coming to Dar es Salaam, where CTRL is located, so that a timely delivery of specimens was ensured. CTRL was informed by a mobile phone text message that a transport was initiated and specimens could be expected. This was to prevent that specimens were left unattended at bus depots. This strategy was found to be very effective in the previously conducted Drug Resistance Survey some years earlier [52]. A courier person (runner) collected specimens from the bus stations and brought them to CTRL at regular intervals. Transport of specimens was arranged two times during the one-week field period. Transport on Wednesday and Saturday allowed specimens to arrive at CTRL within 4 days of collection. If longer transit times were expected, Cetyl pyridinium chloride (CPC) was added in the field to prevent contamination. Specimens without CPC were stored in a dark cool place at the field site until transport. Specimens with CPC added were kept at room temperature at all times.

Interview for additional information

Interview of individuals with presumptive tuberculosis was conducted with the purpose of obtaining information on additional demographics (marital status, education, profession), health care-seeking behaviour, the knowledge of tuberculosis (transmission, diagnosis, treatment, prevention), and the presence of factors associated with tuberculosis (smoking, alcohol use, diabetes, etc.).

HIV testing

All individuals with presumptive tuberculosis were offered HIV testing. The diagnosis of HIV followed national guidelines. In the initial clusters the sequence of rapid tests was *SD Bioline*, followed by *Determine*. The diagnosis was made if both the initial test and the conformation test were positive. If still indeterminate after two tests, the final diagnosis was made by *Unigold* [53]. During the survey, the national guideline changed. Accordingly, the diagnosis of HIV in the survey was made by the successive use of *Determine* and *Unigold*. Again, HIV was diagnosed when both rapid test were positive [54].

Field Data entry

During the field activities, data from the census, symptom interview, screening chest X-ray, and field laboratory were entered into an electronic database. These data were analysed and used in the field to identify participants who needed to be actively traced: those invited but not enrolled; and individuals with presumptive tuberculosis who had not given sputum specimens.

3.6.3 Central activities

Central laboratory

All morning sputum specimens were sent to CTRL for processing. After LED smear microscopy without a concentration procedure, specimens were prepared for culture on Lowenstein-Jensen medium according to routine procedures [4].

X-ray diagnosis

The chest X-ray of all individuals with presumptive tuberculosis and 20% of those without presumptive tuberculosis were re-read at the central radiology department of Muhimbili University of Health and Allied Sciences to make a final verdict on the presence of abnormalities consistent with pulmonary tuberculosis. The assessment used a pre-specified form on which specific lesions and abnormalities were recorded.

Data entry

The central data unit was located at the National Institute for Medical Research (NIMR)-Muhimbili Centre. All data forms were entered twice in an electronic database by two independent teams. For those forms with expedited data entry in the field, the central data unit entered the data a second time. For the non-expedited forms, the central team entered all data twice.

GeneXpert® MTB/RIF

After finalization of the survey and at the request of WHO, smear-positive slides were re-examined by GeneXpert® MTB/RIF (Xpert) to confirm the presence of *M. tuberculosis*, thereby assessing the risk of false smear-positivity due to Mycobacteria Other Than Tuberculosis (MOTT) and the reliability of the culture results. This strategy was not part of the original study protocol. The testing was done at the Supra-National Tuberculosis Reference Laboratory (SRL) in Antwerp, Belgium.

3.7 Statistical analysis

Data was double entered using EpiData version 3.1 (The EpiData Association, Odense Denmark). Inconsistencies were resolved by returning to the source data. Data analysis was performed using STATA 12.1 and 13.1 (StataCorp LP, USA).

In Paper I the outcome measurements were the prevalence of smear-positive tuberculosis and bacteriologically-confirmed tuberculosis in the adult population. For

each of the outcome measurement, we calculated the crude prevalence, the weighted prevalence, and the prevalence after imputation. For paper II the outcome measurement was seeking care for tuberculosis symptoms. For paper III the outcome measurement was population-based estimates of the risk of having bacteriologically-confirmed tuberculosis.

We corrected for potential selection bias by using survey weights that reflected different sampling probabilities in the strata, and selective enrolment in each of the clusters. A sampling weight to correct for differential sampling between the strata was derived for each stratum separately, while an attrition weight to correct for non-response was calculated for each cluster separately. For paper I and II, the overall weight was the inverse of the product of the sampling weight and the attrition weight. The weights were rescaled to the size of the enrolled population to arrive at the correct degrees of freedom in the statistical analyses.

For paper III we had an additional ‘assessment weight’ to account for selective interview on factors associated with tuberculosis and sputum testing, which was calculated separately for each cluster. This weight was calculated as the inverse of the probability of having interviewed and undergone sputum testing in enrolled individuals. The probability of having interviewed and sputum testing was derived by a logit analysis using the variables gender, age (six groups), previous diagnosis of tuberculosis (yes/no), and current tuberculosis medication (yes/no). The overall weight was the product of the sampling weight, attrition weight and the assessment weight. The weights were rescaled to the size of the enrolled population to arrive at the correct degrees of freedom in the statistical analyses and to ensure that the controls are representative of the general population.

To accommodate missing data in key laboratory and chest X-ray parameters used for defining the outcomes, we performed missing imputation analyses for 20 sets. Use of the GeneXPert MTB/RIF test was not included in the initial protocol, but later it was made available for positive smears only. Since this test was not done on smear negative specimens, we did not use its results in multiple imputations. Therefore, we

did not perform an estimation using multiple imputations for the sensitivity analyses incorporating Xpert results.

Pearson's χ^2 test was used to compare group differences of categorical variables. Due to the use of complex survey design approach in paper II, nested logistic models could not be assessed with the likelihood ratio test. Instead we used the 'test' command, which performs an overall Wald test to assess differences between models. The level of significance was set at $P < 0.05$ in all analyses. Where appropriate, adjusted odds ratios with 95% confidence intervals were reported.

3.8 Ethical issues

The National Medical Research Coordinating Committee and Zanzibar Medical Research and Ethics Committee approved the study. Publication of data for paper III had additional ethical clearance from Ethics Advisory Group of the International Union against Tuberculosis and Lung Disease. The research ethics board in Norway for projects abroad (REK Vest) were given a copy of the national ethics permit and did not require a separate ethics permit. Permission to conduct the study was also granted by local authorities where the study was conducted. The goal and the benefits of the study were explained to the participants and written informed consent were obtained from the participants prior to enrolment. The interviewees were ensured that participation was on a voluntary basis and that they were free to withdraw from the study at any time if they wished to do so. They were also told that there would be no penalty if they decided to withdraw. Participants were guaranteed confidentiality throughout the research process. Completed questionnaires were kept in a secure place, only accessible to the research team. The results of the study have been made accessible to the community through publications and dissemination workshops organized by NTLP.

4. SUMMARY OF THE RESULTS

4.1 Prevalence of pulmonary tuberculosis in the adult population of Tanzania: A national survey, 2012 (*Paper I*)

This was a community-based cluster randomized survey which was done to assess the prevalence of bacteriologically-confirmed tuberculosis in the adult population. The population eligible included individuals aged 15 years or more who had slept in the selected household for the past 2 weeks or more before the survey. The study period was from December 2011 to November 2012. Eligible participants were screened for tuberculosis-related symptoms using a standardised questionnaire and chest X-ray. Participants suspected for tuberculosis were further investigated with expectorate examined by microscopy and culture. A bacteriologically-confirmed tuberculosis case was defined as any person with positive culture for tuberculosis and/or positive sputum smear.

The study showed that the weighted prevalence for sputum smear-positive was 249 per 100000 adult population and that for bacteriologically-confirmed tuberculosis cases was 293 per 100000 adult population. The bacteriologically-confirmed tuberculosis prevalence was markedly higher in mainland Tanzania (298/100000 adult population) than in Zanzibar (124/100000 adult population). The prevalence was twice as high in men as in women. The highest point estimates of bacteriologically-confirmed prevalence was found in the oldest age group of 65 years and older. In addition, there was a higher tuberculosis prevalence among participants in the lower socioeconomic position than the higher. Individuals 45 years or older constituted 55% (71/129) of the identified smear positive cases, but just 28% (6793/24648) of the notified tuberculosis cases. Chest x-ray screening identified more tuberculosis cases than symptom screening. Weighted for the prevalence of HIV in the notified new smear-positive cases, the overall case detection in Tanzania of incident smear-positive tuberculosis cases in 2012 was between 37% and 48%.

We concluded that the prevalence of bacteriologically-confirmed tuberculosis was higher than previous WHO estimates, and the age distribution of prevalence cases suggests an epidemiological shift to older age groups that could be a result of tuberculosis control activities in the past. The survey also indicates a situation where a significant proportion of infectious tuberculosis cases are missed or not detected early by the programme, which should be addressed by the NTLP of Tanzania.

4.2 Health care-seeking behavior among people with cough in Tanzania: findings from a prevalence survey (*Paper II*)

This study was carried out within the tuberculosis prevalence survey described above. The objective was to assess the health care-seeking behavior of coughers presumed to have tuberculosis. The population eligible included individuals aged 15 years or more who had slept in the selected household for the past 2 weeks or more before the survey. The study period was from December 2011 to November 2012. Eligible participants were screened for tuberculosis-related symptoms using a standardised questionnaire and chest X-ray. An individual with presumptive tuberculosis was defined as a person who has been coughing for 2 weeks or more at the time of the survey and/or was coughing blood. Individuals with presumptive tuberculosis were interviewed about their health care-seeking behaviour using a structured questionnaire.

The study showed that of the 3,388 individuals with symptoms of tuberculosis, only 1,053 (31.0%) had sought care for their symptoms at the time of the survey. Persons having symptoms in addition to cough and hemoptysis were more likely to seek care. The majority sought care at sites without adequate investigations for tuberculosis. Individuals with presumptive tuberculosis visiting sites with limited tuberculosis diagnostic capacity as their first point of care were referred for examination of sputum or chest X-ray in less than one percent. Care seeking at health facilities with tuberculosis diagnostic capacity was done by 42.3% of the individuals with presumptive tuberculosis. Actual tuberculosis diagnostic procedures (appropriate evaluation) in these facilities were performed in a minority of these presenting

individuals with presumptive tuberculosis: smear microscopy 37.1%; chest X-ray 28.1%. Of all individuals with presumptive tuberculosis, 211 (6.7%) got appropriate evaluation. For individuals with presumptive tuberculosis who did not seek any care, lack of money (29.6%) and perceiving symptoms as not serious (23.9%) were the main reasons given for not seeking care.

We concluded that only a third of the persons with cough symptoms or hemoptysis indicative of tuberculosis actually sought care for it. Of them, 42 % sought care in sites with tuberculosis diagnostic capacity but most of them were not offered tuberculosis-diagnostic procedures at initial visit, making a timely diagnosis unlikely.

4.3 Population impact of factors associated with prevalent pulmonary tuberculosis in Tanzania (*Paper III*)

This study was carried out within the nation-wide tuberculosis prevalence survey described in Paper I. The objective was to determine the demographic, behavioural and clinical factors associated with tuberculosis among adult population of Tanzania. The eligible population included individual aged 15 years or more who had slept in the selected household for the past 2 weeks or more before the survey. The study period was from December 2011 to November 2012. Tuberculosis cases and controls were interviewed about factors associated with tuberculosis using a structured questionnaire. A case was a participant with bacteriologically-confirmed tuberculosis. A control was either a participant with “presumptive tuberculosis” who tested bacteriologically negative or a selected participant without any symptoms at all.

The study showed the mean age in years (standard deviation) was 39 (17) for cases and 38 (18) for controls. Multivariable analysis showed that compared to persons aged 15-24 years tuberculosis was more common among persons aged 25-34 years, and 55-64 years. Tuberculosis was more common among men than women, and also more common among individuals with a low BMI than normal BMI. Population attributable fraction was 2% for diabetes and 3% for HIV.

We concluded that belonging to older age group (55 to 64 years), being male, and having low BMI were associated with bacteriologically-confirmed tuberculosis and that NTLP should consider systematic approach to detecting tuberculosis in these groups who are more likely to have tuberculosis in order to reach ‘missed’ cases and eliminate tuberculosis in line with “End TB strategy” of the WHO. On a population level, we could not show HIV and diabetes to have any major effect on prevalent tuberculosis from which future transmission can derive.

5. DISCUSSION

5.1 Methodological issues

5.1.1 Discussion on the study design and sample size

Our main study (Paper I) was a community-based cluster randomized prevalence survey with selection of the clusters following a stratified proportional-to-population size approach. Surveys can measure the prevalence of disease and thus are often also called prevalence studies [55]. We had two separate studies (Paper II and Paper III) nested in our main study. The nested study on health care-seeking behavior (Paper II) was a cross-sectional type of a study in which the measurements of exposure and effect are made at the same time, and this was relevant for answering our research question [55]. The nested study on factors associated with tuberculosis (paper III) had a case-control design. Case-control studies are good when studying a rare disease like tuberculosis, and the odds ratio is very similar to the risk ratio that we want.

However, because exposure and outcome are also identified at one time point or retrospectively, in case-control studies, it is difficult to know the sequence in time of the disease of interest and the possible risk factor [56, 57]. For example, it is not possible to say from our study whether a low BMI predisposes for tuberculosis, or is the result of tuberculosis, or both. Cohort studies provide the most direct measurement of the risk of developing disease [55]. However, in our cohort we did not have data on all determinants from all the non-tuberculosis participants and hence we could not analyze in a cohort design the risk of tuberculosis.

Cluster sampling is commonly used instead of a simple random sampling in order to cover a large area with a smaller sample size, mainly to save money and time. The disadvantage of cluster sampling is that it causes loss of effectiveness (design effect) since respondents in the same cluster are likely to be somewhat similar to one another [58, 59]. However, in our study, this was considered and taken care of during sample size calculation (see section 3.2).

Ideally, the sample size must be large enough for the study to have sufficient statistical power to detect the differences deemed important [55]. Our sample size was calculated for the main study only, while the two nested studies had no specific sample size calculated for them. Nevertheless, we believe that the resulted sample size for the study on health seeking behavior (Paper I) was sufficient to detect some important differences between various groups. Unfortunately for the study on factors associated with tuberculosis (Paper III), given the low number of tuberculosis cases detected in the survey, for several of the analyzed associations there was not sufficient statistical power. HIV is one such risk factor.

5.1.2 Discussion on validity

Validity can be compromised by bias, confounding and chance. Bias is a systematic error that results in a mistaken estimate of an exposure/disease association and can occur because of the way in which the subjects have been selected, the way variables are measured, or some confounding factor that is not controlled for [60]. Thus, bias can be classified into three broad groups; selection bias, information bias, and statistical confounding [61].

Selection bias is a distortion that results from procedures used to select subjects and from factors that influence study participation [60]. To reduce selection bias introduced by staff of the survey, the selection of the house where invitation to participate in the study started was done by chance. Thereafter the houses were added in a consecutive manner until the required number of participants (900 people) was reached. There is still a chance that selection bias occurred in our study since not all those who were invited came and participated. We compared these two groups in terms of age, sex, currently on tuberculosis treatment and previously diagnosed with tuberculosis. The results indicated that for those who participated, fewer were on tuberculosis treatment, they were more females, and they were older compared to those who did not come, but this was adjusted for using survey weights in the analysis.

Information bias is a distortion in the measure of association caused by inaccurate information or measurement, that can result from poor interviewing or measuring techniques, or differing level of recall by respondents [60]. Although using a structured face

to face interview is an effective method of gathering information, in our studies there is potentially low precision of respondents' recall of events and locations, such as the first site where they went to seek treatment or advice for their symptoms, and health services provided at those sites. To minimise error in the collection of information, interviewers were trained and the questionnaires were pre-tested.

Confounding implies that the observed relationship exhibits an endpoint association with a variable other than the one under study. Confounding can often be partly controlled for, provided the variables in question have been examined [61]. We handled the problem of confounding during the analysis by using multiple logistic regression models to examine the potential effect of one variable while controlling for the effect of the other factors. For example, in Paper II, multiple logistic regression analysis was used to assess how having symptoms in addition to cough was associated with health care seeking while controlling for sex, age, marital status and history of previous diagnosis of tuberculosis.

5.1.3 Discussion on practical issues and challenges during survey.

We had some breakdowns of the X-ray equipment during the field activities; this caused some of the participants not to be screened by X-ray resulting in missing X-ray data. For example a full cluster (866 individuals) was screened by symptoms only, as the X-ray machine was not working throughout field activities in that cluster. Unfortunately we did not document the frequency of the X-ray breakdown.

Provision of sputum had some challenges especially for the morning specimen which was used for culture. Some of the participants didn't return to the field site to provide the morning specimen even after being tracked by the survey team. Another reason for not having a morning specimen for culture was inability of the participants to produce sputum. The additional loss of a morning specimen was due to specimens not arriving at CTRL (spillage or lost during transportation) and initial problems with the personal identifiers on the specimen cups, precluding linking the specimen to a survey participant.

We suspect that there might be some delays in the processing of the culture specimens after arriving at CTRL. With this delay, and the additional 3 to 4 days which most of the samples

took to reach CTRL, a considerable number of samples may have not been processed to culture within 5 days after the sample collection. We do not have data to show time taken between sample collection at the sites, and receiving and processing at CTRL.

5.2 Discussion of the major study findings

5.2.1 Burden of bacteriologically-confirmed tuberculosis

Paper I focused on the prevalence of bacteriologically-confirmed pulmonary tuberculosis and the results showed a prevalence bacteriologically-confirmed tuberculosis of 293/100000 adult population, which was higher than previous WHO estimates.

The point estimates of tuberculosis prevalence within subgroups of the population was higher in rural than urban areas, as shown in other studies [62-64]. One explanation may be less access to health services in rural compared to urban areas leading to a marked number of undiagnosed tuberculosis cases who were eventually identified through active case finding in the survey. Also, people living in rural areas are less affluent than the urban population [65] and poverty is a well-known risk factor for tuberculosis [66]. As shown in data from routine case finding and results from other studies, results of paper I showed a higher tuberculosis prevalence in men than in women [30, 62, 63]. This suggests that the sex difference in the tuberculosis notification in Tanzania reflects a difference in disease occurrence rather than a difference in access to diagnosis and treatment, as some studies have suggested [67, 68]. In this study we screened the study population, therefore access to diagnosis and treatment did not play a part; differential non-response related to disease status or sex was addressed by the analysis approach.

Tanzania has reached geographical DOTS coverage of 100%, a stable case detection, and good treatment success rates for the past few years. The decline in annual risk of tuberculosis infection (ARTI) of on average 2.7% per year for the last two decades, suggests a reduction in transmission in the general population [37]. This is also supported by results from paper I showing that the prevalence of bacteriologically-

confirmed cases is lowest in the age group of 15 to 24 years and highest in the age group of 65 years and older. This may indicate an epidemiological shift that fits control of population-wide active transmission with active disease being more often a result of re-activation of latent infections reflecting a decreasing new transmission [7, 69, 70]. Despite the higher than expected prevalence, the presence of an epidemiological shift may be a sign of successful tuberculosis control activities over a number of years [7, 69]. Tanzania, as most of the African countries, experiences a migration of young people from rural to urban areas, leaving behind old people. Since our results showed a higher tuberculosis prevalence rate in the older population, and these are often left behind in rural areas, this might also be another explanation as to why tuberculosis prevalence was higher in rural than urban areas as was shown above. On the other hand, 2012 routine program data showed that 72% of the notified tuberculosis cases were younger than 45 years, thus probably missing cases in the older generation. One possible reason for the age difference between the populations of prevalent and notified tuberculosis cases can be differences in level of suspicion by health staff between these populations. This might lead to differential clinical work-up with a biased identified population of presumptive tuberculosis patients as a result, and missed tuberculosis cases in the non-screened older population. The strong influence of HIV on the tuberculosis epidemiology in Tanzania may have led to over-emphasis of case finding in the younger population with less vigilance among the older HIV-negative tuberculosis patient [4]. The NTLP of Tanzania may need to modify the strategies for addressing the burden of tuberculosis in the country based on the changing epidemic. Another reason could be differential health care-seeking behaviour between older and younger individuals with tuberculosis-associated symptoms. However, results of paper II showed that there was no difference in health care-seeking behaviour between the two groups.

5.2.2 Health care-seeking among individuals with presumptive tuberculosis

Results of paper II showed that only a third of individuals with presumptive tuberculosis in the Tanzanian adult population had sought care at the time of the survey. The propensity for care seeking in our study was low compared to studies

among tuberculosis patients done in Ethiopia, where 78% of the individuals with presumptive tuberculosis sought care [47], and in rural India where 71% of the women and 69% of the men reported seeking care for their symptoms [71]. However, this does not imply that the individuals with presumptive tuberculosis not seeking care would have been missed by the NTLP altogether. With data from a population survey, individuals with presumptive tuberculosis were identified actively by screening allowing right-censored observations, as those who did not yet seek health care might have done so later in absence of the survey. Furthermore, we assessed only the first place of care-seeking. Care seeking is a complex process and often involves a cascade of different care providers, including those in the informal sectors.[72] Some of the individuals with presumptive tuberculosis in our study might have sought care at places connected with the NTLP at a later stage in their care-seeking process.

Our study showed that 42% of the persons with tuberculosis symptoms who sought care went to sites with tuberculosis diagnostic capacity as their first place to seek treatment. This is higher than what was reported in studies in India (33%), Vietnam (24%) and Ethiopia (30%), [47, 73, 74] but lower than what was reported in a study done in Malawi (70%) [75]. Our results therefore suggest that more can be done by the NTLP with regards to the social marketing campaigns which should be continued. Former tuberculosis patients could be used as peer-educators for sensitizing the community to seek for care and treatment when having tuberculosis symptoms.

We also found that presence of other symptoms in addition to cough was associated with seeking treatment, as was seen earlier in India [71]. This could be because suffering only from cough may often be regarded as very common and not a serious illness, but having cough together with other symptoms like fever is more consistently felt as a disease.

Tuberculosis health services are provided free of charge in Tanzania, but not before you are categorized as an individual with presumptive tuberculosis or diagnosed with

tuberculosis. Almost 30% of those who did not seek treatment mentioned lack of money as the major reason. These results are in line with studies indicating that wealth is a determinant of use of health service [76-78]. Even though drugs and smear examination are provided free of charge, there are many other costs which are incurred by the patient, both direct cost (transport, food), and indirect costs (loss of income during absence).

5.2.3 Health care services received by individuals with presumptive tuberculosis

Paper II also revealed some disturbing findings: at initial presentation at health facilities with tuberculosis diagnostic capacity, the standard diagnostic procedures were often not carried out. Both cough for more than two weeks and hemoptysis identify individuals with presumptive tuberculosis for the tuberculosis-control activities in the country [29]. All patients presenting with these symptoms should have a clinical assessment to consider tuberculosis. The results show that many of these individuals with presumptive tuberculosis did not receive appropriate care and this can be due to lack of supplies at health facilities or lack of suspicion of tuberculosis among health care personnel. This lack of awareness might be due to inadequate or lack of supportive supervision from the district, regional and national level. To ensure that the diagnosis of tuberculosis is done correctly and timely there is a need for regular retraining, reminders, supportive supervision and mentorship of health personnel on identification of individuals with presumptive tuberculosis and performance of at least sputum examination.

Engagement with care-providers outside the NTLTP needs to focus on identification and referral of individuals with presumptive tuberculosis. The results from paper II showed that less than one percent of those who went to sites with limited tuberculosis diagnostic capacity were referred to other facilities for proper management.

Pharmacy staffs are frequently approached by individuals with cough when these symptoms arise, and could be a good entry point for tuberculosis-control activities by linking with the NTLTP. Pharmacies have been shown by several studies to be an

important place for individuals with presumptive tuberculosis to seek treatment [79-81]. A study in the Dominican Republic showed that simple sensitization of pharmacy staff on the importance of recognizing tuberculosis improved the referral from pharmacy to a formal tuberculosis diagnostic facility [82], resulting in improved case finding. Another possibility is remote smear and fixation of the slides then sending them to sites with diagnostic capacity for staining and reading. This will have to go hand in hand with corresponding training of health personnel at sites without diagnostic capacity. Private providers could be another entry point for NTLTP. Currently there are private providers in the country who are capable of diagnosing tuberculosis, hence providing a platform for NTLTP to expand its services. They could participate in tuberculosis control, as have many of the hospitals run by churches since the start of the programme.

5.2.4 Factors associated with tuberculosis

In our study (paper III), age was observed to be associated with tuberculosis disease, as demonstrated in other studies [83-85], with a higher chance of having tuberculosis disease observed amongst older individuals (55 to 64 years). This correlates with the results of paper I which showed an ageing tuberculosis epidemic with fewer adolescents with tuberculosis signifying less new transmission. This is in contrast to the tuberculosis programme notification data where the notification rates among older people are less as compared to younger age groups [30, 31], thus indicating that older age groups are under-diagnosed in the programme. Results from paper II have shown that there was no difference in care seeking behavior between the older and the younger individuals with tuberculosis-associated symptoms. The low number of notified cases from older age group could be a consequence of low level of suspicion by health staff when dealing with old people. Therefore, general clinicians should be trained or reminded to ask their older patients about tuberculosis symptoms and have a low threshold for further investigations, and hence clinicians' awareness that older people also have a substantial risk of tuberculosis. Intensified case finding among elderly people could be another strategy to improve case finding. NTLTP could train

community health workers to screen elderly people in the community for tuberculosis symptoms (e.g., cough of >2 weeks' duration), and to refer those with symptoms to a nearby health facility for tuberculosis testing and further management. However, this method has got financial constraints as tuberculosis is a rare disease, many elderly people will be needed to be screened to get few tuberculosis cases. Therefore, it remains to be seen what an appropriate screening algorithm is in the elderly population.

The increased risk of tuberculosis in men is well known and has been attributed to multiple factors. Some have suggested biological factors [86] while others attribute to social behaviors of men which increases their chance of exposure to tuberculosis [67, 86]. The higher risk among men is reflected in the tuberculosis notification in Tanzania where 65% of reported cases in 2012 were men [30].

A person who had tuberculosis in the past (treated or not) has a higher risk of tuberculosis than a person who never had tuberculosis [87]. In paper III we see a point estimate indicating an association of tuberculosis with past history of tuberculosis, but this was statistically significant only in the univariable analysis and not in multivariable analysis, probably due to few numbers of events. This group could be targeted for increased case detection. One possible approach could be to follow-up the successfully treated tuberculosis patients for a period of two years after treatment, to detect recurrent tuberculosis at the earliest and start appropriate treatment. Another approach could be systematic emphasize on information to cured patients that if the symptoms re-appear, they should come back as soon as possible. It is suggested that the risk of recurrence in two years is about 4% and that about 90% of the relapses occur within two years of treatment completion [87], and this information could be shared with cured patients.

Malnutrition (both micro- and macro-deficiency) causes impairment of immune response [88]. Several studies have shown low BMI to be a risk factor for tuberculosis [56, 89]. In our study those with low BMI were 70% more likely to have

tuberculosis compared to those with normal BMI. But these results should be interpreted with care as low BMI is also fairly consistently a result of tuberculosis [56]. The strong and consistent association between tuberculosis and malnutrition can work both directions, as a “cause” and an “effect”.

Diabetes is known to adversely affect body immunity by impairing the innate and adaptive immune responses, thereby accelerating the development of tuberculosis [88]. Several studies have shown diabetes to be a risk factor for tuberculosis [88, 90], but the association was not statistically significant in this study. Since the ascertainment of diabetes in our study was done by self-reporting, people with undetected diabetes will have been misclassified [91, 92]. This misclassification might have underestimated the tuberculosis-diabetes association [92]. The best method would have been to test everybody using glycosylated haemoglobin (HbA1c) to ascertain diabetes, and we propose this for future studies on factors associated with tuberculosis. On the other hand, given the evidence from other studies and the increasing burden of diabetes in Tanzania [93], this is an important group which tuberculosis program should consider including in their enhanced case finding programs [94]. WHO and The Union have developed a collaborative framework for care and control of tuberculosis and diabetes. One of the recommendations in the framework is to screen all diabetes patients for chronic cough (that is, cough lasting more than 2 weeks) at the time of their diagnosis and, if possible, during regular check-ups. Those with positive tuberculosis symptoms should be examined as per national guidelines [94]. In Tanzania, diabetes clinics have been set-up as separated units within the health system [95, 96]. These diabetes clinics provide a platform in which NTLP can use as entry points for active tuberculosis case finding. A study which was done in Mwanza, Tanzania, revealed that screening of tuberculosis at diabetes clinics is possible and the point prevalence of tuberculosis among adults with diabetes was 7-fold higher than that reported in the general population [97].

While several studies have shown HIV as an independent risk factor for tuberculosis [84, 88, 98], we did not find a statistically significant association in our study. This

may be due to several factors. First, we had small number of cases and hence were underpowered to detect an association. Second, we used prevalent tuberculosis cases (which are by definition survivors), so it is possible that some of the HIV cases might have died early and are not included in the study [99]. Third, declining HIV burden and increasing coverage of anti-retroviral therapy in Tanzania might be influencing this risk analysis [100-102]. Studies in 1990s showed that about 30% of incident tuberculosis cases were attributable to HIV [103, 104], but in our study the population attributable fraction (PAF) for HIV in prevalent tuberculosis cases was 3%, indicating that HIV may not be as strong driver of the tuberculosis prevalence in Tanzania as before.

5.2.5 Public health use of the findings

This study is the first tuberculosis prevalence survey ever to be done in Tanzania. Our study produced an estimate of the prevalence of smear-positive tuberculosis and bacteriologically-confirmed tuberculosis in the Tanzanian population aged 15 years and above. This population-based information will provide the much-needed context in which other available tuberculosis data in Tanzania such as tuberculosis notification and mortality can be re-assessed. Also, the results show the need for adapting the current tuberculosis strategy to serve the older population, the rural setting, and populations from low social economic positions.

Furthermore, the results will contribute data for the evaluation of the Millennium Development Goals as formulated by The United Nations and signed by 189 countries in the year 2000 and the Sustainable Development Goals 2015-2030. Millennium development goal number 6c, refers to tuberculosis and aims to halt and reverse the incidence tuberculosis [44]. In the Sustainable Development Goals 2015-2030 tuberculosis is mentioned in target number 3.3 of Goal 3 [105].

Recognizing the strength of the prevalence surveys, the Global Fund against AIDS, Tuberculosis and Malaria sees the use of their results for future funding strategies [106].

Also, the MoHSW in Tanzania, in collaboration with WHO and other implementing partners, has developed a guideline to engage civil society organizations (CSOs) in tuberculosis care and control. The proposed approach has been given the name “ENGAGE-tuberculosis” [107]. Tuberculosis control activities and tasks to increase case detection identified as possible to be implemented by CSOs and stakeholders, included 1) awareness creation to generate demand for services, 2) communicating behavior change by community mobilization, and 3) active community-based tuberculosis case-finding (e.g., through campaigns or house-to-house visits) [107]. Paper II results can be used by the CSOs during the implementation of the first and the second control activities and results from paper III can be used when implementing activity number three.

Lastly, because tuberculosis is a rare disease in spite of being an important killer, regular population screening will be too expensive. In its post-2015 ‘End TB strategy’, WHO recommends ‘early detection of tuberculosis by systematic screening in selected risk groups’ to reach missing cases. Therefore, results from paper III can be used by NTLP in Tanzania for considering systematic approach to detecting tuberculosis in risk groups, as the program begins to adapt the global End TB strategy for the country. We suggest that clinicians think about tuberculosis among persons with low BMI, and keep it in mind in older age groups. Groups well known to have increased risk should continue to be screened, like HIV positive patients, diabetes patients, and household contacts of pulmonary tuberculosis patients.

5.3 Strength and limitations

5.3.1 Strength of the study

This survey and the studies embedded in it have several strengths. There was a representative coverage of the whole country, a strong internal and external monitoring of field activities, no major deviations from the survey protocol and SOPs, adequate participation rate, and adequate analytical strategies to adjust for potential sampling and selection bias.

5.3.2 Study limitations

Some limitations of the survey are noted. The culture results in a considerable number of individuals with presumptive tuberculosis were lacking due to administrative problems in linking identification numbers from clinical information and laboratory results. The mechanism that generated the missing data was random, making the strategy of multiple imputation valid. Survey estimates and imputation estimates therefore differ only modestly. These missing results, and processing only one specimen per patient for culture, may have led to underestimation of the prevalence of culture-positive tuberculosis. Another potential limitation is the negative culture results in smear-positive cases which could have resulted due to delays in culture specimen processing, influence of CPC in specimens from remote cultures, or MOTT. We do not have data to show time taken between sample collection, transportation, reaching the laboratory and culturing. It was shown earlier in a drug resistance survey that the yield of culture at CTRL was not influenced by CPC addition [52]. In a setting with a marked prevalence of MOTT, the smear status would over-estimate smear-positive tuberculosis. The findings from a sensitivity analysis showed that a potential over-estimation of the prevalence estimates incorporating smear-status should be minimal.

We did not include prisons, schools, and other institutionalised populations in the study. Data from other studies have shown the prevalence of tuberculosis in prisons to be high [108, 109]. Lastly, the initial clusters in the survey had a low participation ratio. Although this was corrected during the later parts of the survey and the analysis, some differential participation may be present. The effect of such a bias on the estimate is unclear.

We had several limitations which were specific for the add-on studies. For example for paper III, we were underpowered to detect many associations, given the low number of tuberculosis cases detected in the survey. Also, we could not establish the temporality of the associations. Furthermore, by definition, a prevalence survey counts only survivors, and associations found in the study (Paper III) are a function of both risk of and survival after the event. A study limitation in paper II was lack of

information on care seeking beyond the initial stage and the actual duration of the symptoms.

6. CONCLUSIONS AND RECOMMENDATIONS

The main objective of this study was to measure the burden of bacteriologically-confirmed pulmonary tuberculosis in Tanzania. The study has also looked at health care-seeking behavior of people with cough of two weeks or more and/or who were coughing blood. Furthermore, the study assessed factors associated with tuberculosis which were present in the general population. Based on the findings the following conclusions are drawn, and recommendations suggested.

6.1 Conclusions

- 1) The national prevalence for bacteriologically-confirmed tuberculosis was estimated 293 per 100000 population (95% CI 228-358/100000) and higher than previous WHO estimates. We estimate that in 2012, the country detected only between 37 and 48% of new smear-positive adult tuberculosis patients.
- 2) The age distribution of prevalent cases suggests an epidemiological shift from younger to older age groups that could be a result of tuberculosis control activities in the past.
- 3) The difference in age distribution between prevalence and notified cases suggests a number of infectious tuberculosis cases of older age are currently missed by the programme.
- 4) Only a third of the persons with cough symptoms or haemoptysis indicative for tuberculosis actually sought care for it. Of those who sought care, many went to sites with tuberculosis diagnostic capacity but were not offered tuberculosis-diagnostic procedures at initial visit, making a timely diagnosis unlikely.
- 5) Bacteriologically-confirmed tuberculosis was associated with age group 55 to 64 years, being male, and a low BMI. The associations with HIV and diabetes were

not statistically significant, but the study was not powered for these specific factors.

6.2 Recommendations

- 1) The high prevalence of tuberculosis shows that there is a need for NTLP to change/ improve the way they are doing things. The NTLP should check whether it caters for the current needs, as things have changed since the current system was formed. We believe that if the current strategies in place to fight tuberculosis are better implemented by NTLP and other stakeholders, the fight against tuberculosis would be achieved to the large extent. So what is needed, and hence we recommend, is just to look at why the current structure of NTLP fails to implement the strategies to combat tuberculosis in full, resulting in high prevalence.
- 2) The situation of missing or delayed detection of the most infectious tuberculosis cases should be addressed. There is a need for regular retraining, reminders, supportive supervision and mentorship of health personnel on identification and follow-up of individuals with presumptive tuberculosis to ensure accurate and timely diagnosis of tuberculosis.
- 3) To improve seeking of care for those with tuberculosis symptoms, NTLP should continue to engage in social marketing and should also explore the possibility of using previous tuberculosis patients as peer educators to sensitize the community to seek care and treatment.
- 4) NTLP should consider targeted intensified case detection in the identified high risk groups in order to reach 'missed' cases and eliminate tuberculosis in line with End TB strategy of the WHO.

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8. ANNEXES

Population impact of factors associated with prevalent pulmonary tuberculosis in Tanzania

Supplementary online appendix

Mbazi Senkoro, Ajay MV Kumar, Palanivel Chinnakali, Sayoki G Mfinanga, Saidi Egwaga, Vedastus Kamara, Frank van Leth, Sven G Hinderaker

Box: Description of weighting in statistical analysis of case control study nested in national prevalence TB survey, Tanzania, 2012

We corrected the study population for potential selection bias by using weights that reflect different sampling probabilities in the strata (urban, rural, semi-urban in the mainland and Zanzibar), selective enrolment in each of the clusters, and selective interview on factors associated with tuberculosis (TB) and sputum testing

First, a 'sampling weight' to correct for differential sampling between the strata was derived for each stratum separately. It was calculated as the inverse of the ratio between invited population and total sample size of adults aged 15 years and above in the stratum.

Second, an 'attrition weight' to correct for non-response was calculated for each cluster separately. This weight was calculated as the inverse of the probability of being enrolled in the group of invited individuals. The probability of enrolment was derived by a logit analysis using the variables gender, age (six groups), previous diagnosis of tuberculosis (TB) (yes/no), current TB medication (yes/no), and Socio-Economic Position (three groups).

Third, an 'assessment weight' to account for selective interview on factors associated with TB and sputum testing was calculated separately for each cluster. This weight was calculated as the inverse of the probability of having interviewed and undergone sputum testing in enrolled individuals. The probability of having an interview on factors associated with TB and sputum testing was derived by a logit analysis using the variables gender, age (six groups), previous diagnosis of tuberculosis (TB) (yes/no), and current TB medication (yes/no).

The overall survey weight was the product of the sampling weight, attrition weight and the assessment weight. The survey weights were rescaled to the size of the enrolled population to arrive at the correct degrees of freedom in the statistical analyses and to ensure that the controls are representative of the general population.

JAMHURI YA MUUNGANO WA TANZANIA
WIZARA YA AFYA NA USTAWI WA JAMII



UTAFITI WA KWANZA WA KITAIFA WA KUTATHMINI KIWANGO CHA TB NCHINI TANZANIA

4: USAILI WA KWANZA

Ijazwe na timu ya Utafiti

Jina la cluster: _____ PIN:

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Namba ya cluster ##	Namba ya Kaya ###	Namba ya mshiriki ##
------------------------	----------------------	-------------------------

Jina la mshiriki: _____

	Ndiyo	Hapana	Sijui
1. Je, umepatwa na yafuatayo:			
1a. Umekuwa unakohoa kwa wiki mbili au zaidi?			
1b. Umekuwa unakohoa makohozi yaliyochanganyika na damu?			
1c. Umekuwa na homa kwa wiki mbili au zaidi?			
1d. Ndani ya mwezi mmoja umekuwa unapungua uzito kwa wastani wa kilo 3?			
1e. Umekuwa unatokwa na jasho jingi wakati wa usiku kwa wiki mbili au zaidi?			

Ikiwa jibu ni Ndiyo
katika jibu moja au
zaidi



**Weka alama ya X ndani ya kisanduku
kilichoandikwa EXTRA katika kadi ya
utambulisho**

Mwisho wa Hajaji/Dodoso



**Weka alama ya X ndani ya
kisanduku kilichoandikwa DONE
katika kadi ya utambulisho**

**JAMHURI YA MUUNGANO WA TANZANIA
WIZARA YA AFYA NA USTAWI WA JAMII**



UTAFITI WA KWANZA WA KITAIFA WA KUTATHMINI KIWANGO CHA TB NCHINI TANZANIA

3: FOMU YA MALI KATIKA KAYA

Jina la cluster: _____ **PIN:**
Namba ya cluster Namba ya Kaya
 ## ###

Jina la mshiriki: _____

1. Kipimo cha GPS cha kaya ni kipi?

Latitudo			Longitudo		
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
##	##	##	##	##	##

2. Je, kwa kawaida ni watu wangapi hula chakula kinachotoka kwenye chungu Kimoja?

Jibu ## *Andika namba sahihi ndani ya kisanduku*

3. Je, ndani ya nyumba ni vyumba vingapi hutumika kama vyumba vya kulala?

Jibu ## *Andika namba sahihi ndani ya kisanduku*

4. Je, katika kaya hii, kuna mfanyakazi wa ndani ambaye si mmoja wa wanafamilia hii?

Ndiyo **Hapana**

5. Je, ndani ya nyumba hii kuna

		Ndiyo	Hapana
5a.	Radio inayofanya kazi?	<input type="checkbox"/>	<input type="checkbox"/>
5b.	Televisheni/runinga inayofanya kazi?	<input type="checkbox"/>	<input type="checkbox"/>
5c.	Jokofu linalofanya kazi?	<input type="checkbox"/>	<input type="checkbox"/>
5d.	Baiskeli inayofanya kazi?	<input type="checkbox"/>	<input type="checkbox"/>
5e.	Pikipiki inayofanya kazi	<input type="checkbox"/>	<input type="checkbox"/>
5f.	Gari linalofanya kazi?	<input type="checkbox"/>	<input type="checkbox"/>
5g.	Simu ya mkononi nzima?	<input type="checkbox"/>	<input type="checkbox"/>
5h.	Pasi nzima?	<input type="checkbox"/>	<input type="checkbox"/>
5i.	Akaunti ya Benki inayotumika?	<input type="checkbox"/>	<input type="checkbox"/>

6. Je maji ya kunywa katika kaya hii ni ya aina gani?

jibu ## *weka alama/ ndani ya kisanduku sahihi*

- Maji ya Bomba ndani ya nyumba = 1
- Maji ya bomba katika bomba la umma = 3
- Kisima cha wazi cha Binafsi = 5
- Kisima cha wazi cha jirani = 7
- Kisima chako au cha jirani kilichofunikwa = 9
- Chemechem = 11
- Chanzo kingine = 13

- Maji ya bomba katika mazingira ya nyumba= 2
- Maji katika bomba la jirani= 4
- Kisima cha wazi cha umma = 6
- Maji ya chupa = 8
- Kisima cha umma kilichofunikwa = 10
- Mto, mfereji, maji ya vidimbwi = 12

7. Je, choo ni cha aina gani?

Jibu ##

Andika namba sahihi ndani ya kisanduku

Choo cha binafsi cha maji = 1

Choo cha kuchangia cha shimo = 4
kuchangia = 6

Choo cha kuchangia cha maji = 2

Choo cha shimo cha VIP cha binafsi = 5
Sina choo = 7

Choo cha binafsi cha shimo = 3

Choo cha shimo cha VIP cha
Aina nyingine ya choo = 8

8. Je, sehemu kubwa ya sakafu ndani ya nyumba hii imetengenezwa na nini?

Jibu ##

Andika namba sahihi ndani ya kisanduku

Ardhi, Udongo, Mchanga = 1
Saruji = 4

Kinyesi cha wanyama = 2
Aina nyingine ya sakafu = 6

Mbao, ngozi ya plastiki, marumaru = 3

9. Je, sehemu kubwa ya paa la nyumba hii kutumia nini?

Jibu ##

Andika namba sahihi ndani ya kisanduku

Nyasi, majani, udongo = 1

Bati = 2

Vigae = 3

Aina nyingine za paa = 4

10. Je, sehemu kubwa ya ukuta wa nyumba hii umejengwa na nini?

Jibu ##

Andika namba sahihi ndani ya kisanduku

Nyasi = 1

Fito na udongo = 2

Vitu vidogo vidogo kwa pamoja = 3

Tofali za kuchoma = 4

Mbao = 5

Tofali za saruji = 6

Mawe = 7

Aina nyingine za kuta = 8

11. Je ni kipi chanzo kikuu cha nishati unayotumia kupikia?

Jibu ##

Andika namba sahihi ndani ya kisanduku

Umeme = 1

Mafuta ya taa = 2

Mkaa = 3

Kuni, majani, kinyesi kikavu cha wanyama,
mabaki ya mazao (pumba) = 4

Vyanzo vingine vya kupikia = 5

12. Je, kipi ni chanzo kikuu cha mwangaza/mwanga?

Jibu ##

Andika namba sahihi ndani ya kisanduku

Umeme = 1

Mafuta ya nyonyo, taa ya kandili, chemni = 2

Mafuta ya nyonyo, Karabai = 3

Mafuta ya nyonyo, taa ya utambi = 4

Moto wa kuni = 5

Mishumaa = 6

Koroboi = 7

Vyanzo vingine vya mwanga = 8

13. Je, kuna ekari ngapi za ardhi kwa ajili ya kilimo?

Jibu ###

Andika namba sahihi ndani ya kisanduku

14. Je, kuna ekari ngapi za ardhi kwa ajili ya kulishia mifugo?

Jibu ##

Andika namba sahihi ndani ya kisanduku

**JAMHURI YA MUUNGANO WA TANZANIA
WIZARA YA AFYA NA USTAWI WA JAMII**



UTAFITI WA KWANZA WA KITAIFA WA KUTATHMINI KIWANGO CHA TB NCHINI TANZANIA

6: USAILI WA PILI

Ijazwe na mhojaji wa pili

Jina la cluster: _____ PIN:

Namba ya kitongoji ##	Namba ya kaya ###	Namba ya mshiriki ##
-----------------------------	-------------------------	----------------------------

Jina la mshiriki: _____

1. Hali ya Ndoa **Jibu** *Andika namba sahihi ndani ya kisansuku*
 Sijawahi /kuoa/kuolewa = 1 Nimeao/Olewa =2 Talaka / Tumetengana = 3
 Mjane/Mgane = 4 Wanaishi bila ndoa/kinyumba=5

2. Kiwango cha juu cha Elimu **Jibu** *Andika namba sahihi ndani ya kisansuku*
 Sijasoma = 1 Sijamaliza Elimu ya Msingi = 2 Nimemaliza Elimu ya Msingi = 3
 Sijamaliza Elimu ya Sekondari = 4 Nimemaliza Elimu ya Sekondari = 5 Elimu ya juu baada ya Sekondari = 6
 Kingine (taja)

3. Shughuli/kazi kuu za kuingiza kipato **Jibu** *Andika namba sahihi ndani ya kisansuku*
 Ukulima/ Ufugaji = 1 Uvuvi = 2
 Uchimbaji madini= 3 Utalii = 4
 Mwanafunzi = 9 Hajiwezi = 10
 Mwanafunzi = 9 Nyingine (taja) = 12
 Hajaajiriwa = 11

4. Je unavuta tumbaku kila siku, pungufu ya siku au huvuti kabisa? **Jibu** *Andika namba sahihi ndani ya kisansuku*
 Kila siku = 1 Pungufu ya Siku = 2 Sivuti kabisa= 3

5. Katika siku za nyuma, uliwahi kuvuta tumbaku kila siku, pungufu ya siku au huvuti kabisa? **Answer** **Kama amesema havuti, nenda swali la 9**
 Kila siku = 1 Pungufu ya Siku = 2 Sivuti kabisa= 3

6. Ni muda gani umepita tangu uache kuvuta sigara kila siku? Miaka Miezi

7. Je ulikuwa na umri gani ulipoanza kuvutatumbaku? Umri (miaka)

8. Je, kwa wastani, kwa sasa ni sigara ngapi huwa unavuta katika siku ambazo huwa unavuta? Kwa siku **(idadi ya sigara)**

9. Katika wiki iliyopita, kwa kukadiria, ni mara ngapi umekuwa katika mazingira ya nyumbani, kazini au kwenye mkusanyiko wa watu ambapo kuna watu walikuwa wanavuta tumbaku

Jibu

Andika namba sahihi ndani ya kisanduku

Sikujitokeza kabisa = 1
Mara nyingi kwa siku katika baadhi ya siku = 3
Mara nyingi kwa siku kwa takribani siku zote = 5

Nyakati chache kwa siku katika baadhi ya siku = 2
Nyakati chache kwa siku kwa takribani siku zote = 4

10. Katika mwaka uliopita, ni mara ngapi ulikunywa kinywaji chenye kilevi?

Jibu

Andika namba sahihi ndani ya kisanduku

Kila siku = 1
Mara 1 hadi 2 kwa wiki = 4
Mara 7 hadi 11 katika mwaka uliopita = 7
Mara 2 hadi 3 katika mwaka uliopita = 9
Sijawahi kunywa kinywaji chochote chenye kilevi katika mwaka uliopita = 11
Sijawahi kunywa katika maisha yangu = 12

Karibu kila siku = 2
Mara 2 hadi 3 kwa mwezi = 5
Mara 4 hadi 6 katika mwaka uliopita = 8
Mara 1 katika mwaka uliopita = 10
Sikumbuki = 13
Mara 3 hadi 4 kwa wiki = 3
Mara moja kwa mwezi = 6

11. Je, umewahi kugundulika kuwa na ugonjwa wa kisukari?

Jibu

Andika namba sahihi ndani ya kisanduku

Ndiyo = 1 Hapana = 2

12. Je, uko kwenye matibabu ya ugonjwa wa kisukari?

Jibu

Andika namba sahihi ndani ya kisanduku

Ndiyo = 1 Hapana = 2

13. Je, umewahi kugundulika kuwa na ugonjwa wa kifua kikuu huko nyuma?

Jibu

Andika namba sahihi ndani ya kisanduku

Ndiyo = 1 Hapana = 2

14. Nakiri vipimo hivi kutoka katika kadi ya mwaliko

Namba

Uzito (Kg)	
Urefu (sm)	

15. Je, zifuatazo ni dalili za kifua kikuu? MSOMEE

weka alama \checkmark ndani ya kisanduku sahihi

	Ndiyo	Hapana	Sijui
15a. Kukohoa			
15b. Homa			
15c. Maumivu ya tumbo			
15d. Kuhara			
15e. Maumivu ya kifua			
15f. Kupumua kwa taabu			
15g. Maumivu ya viungo			
15h. Kutokwa na jasho jingi wakati wa usiku			
15i. Kupungua uzito			
15j. Kukosa hamu ya kula			
15h. Kukohoa damu			

16. Je kifua kikuu kinaweza kuambukizwa kutoka mtu mmoja hadi mwingine?

weka alama \checkmark ndani ya kisanduku sahihi

	Ndiyo	Hapana	Sijui

17. **Kifua kikuu huambukizwa kutoka mtu mmoja hadi mwingine kupitia... MSOMEE**

weka alama ✓ ndani ya kisanduku sahihi

	Ndiyo	Hapana	Sijui
17a. coughing / sneezing			
17b. Spitting			
17c. Sharing cups / bowls			
17d. Shaking hands			
17e. Sexual intercourse			
17f. Mosquitos / flies			
17g. Mother to child in pregnancy			

18. **Je, kifua kikuu kinatibika kwa dawa?**

weka alama ✓ ndani ya kisanduku sahihi

	Ndiyo	Hapana	Sijui

19. **Je, matibabu ya kifua kikuu hutolewa bure kwenye vituo vya tiba vya serikali?**

weka alama ✓ ndani ya kisanduku sahihi

	Ndiyo	Hapana	Sijui

20. **Je, unamfahamu mtu yeyote anayeugua kifua kikuu?**

weka alama ✓ ndani ya kisanduku sahihi

	Ndiyo	Hapana	Sijui

21. **Je, umepatwa na yafuatayo:**

weka alama ✓ ndani ya kisanduku sahihi

	Ndiyo	Hapana
21a. Umekuwa unakohoa kwa wiki mbili au zaidi?		
21b. Umekuwa unakohoa makohozi yaliyochanganyika na damu?		
21c. Umekuwa na homa kwa wiki mbili au zaidi?		
21d. Kwa mwezi mmoja sasa umekuwa ukipungua uzito kwa wastani wa kilo 3 kwa mwezi?		
21e. Umekuwa unatokwa na jasho jingi wakati wa usiku kwa muda wa wiki mbili au zaidi?		

Ikiwa hakuna dalili miongoni mwa hizi ilitajwa nenda swali la 30

22. **Je ulitafuta matibabu kwa ajili ya dalili yoyote kati ya hizo hapo juu?**

	Ndiyo	Hapana

Ikiwa jibu ni Ndiyo, nenda swali la 25

23. **Je, ni sababu gani zilikufanya usitafute matibabu au ushauri?**

weka alama ✓ ndani ya kisanduku sahihi

	Ndiyo	Hapana
23a. Symptoms not serious enough		
23b. Lack of time		
23c. Lack of transport		
23d. Lack of finance		
23e. Health facility too far away		
23f. Service expected of poor quality		
23g. Afraid or worried for serious disease		
23h. No particular reason / other		

- 24. Je ni sababu gani kubwa ilikufanya usitafute matibabu au ushauri wa dalili ulizokuwa nazo?** **Jibu**
 Andika namba sahihi ndani ya kisanduku

Hali haikuwa mbaya sana = 1

Kukosa usafiri = 3

Kituo cha tiba kipo mbali = 5

Kuogopa au wasiwasi wa ugonjwa kuwa mkubwa = 7

Kukosa muda = 2

Kukosa fedha = 4

Huduma si nzuri = 6

Hakuna sababu maalum/nyingine = 8

- 25. Je, ni wiki ngapi tangu kuanza kwa dalili ulitafuta matibabu au ushauri kwa mara ya kwanza?** **Jibu**
 Andika namba sahihi ndani ya kisanduku

- 26. Ni wapi ulikwenda kwanza kwa ajili ya kutafuta matibabu au ushauri kutokana na dalili ulizokuwa nazo?** **Jibu**
 Andika namba sahihi ndani ya kisanduku

Hospitali ya Mkoa = 1

Kituo cha Afya = 4

Mganga wa jadi = 7

Hospitali ya Wilaya = 2

Zahanati = 5

Duka la dawa = 8

Hospitali ya Misheni = 3

Mhudumu wa afya binafsi = 6

Nyingine = 9

- 27. Je, kwenye kituo cha kwanza cha tiba ulichokwenda kwanza kwa ajili ya hali yako, je ulifanyiwa yafuatayo? MSOMEE** *weka alama ✓ ndani ya kisanduku sahihi*

	Ndiyo	Hapana
27a. Uchunguzi wa makohozi		
27b. Kupiga picha ya kifua		
27c. Kupewa rufaa kwenda katika kituo kingine kwa uchunguzi wa makohozi		
27d. Rufaa kwenda katika kituo kingine kwa kupiga picha ya kifua		

- 28. Je, kwa kawaida huwa unatumia usafiri gani kwenda kwenye hiki cha huduma?** **Jibu**
 Andika namba sahihi ndani ya kisanduku

Kwa kutembea = 1

Gari binafsi = 5

Baiskeli = 2

Kingine (taja)

Pikipiki = 3

Daladala / Basi = 4

- 29. Je, kwa kawaida inakuchukua muda gani kufika katika kituo hicho cha huduma?** **Jibu**
- | hours | minutes |
|-------|---------|
| | |

weka alama ✓ ndani ya kisanduku sahihi

- 30. Je, ulishawahi kugundulika kuwa una kifua kikuu?** **Ndiyo** **Hapana**
- | Ndiyo | Hapana |
|-------|--------|
| | |

weka alama ✓ ndani ya kisanduku sahihi

- 31. Je, ulishawahi kutumia dawa zozote kwa zaidi ya mwezi mmoja?** **Ndiyo** **Hapana**
- | Ndiyo | Hapana |
|-------|--------|
| | |

weka alama ✓ ndani ya kisanduku sahihi

- 32. Je, umeshawahi kuchomwa sindano kwa zaidi ya mwezi mmoja?** **Ndiyo** **Hapana**
- | Ndiyo | Hapana |
|-------|--------|
| | |

Mwisho wa Hojaji/Dodoso



Weka alama ✓ ndani ya kisanduku kilichoandikwa "SAWA" kwenye kadi ya mwaliko

THE UNITED REPUBLIC OF TANZANIA
MINISTRY OF HEALTH AND SOCIAL WELFARE



THE FIRST NATIONAL TB PREVALENCE SURVEY
11: CHEST X-RAY DIAGNOSIS

To be filled by Radiology Team

Cluster name: _____	PIN: _____	Cluster number ##	Household ID number ###	Subject's number ##
----------------------------	-------------------	----------------------	----------------------------	------------------------

Subject's name: _____

1) Quality of Chest X-ray image	Yes	No
i. Adequate		
ii. Not adequate but Interpretable		
iii. Not adequate and not interpretable		

if iii is YES then end questionnaire

2) General:	Yes	No
a. Radiograph completely normal		
b. Any abnormality consistent with TB		

if a is YES then end questionnaire

3) Parenchymal Abnormalities		
a. Primary	Yes	No
i. Infiltrates		
ii. Nodules		
iii. Lymph node		

b. Secondary	Yes	No
i. Cavities		
ii. Fibrosis		
iii. Infiltrates		
iv. Nodules		

c. Zones	Yes	No	R	L
i. Upper				
ii. Middle				
iii. Lower				

4) Nodular Abnormalities	Yes	No	R	L
a. Localised				
b. Diffuse				

PIN:		
Cluster number ##	Household ID number ###	Subject's number ##

5) Mycetoma	Yes	No	R	L

6) Granulomas Calcified	Yes	No

7) Lobar Volume loss/Collapse/Bronchiectasis	Yes	No	R	L
a. Upper lobe				
b. Middle lobe				
c. Lower lobe				

8) Pleural Abnormalities	Yes	No	R	L
a. Apical cap.				
b. Pleural thickening.				
c. Pleural Effusion				
d. CP Angle obliteration				

9) Central Structure Abnormalities	Yes	No
a. Tracheal Deviation		
b. Hilar Elevation		
c. Mediastinal shift		
d. Pericardial effusion		

e. Lymphadenopathy	Yes	No
i. Hilar		
ii. Mediastinal		
iii. Calcified		

10) Any other Abnormality consistent with Tuberculosis	Yes	No
Specify: _____		

11) Any other abnormality	Yes	No
Specify: _____		

THE UNITED REPUBLIC OF
TANZANIA



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22nd November 2006

Dr Saidi Egwaga
Ministry of Health and Social Welfare
P O Box 9083
DAR ES SAALAM

**CLEARANCE CERTIFICATE FOR CONDUCTING
MEDICAL RESEARCH IN TANZANIA**

This is to certify that the research entitled: First national tuberculosis prevalence study, (Egwaga *S et al*), whose Principal Investigator is Saidi Egwaga has been granted ethics clearance to be conducted in Tanzania.

The Principal Investigator of the study must ensure that the following conditions are fulfilled:

1. Progress report is made available to the Ministry of Health and the National Institute for Medical Research, Regional and District Medical Officers after every six months.
2. Permission to publish the results is obtained from National Institute for Medical Research.
3. Copies of final publications are made available to the Ministry of Health and the National Institute for Medical Research.
4. Any researcher, who contravenes or fails to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine.

Name: Dr Andrew Y Kitua

Name: Dr Z A Berege

Signature

CHAIRMAN
MEDICAL RESEARCH
COORDINATING COMMITTEE

Signature

AG CHIEF MEDICAL OFFICER
MINISTRY OF HEALTH, SOCIAL
WELFARE

CC: RMOs, DMOs



HAKAZA LA UFAJILI WAU
HAKA LA MATAJIRI WAU
HAKA LA MATAJIRI WAU



META KUSHEWAJAZI COUNCIL
META KUSHEWAJAZI COUNCIL
ZANZIBAR

ETHICAL CLEARANCE LETTER

PROTOCOL NUMBER: ZAMREC /0002/MARCH/012

DATE: 05 JULY, 2012.

Dr. Senkoro Egwaga NIMR
Principal Investigator

PROTOCOL TITLE: First National Tuberculosis Prevalence Study

RE: ETHICAL CLEARANCE FOR CONDUCTING MEDICAL RESEARCH IN ZANZIBAR.

This is to certify that the research protocol entitled “**First National Tuberculosis Prevalence Study**” was received and reviewed by the Zanzibar Medical Research and Ethics Committee on July, 2012.

We would like to inform you that the decision of the committee to this protocol was “**Approved**”.

The permission to undertake data collection is for one year beginning from the date of this letter.

The principal investigator must ensure that the progress report is made available to the Ministry of Health and the Zanzibar Medical Research and Ethics committee.

Any change made to the protocol need to be submitted to the committee for approval prior to its implementation

Thanks in advance,

DR. JAMALA A. TAIB
CHAIRPERSON
ZAMREC
ZANZIBAR.



DR. MSAFIRI MARIJANI
SECRETARY
ZAMREC
ZANZIBAR.



Ethics Advisory Group

3rd August, 2014

To **Mbazi Senkoro**

Title of research project:

Risk factors for Tuberculosis: results from a nationally representative case-control study in Tanzania

EAG number: 58/14

Investigators:

PI: Mbazi Senkoro, National Institute for Medical Research, Muhimbili Medical Research Center, Dar es Salaam, Tanzania

Co-investigators:

Ajay MV Kumar, The Union, South East Asia Office, New Delhi, India

Palanivel Chinnakali, Jawaharlal Institute of Postgraduate Medical Education & Research, India

Frank van Leth, Department of Global Health, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Sayoki G Mfinanga, National Institute for Medical Research, Muhimbili Medical Research Center, Dar es Salaam, Tanzania

Saidi Egwaga, National Tuberculosis and Leprosy Programme, Ministry of Health and Social Welfare, Dar es Salaam, Tanzania

Beatrice Mutayoba, National Tuberculosis and Leprosy Programme, Ministry of Health and Social Welfare, Dar es Salaam, Tanzania

Sven G Hinderaker, Centre for International Health, University of Bergen, Bergen, Norway

Thank you for your application to the Ethics Advisory Group of the Union.

Your study has our formal approval.

⑤ Any changes to the approved protocol need to be sent to the EAG, using the form for **extension/modification** of proposals (to be found on the Union website under EAG)

⑤ **Final report** : The EAG requires the executive summary or the abstract of all study reports or papers within 90 days of the completion of the study

We trust that your study proceeds well and that it will be productive.

With best wishes,

Prof. Mary Edginton
Chairperson