MANTOUX SKIN TEST REACTIVITY AMONG HOUSEHOLD CONTACTS OF HIV POSITIVE AND HIV NEGATIVE PATIENTS WITH SPUTUM SMEAR POSITIVE TUBERCULOSIS

By

DR. ENGERASIYA JULIUS KIFAI, MD (DAR)

A Dissertation Submitted in Partial Fulfillment of the Requirements for Degree of Master of Medicine (Internal Medicine) of the Muhimbili University of Health and Allied Sciences

Muhimbili University of Health and Allied Sciences

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for submission a dissertation entitled: "Mantoux skin test reactivity among household contacts of HIV positive and HIV negative patients with sputum smear positive tuberculosis", in partial fulfillment of the requirements for the degree of Master of Medicine (Internal Medicine) of the Muhimbili University of Health and Allied Sciences.



.....

Dr. Muhammad Bakari

(Supervisor)

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I, Engerasiya Julius Kifai, declare that this is my original work and that it has not been presented nor will it be presented to any other University for a similar or any other degree award.

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DEDICATION

To Erica, our daughter

To Riemann Ray Dr, my husband

ABSTRACT

Background: Tuberculosis has been increasing in many parts of the world since the late 1980s. In Africa much of this increase has been attributed to the HIV epidemic. The increased risk of tuberculosis in those infected by HIV is well known. It is likely that this increase will be accompanied by the onward transmission of Mycobacterium tuberculosis. The increased potential for HIV-associated TB cases to transmit *M. tuberculosis* and to produce a secondary increase in TB morbidity is controversial.

Objectives: To compare the prevalence of Tuberculosis infection as demonstrated by a positive Mantoux skin test (MST) reactivity among household contacts of sputum smear positive HIV positive and HIV negative Tuberculosis patients.

Methodology: The study took place at the Muhimbili National Hospital, outpatient Tuberculosis clinics of Infectious Disease Control Centre (IDC), and the three Municipal hospitals in Dar es Salaam. Consenting male and female Index cases (both HIV positive and HIV negative) aged 18 and above with sputum smear positive tuberculosis were enrolled so as to obtain their respective household contacts aged 1 year and above. The contacts were injected intradermally with protein purified derivative (Mantoux test) and the results were read after 72 hours. Contacts found to be infected (mantoux skin test positive) were counseled for medical examination to exclude Tb disease.

Results: The prevalence of Tb infection among household contacts of HIV positive and HIV negative index cases were 61.6% and 62.5% respectively, (OR 1.04 [95% CI 0.61 – 1.76], p=0.887). In order to minimize the effect of environmental Mycobacteria on the MST response, the analysis was restricted to household contacts aged 1 -14 years of the HIV positive and HIV negative index cases, again in this analysis the prevalence of Tb infection in this group did not differ, (OR 1.39 [95% CI 0.63 – 3.07], p=0.419). Factors associated with an increased risk of Tb infection in household contacts of both HIV positive and HIV negative index cases were older age of the contacts (25 years and more), long duration of living with the index case prior to Tb diagnosis (one year and more), and

sharing a room with the index case. Among index cases, female gender was associated with a higher infectiousness to their contacts.

Conclusion and Recommendation: The patients with Pulmonary Tuberculosis and HIV co-infection have the same likelihood of infectiousness to their contacts as those who are not HIV infected.

Efforts towards contact tracing and screening for TB among close contacts of smear-positive pulmonary TB patients should be enhanced as this could have a positive impact on TB prevention and control.

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ABBREVIATIONS/ACRONYMS

AFB = Acid Fast Bacilli

AIDS = Acquired Immunodeficiency syndrome

AMMP = Adult Morbidity and Mortality Project

ANOVA = Analysis of Variance

CI = Confidence Interval

CTC = Care and Treatment Clinic

Dx = Diagnosis

ELISA = Enzyme linked Immunosorbent assay

HAART = Highly Active Anti Retroviral Therapy

HIV = Human Immunodeficiency Virus

HIV +ve = HIV seropositive

HIV –ve = HIV seronegative

IDC = Infectious Disease control Center

MNH = Muhimbili National Hospital

MOH & SW = Ministry of Health and Social Welfare

MST = Mantoux Skin test

MUHAS = Muhimbili University of Health and Allied Sciences

NIMR = National Institute for Medical Research

NTLP = National Tuberculosis and Leprosy Control Programme

OR = Odds Ratio

PPD = Purified Protein Derivative

Research team = Included study investigator and two research assistants

Sx = Symptoms

Tb = Tuberculosis

TU = Tuberculin Unit

TST = Tuberculin Skin Test

WHO = World Health Organization

<: less than

≤: less than or equal to

≥: greater than or equal to

CHAPTER ONE

1.0 INTRODUCTION

Tuberculosis (TB) is a major cause of illness and death worldwide, especially in Asia and Africa where the incidence of Tb is increasing in HIV infected patient and Tb endemic is high reflecting the susceptibility of this group of patient to Tb[1]. It is likely that this increase will be accompanied by the onward transmission of Mycobacterium tuberculosis as there is direct increase in those who are HIV infected, but also a doubling in tuberculosis incidence in those remaining HIV negative [2]. The potential for HIV-associated TB cases to transmit Mycobacteria tuberculosis and to produce a secondary increase in TB morbidity is unknown [3].

1.1. BURDEN OF TUBERCULOSIS

1.1.1 Global burden of tuberculosis

According to WHO 2008 Global report, the prevalence of Tb cases by the year 2006 was estimated 14.4 million cases, and the new Tb case was estimated 9.2 million (139 per 100,000 population), including 4.1 million new smear-positive cases (44% of the total) and 0.7 million HIV-positive cases (8% of the total). This is an increase from 9.1 million cases in 2005, due to population growth. In 2006, the multi-drug resistant TB (MDR-TB) was estimated 0.5 million cases and there were an estimated 1.5 million deaths from TB in HIV-negative people and 0.2 million among people infected with HIV [4].

In 2007, a total of 202 (out of 212) countries and territories reported TB notification data for 2006 to WHO. A total of 5.1 million new cases (out of the estimated 9.2 million new cases) were notified for 2006 among these 202 countries and territories, of which 2.5 million (50%) were new smear-positive cases. The African, South-East Asia and Western Pacific regions accounted for 83% of total case notifications [4].

The global burden of tuberculosis remains enormous mainly because of poor TB control in South East Asia, Sub-Saharan Africa and Eastern Europe and also because of high rates of Mycobacteria and HIV co–infections in some African countries [5].

1.1.2 Tanzania burden of tuberculosis

In 2004, in Tanzania 65,665 cases of tuberculosis were notified, in which 25,823 (39.3%) were new sputum smear positive, 1,778 (2.7%) were relapses, while the remaining 38,064 (58%) were smear negative and extra-pulmonary tuberculosis combined. As seen in all other high HIV prevalence areas, the smear positive rates among TB patients have declined compared to 1984 (pre HIV era). In 1984 more than 62% of the newly diagnosed TB patients were sputum smear positive against 46% in 1999. In contrast, the proportion of smear negative and extra-pulmonary TB cases has increased nearly one and half fold from 35.5% to 50.7% [6].

The age-sex distribution of the new smear positive cases notified in 2004 shows that the most affected age group is 25-34 years age group among both males and females, with prevalence of 32.2% and 36.6% respectively, and the least affected age group was 0-14 years, whose prevalence among males and females were 1.29% and 2.90% respectively [6].

1.2 BURDEN OF HIV

1.2.1 Global burden of HIV

The AIDS epidemic update of December 2007 showed the estimated number of persons living with HIV worldwide in 2007 was 33.2 million [30.6–36.1 million], a reduction of 16% [7] compared with the estimate published in 2006 (39.5 million [34.7–47.1 million]) [8]. By the year 2007, adults living with HIV were 33.2million, women 15.4million, and children less than 15 years old were 2.5million. People newly infected with HIV in 2007 totaled 2.5million, of which adults were 2.1million and children < 15 years were 420,000.

1.2.2 Burden of HIV in Sub-Saharan Africa

Sub-Saharan Africa remains the most affected region in the global AIDS epidemic. In 2007, there was an estimate of 22.5 million [20.9 million–24.3 million] people living with HIV in the region [7] compared with 20.9 million [19.7 million–23.6 million] in 2001. In sub-Saharan Africa, adult (15–49 years) HIV prevalence declined from 5.8% [5.5%–6.6%] in 2001 to 5.0% [4.6%–5.5%] in 2007. AIDS continues to be the single largest cause of mortality in sub-Saharan Africa [9]; of the global total of 2.1 million [1.9 million–2.4 million] adult and child deaths due to AIDS in 2007, 1.6 million [1.5 million–2.0 million] occurred in sub-Saharan Africa and orphans living in this region due to AIDS are estimated to be 11.4 million [10.5 million–14.6 million].

Gender and HIV infection in Sub-Saharan Africa: Unlike other regions, the majority of people living with HIV in sub-Saharan Africa (61%) are women [7], while in the Caribbean that percentage was 43% (compared with 37% in 2001). The proportions of women living with HIV in Latin America, Asia and Eastern Europe are slowly growing, as HIV is transmitted to the female partners of men who are likely to have been infected through injecting drug use or during unprotected paid sex or sex with other men. In Eastern Europe and Central Asia, it is estimated that women accounted for 26% of adults with HIV in 2007 (compared with 23% in 2001), while in Asia that proportion reached 29% in 2007 (compared with 26% in 2001).

1.2.3 Burden of HIV in Tanzania

HIV infection in Tanzania was first reported in 1983 in the northwestern region bordering Uganda. Since then the infection has spread to affect all regions of Tanzania. In 2003 over 1.8 million persons were estimated to be living with HIV and AIDS. The overall prevalence of HIV infection among blood donors during 2003 was 8.8%. In the WHO global AIDS epidemic report of 2004 the HIV prevalence among Tanzanian adults aged

15- 49 yrs was 9.0% according to the population based survey of 2003. On the mainland, a national population-based HIV survey in 2003–2004 found adult HIV prevalence of 7% [10].

1.3 HIV INFECTION AND TUBERCULOSIS

Co-infection with HIV-TB presents serious medical and scientific challenges; among them are difficulties in diagnosis, infection control, and managing co-toxicities between drugs previously used independently to treat the two diseases.

Approximately one-third of the world's 40 million people with HIV/AIDS are co-infected with TB. The association between tuberculosis and HIV infection is supported by other epidemiologic observations. First, the rate of HIV seropositive patients with tuberculosis is several times higher than that among the general population: in African countries it reaches 60 to 70%. Second, marked increases in numbers of tuberculosis cases have been reported at locations hard hit by the HIV epidemic, such as large parts of Africa (including Kenya, Tanzania, and Malawi), northern Thailand and New York City [11].

The mortality rate for HIV-TB co-infection is five-fold higher than that for tuberculosis alone. This situation is made yet more urgent by the surging rates of multi-drug resistant TB in some areas with high HIV prevalence, according to the report. [12]

The challenges of HIV and Tb co-infection is on diagnosis, the response of HIV-infected TB patients to TB treatment, the benefits of antiretroviral therapy (ART), and the quality and continuity of care for TB patients [12, 13], this is because the HIV directly attacks the critical immune mechanisms involved in protection against tuberculosis. Tuberculosis can appear at any stage of HIV infection, but its presentation varies with the stage. When cell-mediated immunity is only partially compromised, pulmonary tuberculosis presents as a typical pattern of upper lobe infiltrates and cavitation, without significant lymphadenopathy or pleural effusion. In late stages of HIV infection, a primary tuberculosis-like pattern, with diffuse interstitial or miliary infiltrates, little or no cavitation, and intrathoracic lymphadenopathy, is more common. Overall, sputum smears may be positive less frequently among tuberculosis patients with HIV infection than among those without; thus the diagnosis of tuberculosis may be unusually difficult, especially in view of the variety of HIV-related pulmonary conditions mimicking tuberculosis.

The diagnosis of tuberculosis in HIV-infected patients may be difficult not only because of the increased frequency of sputum-smear negativity (up to 40% in culture-proven pulmonary cases) but also because of atypical radiographic findings, a lack of classic granuloma formation in the late stages, and negative results in PPD skin tests. Delays in treatment may prove fatal. The response to short-course chemotherapy is similar to that in HIV-seronegative patients whereas a person with skin test-documented M. tuberculosis infection HIV infected has a 3 to 15% annual risk of developing active tuberculosis [(11)].

In Africa, Nine percent (7% - 12%) of all new TB cases in adults (aged 15-49 years) were attributable to HIV infection, but the proportion was much greater in the WHO African Region (31%) and some industrialized countries, notably the United States (26%) [(14)].

The prevalence of HIV among smear positive TB in Mainland Tanzania varies from 24.3% to 75%, with an average of 40%. The prevalence of over 80% and 75% was recorded in smear negative PTB and extra pulmonary PTB in Rukwa region [(15)], data from the Adult Morbidity and Mortality Project (AMMP) in 2002 showed that HIV/AIDS and TB were the leading causes of mortality in Hai (Kilimanjaro), Temeke and Morogoro Rural districts [(16)], whereas in Kenya, 30% of newly diagnosed TB patients were reported to be HIV seropositive [(17)]. Hence Tuberculosis is an extremely important complication of HIV infection in Sub-Saharan Africa.

In many parts of Tanzania, the increase in HIV prevalence (2002 estimate 8.8% among adults) and tuberculosis notification started only in the early 1990s [(18)] and the notification rate of tuberculosis in mainland Tanzania has increased threefold, and that of new sputum smear-positive tuberculosis twofold compared to that of early 1980s. Therefore, the increase in notification of smear-positive tuberculosis has been mainly attributable to an increase in notification of HIV-co infected patients [(19)] as the periods between 1991–1993 and 1994–1998, the prevalence of HIV infection among smear-positive tuberculosis cases increased from 28 to 40% [(20)].

1.4 LITERATURE REVIEW

Tuberculosis is caused by a bacterium called Mycobacterium tuberculosis (MTB). The disease usually affects the lungs, although in up to one-third of cases other organs are involved. Transmission usually takes place through the airborne spread of droplets nuclei produced by patients with infectious pulmonary tuberculosis [21].

The degree of infectiousness of an HIV patient with tuberculosis remains unknown. Whether the risk of infection of tuberculosis among household contacts is similar regardless of whether the TB source case is infected with HIV or not remains conflicting based on data gathered from cross-sectional and cohort studies.

An earlier cross-sectional study done in Philippines to determine the prevalence of tuberculosis infection among household contacts of TB patients with HIV as compared to a similar population of household contacts of TB patients without HIV using PPD skin testing as a diagnostic parameter for TB infection. The study was conducted for a period of 6 months from May to October 1994. There were 11 HIV seropositive index cases with pulmonary tuberculosis that were entered in the study. A total of 25 household contacts for the HIV seropositive index cases were entered in the study while a total of 90 household contacts of the index cases with PTB without HIV were enrolled in the study. This study demonstrated a higher percentage of skin test reactivity among those who were exposed to an HIV seropositive case compared to the HIV seronegative case (50% vs. 37%) [22].

On the other hand, reports from Kenya and Zaire showed that household contacts of HIV seropositive index cases had a risk similar to that of household contacts of HIV seronegative index cases. In a study done in Kenya to compare the prevalence of TST positivity among household contacts of HIV-1 positive and HIV negative cases with PTB, the TST rates were the same among HIV-1 negative contacts of HIV-1 positive and HIV

negative cases (OR = 1.1 [95% CI 0.7 – 1.6]) [23] and in the study done in Zaire, rates of infection with Mycobacterium tuberculosis were compared among 521 household contacts of 74 HIV-1 positive index patients and in 692 household contacts of 95 HIV-1 negative index patients with sputum smear-positive pulmonary tuberculosis: No difference was noted between contacts of HIV-1-seropositive and -seronegative patients [24].

In cohort studies, from Zambia, Brazil and Dominican Republic pulmonary tuberculosis was found to be less infectious in HIV patients based on the demonstration of a higher frequency of tuberculin positivity among contacts of HIV negative patients 71%, 26% and 76% resp than in contacts of HIV seropositive cases 52%, 8% and 61% resp (52% and 54% resp.) [25, 26, 27].

However, data from low tuberculosis prevalence countries such as the United States show that patients with HIV and smear positive tuberculosis maybe as infectious as any patient with a positive sputum AFB smear or cavitations [28].

1.4.1 Tuberculosis development

Development of tuberculosis is a two-stage process in which a susceptible person exposed to an infectious tuberculosis case first becomes infected and may later develop the disease, depending on various factors:

1) The risk of exposure (exposure to *Mycobacterium tuberculosis*)

2) The risk of infection (indicated by a positive Mantoux skin test)

3) The risk of developing disease

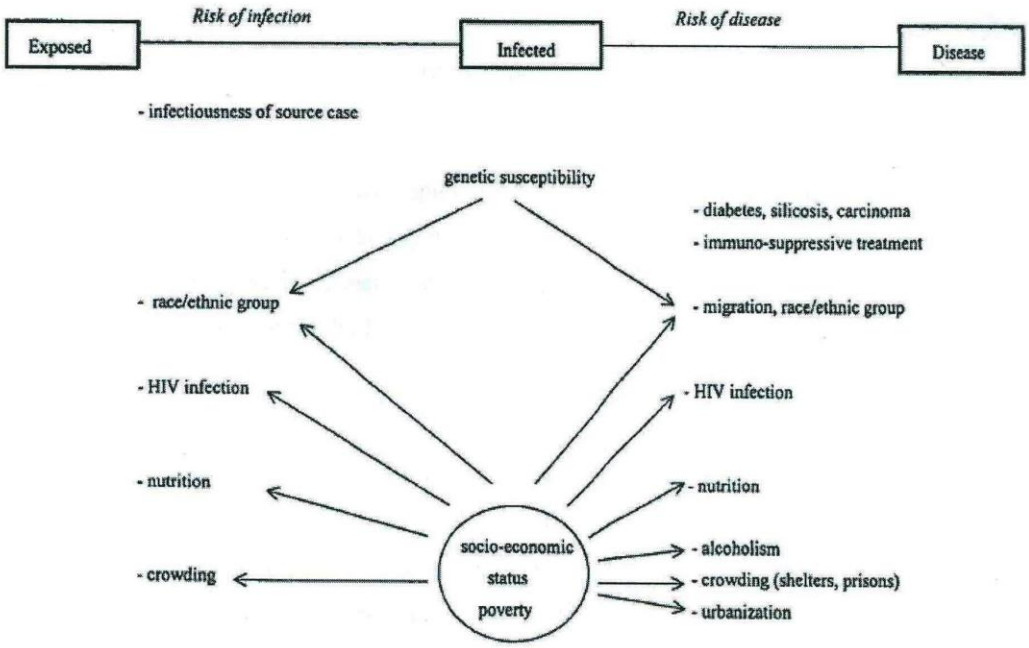


FIGURE 1: Impact of environmental factors on the risk of infection and development of disease after infection and their link with host-related factors [29].

Risk of exposure

The first step is to come in contact with an infectious tuberculosis case who expectorates bacilli in the surrounding airspace. The likelihood of contact between a susceptible person and an infectious tuberculosis case depends on the prevalence of active pulmonary tuberculosis in a given population and is influenced by several factors, the most important being crowding [30].

Risk of infection

The risk of becoming infected is determined primarily by the combined action of three factors:

1). The infectivity of the source case: sputum-smear-positive pulmonary tuberculosis cases are more likely than sputum smear-negative tuberculosis cases to infect their contacts and the infectivity of the case is a function of the frequency of coughing, the density of bacilli in the sputum [31] and the microbial "virulence" [32].

2). The degree of exposure of the susceptible person to the case. Factors that have been shown to influence this balance include HIV infection, immunosuppressive treatment, diabetes, malnutrition, and alcoholism, and all are considered *intrinsic* to the susceptible host [33] and factors that affects the risk of infection are closeness of the exposure to the case [31], crowding (average number of persons per house) and was highly correlated with overcrowding (defined as the proportion of houses with more than two persons per room), urban residence and low socioeconomic status (SES).

3). The degree of susceptibility of that person to infection depends on the health status of the person [34, 35] and genetic susceptibility which has been recognized in certain populations; this extreme genetic susceptibility to the disease has been observed in Eskimo populations in North America, in Yanomami Indians in the Brazilian Amazon, and in black populations in the United States [36]. There are several polymorphisms in the human *NRAMP1* gene that have been identified to increased relative risk of a susceptible individual to move from latent Tb infection to active disease [37], other genes, including those for vitamin D receptors and the components of IFN- signaling pathways [38].

Risk of development of disease

In patients infected with *Mycobacterium tuberculosis,* tuberculosis can develop at a variable time through reactivation of a previously acquired (latent) infection or exogenous re-infection [39]. The relative contribution of reactivation and re-infection is likely to depend on the epidemiologic context [40]. It is generally accepted that in populations at high risk of infection, re-infection might be a major contributor to the overall rate of tuberculosis in adults, whereas, in populations that have a low risk of infection, most cases of post-primary disease in adults probably result from reactivation [39, 41]. The time from infection to disease ranges from a few weeks to a lifetime. The cumulative lifetime risk of developing disease classically has been estimated to be approximately 10 percent [29], but data from England and Wales showed that the lifetime risk of developing tuberculosis is strongly depending on time and the contact's age for the disease to occur [42].

1.4.2 Tuberculosis clinical presentation

The clinical manifestations of tuberculosis represent a complex interaction between the causative organism, *Mycobacterium tuberculosis*, and the human host immune response [43].

The symptoms of the disease depend on where in the body the bacteria are multiplying. For TB disease of the lungs, the symptoms include: Coughing that lasts more than 2 weeks (sometimes bringing up blood or bloody mucus), Difficulty breathing, Chest pain and the overall symptoms of TB disease include: Unexplained weight loss, Feelings of being run down and easily fatigued, fever and sweating (in some cases, especially at night) and Loss of appetite [44].

In a study conducted in Dar es Salaam, it has been shown that coexisting HIV and Tb infections affect the clinical and laboratory features found among such patients, where by dyspnea, fever, night sweat, fatigue, and diarrhea, severe tachypnea, hepatomegally, splenomegaly, and lymphadenopathy were significantly more common in HIV-infected than in HIV-negative patients with TB [45].

1.4.3 Tuberculosis diagnosis

Microscopic smears

Examination of microscopic smears for Acid Fast Bacilli (AFB) remains an important tool for TB diagnosis, and of late more rapid molecular techniques for TB diagnosis have been developed whereby the results are usually available within one working day [46].

Cultures

This is the gold standard for Tb diagnosis, although the organism can take 6 weeks or longer to grow on solid culture media (egg-based Lowenstein-Jensen medium or the agar-based Middlebrook 7H10 or 7H11). More rapid results are obtained from liquid media, which usually grows M tuberculosis in 7 to 28 days [46]. These are also good in the identification of Mycobacterium based on morphology, growth and biochemical characteristics.

Other techniques

Rapid gene probes are less sensitive than cultures and are used mainly on respiratory specimens. These are often requested when it is important to differentiate the diagnosis of MTB from other Mycobacteria for which treatment may be different, and where there are no infection control concerns.

Polymerase Chain Reaction (PCR) still requires culture and it is known that a negative PCR does not exclude TB. The other weakness of PCR is that a positive PCR does not indicate the drug susceptibility profile [47].

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Chest radiography:

Radiographic findings suggesting tuberculosis include upper-lobe infiltrates, cavitary infiltrates, and hilar or paratracheal adenopathy. In many patients with primary progressive disease and those with HIV infection, radiographic findings are more subtle and can include lower-lobe infiltrates or a miliary pattern [46, 47].

Drug susceptibility tests

These are usually available within 10-21 days of the laboratory receipt of the isolates and are performed by standard assays. Molecular detection of rifampicin resistance (and pyrazinamide) is available although it is not 100 percent sensitive. These molecular tests are useful when drug resistance is suspected, as about 95% of patients who are rifampicin resistant will also be isoniazid resistant. Patients with gene probe positive rifampicin resistance should be treated as MDR-TB, until the full resistance profile from cultures are available [48].

Rapid detection of active and latent tuberculosis infection in HIV positive Individuals

The lack of sensitivity of the tuberculin test and the poor specificity because of antigenic cross-reactivity with BCG vaccination means that an accurate test for active or latent TB in HIV individuals is needed. Tests using either whole blood or blood mononuclear cells have been developed which measure interferon gamma production from TB-specific T cells responding to *M. tuberculosis* antigens ESAT-6 or CFP-10.

In a study done in Zambia basing on detectable ESAT-6- or CFP-10-specific T cells on enzyme linked immunospot [ELISPOT] assay, 90% of 39 HIV positive Tb patients and 100% in 11 HIV negative Tb patients were diagnosed to have active Tb, and 37 out of 54 HIV negative health Zambian were positive for ESAT-6/CFP-10-based ELISPOT assay suggesting 69% prevalence of latent M. tuberculosis infection. Therefore, ELISPOT assay detects active tuberculosis in HIV-positive individuals with high sensitivity. Also, it is

more specific, and more sensitive, than MST-based methods in detecting latent M. tuberculosis infection in HIV positive persons but it was not sensitive when compared to HIV negative patients [49].

In prospective blinded study of 293 African children with suspected tuberculosis in kwaZulu-Natal, a region with high HIV prevalence [50], sensitivity of MST was reported to be reduced significantly in children younger than three years, those with HIV co-infection, or with malnutrition while the sensitivity of ELISPOT was not significantly adversely affected by these factors. Thus, IFN-g assays seem to have a higher specificity and less cross-reactivity due to BCG vaccination; HIV infection does not seem to interfere with the test result; and IFN-g assays seem to be potentially useful in children. Since the antigens ESAT-6, CFP-10 are more specific to *M. tuberculosis* than MST, and are not shared with BCG substrains or most of the Non-Tuberculous Mycobacteria, these factors do not seem to adversely affect the performance of IFN-g assays. As these tests do not involve measurements such as skin in-duration, the results are less subjective, and a single visit by the patient would seem adequate.

In view of all benefit of IFN-g assays, these assays are expensive tests and their higher cost appears to limit their wider applicability, especially in resource limited settings and developing countries where TB is highly rampant. Given the cost constraints, researchers should continue to focus on the development of cost-effective tests so that they are more widely applicable in resource limited settings from a public health point of view [51].

Mantoux skin testing

Testing for tuberculosis infection using Mantoux skin test (MST) should be performed only in persons who are at high risk for infection because it can't distinguishing active and latent Tb infection and has antigenic cross-reactivity with BCG vaccination [49]. The sensitivity and specificity of MST varies depending on the prevalence of infection in the tested population, in population with Tb prevalence >10%, the recommended cut-off value for MST is ≥10mm, this has sensitivity of 95.4% and specificity of 98.8% with Positive

Predictive Value (PPV) >75%. For the population with low Tb prevalence, the MST cut-off value of ≥15mm is proposed which has sensitivity of 79.8% and specificity of 99.6% [52]. In HIV-infected patients, the cut-off value for MST is reduced from ≥10mm induration (sensitivity 67.6%) to ≥ 5mm induration (sensitivity 74.5%) in order to compensate for loss of sensitivity, which is explained by a gradual decrease in skin test responsiveness with decreasing immunocompetence (an all-or-nothing switch to complete anergy) [53].

Groups that are at high risk for tuberculosis infection and should be targeted for mantoux testing include contacts of sputum smear positive Tb patients, HIV-infected persons, immigrants from countries with high rates of tuberculosis, health care professionals, and persons living or working in long-term care facilities [31].

BCG vaccination had minimal effect on mantoux reaction sizes that are most relevant for determining the prevalence of tuberculosis infection. This is consistent with the observation from several studies that BCG vaccination given at birth, as happens in Tanzania, does not affect the proportion of tuberculin reactions ≥ 10 mm after the first year of life, and that these reactions may even be 0 mm [54].

An alternative to Mantoux skin test in resource-limited settings where Bacille Calmette-Guérin (BCG) vaccination is commonly used, interferon-γ response to non-specific mycobacterial antigens may be used to diagnose an early tuberculosis infection in household contacts of tuberculosis patients [55].

In HIV and TB co-infection there is a reduction in the proportion of those reacting to Mantoux/PPD as the CD4 count falls, from 50%-90% in those who have a CD4 count of ≥500 cells/ul and down to 0% - 20% in those patients who have AIDS or advanced HIV infection with CD4 count of ≤200cells/ul. This limits the usefulness of the tuberculin test as a diagnostic tool in this group [56].

1.4.4 Tuberculosis treatment

Treatment with several drugs for 6 months or more can cure more than 95% of patients. Direct observation of treatment (DOT), a component of the recommended five-element DOTS strategy, is judged to be the standard of care by most authorities, but currently only a third of cases worldwide are treated under this approach [46].

The resistance to anti-tuberculosis drugs is an emerging challenge according to the information collected between 2002 and 2006 in more than 91,000 patients with tuberculosis in 81 countries, documenting MDR tuberculosis at its highest rates, 5.3% of all cases [57]. This is because in many nations, fewer than half of patients with active Tb disease receive a diagnosis, and fewer than half of those begin treatment and complete it [58]. Apart from that, World Health Organization (WHO) also reported the existence of extensively drug-resistant (XDR) tuberculosis in no fewer than 45 countries; although this is certainly an underestimate because few countries have the necessary well-equipped laboratory [59].

Drug/drug interactions

The treatment of TB is difficult to manage in HIV-infected patients as a result of drug interactions between HIV and TB therapies [56]. These are particularly pharmacological interactions secondary to inhibition or induction of hepatic cytochrome P450 enzymes (isoform CYP3A4) by protease inhibitors with rifampicin or rifabutin, respectively [1]. These potential drug interactions may results in ineffectiveness of antiretroviral drugs, ineffective treatment of Tb and an increased risk of drug toxicities.

Also the immune restoration induced by highly active anti-retroviral therapy (HAART) may be responsible for a paradoxical worsening of TB manifestations [1, 60]. Furthermore, it is known that the inducing effect of rifampicin not only takes at least 2 weeks to become maximal but will also persist for at least 2 weeks after the rifampicin has been stopped [61].

1.4.5 Control and Prevention of tuberculosis transmission

It is reported that early case identification and adherence to treatment regimens are the main barriers to successful control of tuberculosis [58]. In order to have good control of tuberculosis there should be: a recognition that tuberculosis is a potential diagnosis; that the diagnosis should be confirmed as soon as possible; that drug resistance should be considered early in non-responding patients or when patients have a history compatible with drug resistance; that there should be no delay in starting treatment, that treatment should be started with appropriate drugs, and that patients should have supervised therapy [48].

For the prevention of tuberculosis (TB) disease among patients who are infected with the human immunodeficiency virus (HIV), administration of isoniazid (INH) has been proposed, evaluated and implemented in communities where TB is highly endemic and at a time when antiretroviral (ARV) treatment was not, or was rarely available [62].

1.5 PROBLEM STATEMENT

The prevalence of Tuberculosis disease is increasing at an alarming rate and this has largely been contributed to by the increase in HIV disease especially in the developing world.

From the literature cited above, it is not clear if there are similarities or differences in infectiousness and transmission of tuberculosis to their household contacts between HIV positive patients with positive sputum smears for AFB and those who are sputum smear positive but who are HIV negative.

1.6 STUDY RATIONALE

There is contradicting information from several studies on the likelihood of transmitting Tb infection among contacts of smear positive index cases on the basis of HIV serostatus of the index case.

The study done in Philippines demonstrated a higher percentage of skin test reactivity among those who were exposed to an HIV seropositive case compare to the HIV seronegative case (50% and 37% resp.) [22].

The quoted studies done in Kenya and Zaire showed that household contacts of HIV seropositive index cases had a risk similar to those of household contacts of HIV seronegative index cases [23, 24].

In other studies, from Zambia, Brazil and Dominican Republic, pulmonary tuberculosis was found to be less infectious in HIV patients based on the demonstration of a higher frequency of tuberculin positivity among contacts of HIV negative patients 71%, 26% and 76% resp. than in contacts of HIV seropositive cases 52%, 8% and 61% resp. [25, 26, and 27]. Data from low tuberculosis prevalence countries such as the United States show that patients with HIV and smear positive tuberculosis maybe as infectious as any patient with a positive sputum AFB smear or cavitations [28].

From the literature, it is known that the following factors could bias the results for Mantoux skin test response and could indicate a response of the immune system, these are: the previous history of BCG vaccination [63] especially those BCG vaccinated persons 4-8 weeks prior to Mantoux/ Tuberculin testing [64], household contacts having Tb exposure other than from Index case, history of prior Tuberculin skin test [63], and contact exposed to environmental Mycobacterium (*non Mycobacterium tuberculosis*) [65].

There is no data in Tanzania on the prevalence of Mantoux skin test reactivity among household contacts of HIV positive and HIV negative patients with AFB sputum smear positive Tuberculosis, while such an information is of relevance in TB control.

1.7 STUDY AIM

To find out, if the HIV positive sputum smear positive Tb patients are as infectious or more infectious than HIV negative Tb patients to their respective household contacts.

CHAPTER TWO

2.0 STUDY OBJECTIVE

2.1 BROAD OBJECTIVE

To compare the prevalence of Tuberculosis infection as demonstrated by a positive Mantoux skin test reactivity among household contacts of sputum smear positive Tb patients who are HIV positive and those who are HIV negative.

2.2 SPECIFIC OBJECTIVES

1. To compare the baseline Socio-demographic, behavioral and clinical characteristics between HIV positive and HIV negative sputum smear positive Index cases.

2. To compare the baseline socio-demographic, behavioral and clinical characteristics between household contacts of HIV positive and HIV negative sputum smear positive Index cases.

3. To compare the Mantoux skin test reactivity (induration size) among the household contacts of HIV positive and HIV negative sputum smear positive Index cases.

4. To compare the characteristics of household contacts of HIV positive and HIV negative index cases that may be associated with acquiring Tb infection from their respective Index cases.

5. To determine characteristics of HIV positive and HIV negative sputum smear positive Index cases that are associated with transmission of Tb infection to their respective household contacts.

CHAPTER 3

3. METHODOLOGY

3.1 Study design

This was a Cross-sectional descriptive study.

3.2 Study Site

The study took place in Dar es Salaam, in out-patient Tb clinics attendees of the three Municipal hospitals (Temeke, Amana, Mwananyamala) and the IDC; as well as among in-patients from the MNH medical wards and the respective household contacts who were seen at their residential premises.

Dar es Salaam is located at 6°48' south, 39°17' east and is an administrative province within Tanzania; has three local government areas or administrative districts: Kinondoni to the north, Ilala in the center of the region, and Temeke to the south, this region had a population of 2,497,940 as of the official 2002 census [66].

3.3 Study Population

Index cases were defined as patients with active pulmonary tuberculosis with sputum smear positive for AFB, either HIV positive or negative. These were newly diagnosed sputum smear positive Tb patients, aged 18 year or above. Index cases living alone were excluded.

Household was defined as a person or a group of persons, related or unrelated, who live together and share a common source of food [67]; and household contact of the Index case was defined as someone who has lived with the index patient for at least four previous weeks.

The included household contacts were those aged 1 year or above, and had stayed with the Index case for at least four previous weeks [Mean duration sufficing an exposed individual to acquire Tb infection from the source is 28 days (range 13-43 days)] [68]. Household

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contacts who gave history of ever suffered from Tb or were on immunosuppressive drugs/ steroids, or pregnant were excluded.

3.4 Sample size calculation

3.4.1 Two Proportion Calculations for household contacts

$$N= \frac{\{Z_1\sqrt{2P`(1-P`)} + Z_2\sqrt{P_1(1-P_1) + P_2(1-P_2)}\}^2}{(P_1-P_2)^2}$$

N= sample size

P_1 - Prevalence of Mantoux skin test reactivity among household contacts of sputum smear positive HIV negative patients in Zambia (0.71)

P_2 - Prevalence of Mantoux skin test reactivity among household contacts of sputum smear positive HIV positive patients in Zambia (0.52)

P`- average of P_1 and P_2 (0.615)

Z_1 - 1.96 (95% confidence interval)

Z_2 - 0.84 (80% power of the study)

N = 111.54 for each group ~ 112 and for two groups = 224.

The minimum total household contacts sample size 224.

3.4.2 Calculation of Index case sample size

In Tanzania the average number of house members per household according to 2002 Census data found to be 4.5 [66].

= Household contacts calculated sample size/ average number of house members per household

= 224/4.5

= 49.78

The minimum total Index cases sample size 50.

3.5 Sampling procedure for the study subjects

Index Cases

All newly diagnosed sputum smear positive index cases and consented to participate into the study, were consecutively enrolled during the week days of the study period from 16th April 2007 to 12th October 2007 from the out patient Tb clinics of Temeke, Amana, and Mwananyamala municipal hospitals, and the IDC, as well as from the MNH medical wards as the research team visited these respective study sites. At the end of the study, 57 index cases were recruited into the study; 25 HIV positive Index cases and 32 HIV negative Index cases were obtained.

Household contacts

The consecutive enrollment procedure was used to obtain the desired number of the household contacts which was hand in hand with the recruitment of the index cases. In total, 237 household contacts consented to participate into the study; 125 subjects were the contacts of the 25 HIV positive Index cases and 112 subjects were the contacts of the 32 HIV negative Index cases.

3.6 Data Collection and Procedure

Index cases and household contacts that fulfilled the inclusion criteria were administered with Swahili consent (Appendix III) to agree and sign after understanding the aim of the study. Then to all those consenting index cases and household contacts, the respective Swahili structured questionnaires (Appendix II) were administered to them by the research team.

Data collected from Index cases included: total number of house members (to assess the house crowding, and was categorized into two: < 4 members/house and ≥ 4 members/house, basing on 2002 Tanzania census data on the average number of house members per household in Dar es Salaam [66], duration of symptoms prior to diagnosis of TB and up to the time the household contact is Mantoux skin tested, length of HIV

positivity (from the time the index case was positive for HIV until the time the household contact was Mantoux skin tested), anthropometric measurements (weight and height) to calculate for Body Mass Index (BMI), results of sputum smear AFB density, and the CD4 count levels of HIV positive index cases.

The anthropometric measurements obtained were weight and height:
Weight: was measured using Personal Analogy Scale, index case had removed his shoes, coat/jacket and left with light clothing; weight was recorded to the nearest 0.5kg.
Height: was measured after the index case had removed his/ her shoes or cap, it was recorded to the nearest centimeters (cm).
BMI of each index case was calculated using the following formula: BMI = Wt (Kg) / Height (M) ^{2} and BMI categories were <18 denoting underweight; 18 – 24.9 denoting Normal BMI; 25 – 29.9 denoting overweight; and ≥ 30 denoting Obesity.

The results of sputum were obtained from the respective Tb clinics, based on the results collected from their respective laboratories.
The grading of sputum AFB microscopy adopted the following criteria:

- +1 = 10-99 AFB seen per 100 immersion fields in a smear
- +2 = 1-10 AFB seen per 1 immersion field in a smear
- +3 = more than 10 AFB seen per 1 immersion field in a smear

The results of absolute CD4+ T-lymphocyte counts (CD4 counts) of the HIV positive index cases were obtained from the respective Tb/HIV CTC clinics.

The information collected from the household contacts included; age, sex, prior tuberculin skin test result (when it was given), BCG vaccination scar (presence or absence of an intradermal scar above the right deltoid muscle), duration of exposure to the index case, the degree of closeness with the index case (sharing a bed/ room or house), previous TB exposure other than the index case, and the induration size of the Mantoux skin testing.

All household contacts that consented to participate into the study underwent HIV pre-test counseling and subsequent HIV testing using ELISA. The post-HIV test counseling was

done during the delivery of results to the individual household contact. Those who wished not obtain their HIV test results had their request honored.

Mantoux skin test was done by an intradermal injection of 0.1 ml of 2 TU of RT23 in Tween-80 (State Serum Institute, Copenhagen, Denmark) into the volar surface of the forearm using a disposable 1.0 ml graduated syringe fitted with a short steel bevel needle gauge 26. The injection site was not cleaned with any antiseptics; the site was slightly stretched and the needle point held almost parallel to the skin surface. With the bevel upwards and inserted into the superficial layer of the dermis, the solution was slowly injected into and a small papule appeared. If a papule did not appear, another injection was repeated into the other volar surface of the forearm [64].

Reading of the Mantoux response was done 72 hours after the injection. A reaction response was defined as a flat, uneven, slightly raised and palpable induration measured transversely at its widest diameter against the long axis of the forearm using a clear, flexible plastic ruler and recorded in millimeters (mm).

All responses of the household contacts' Mantoux/ Tuberculin skin test results were recorded, and the results were interpreted as follows:

- 0 – 4 mm induration: Negative Mantoux responsive.
- ≥ 5mm induration: Positive Mantoux/ Tuberculin response in HIV positive household contacts.
- ≥ 10mm induration: Positive Mantoux/Tuberculin response in HIV negative household contacts.

3.6.1 Laboratory procedure

All consenting household contacts and those who had already received pre-HIV test counseling, their venous blood specimens taken and put into vacutainers with no anti-coagulant. The blood samples were taken to MUCHS-HAVARD lab where serum was tested for antibodies to HIV using Enzyme Linked Immunosorbent Assay (ELISA) in order

to determine the HIV serostatus of the household contacts. Each of the household contact's blood sample was tested twice; first by using Murex antigen antibody combination ELISA (Abbot Murex, Germany), and then followed by Enzygnost anti-HIV-1/2 plus ELISA (Dade Behring, Marburg, Germany). Discordant results were confirmed using Western Blot Assay (Bio-Rad Laboratories, USA).

3.7 Disposal of household Contacts

Newly diagnosed Households contacts infected with HIV were advised to attend the near by HIV Care and Treatment Centre (CTC), and those HIV positive household contacts with MST induration of at least ≥ 5mm, as well as those HIV negative household contacts with induration of ≥10mm were counseled and advised to have thorough medical examination to exclude tuberculosis disease at their nearby municipal hospitals. If indicated, they would be offered treatment in accordance with the national guidelines for treatment of tuberculosis [69].

3.8 Ethical Clearance

Ethical clearance was sought and obtained from the MUHAS ethics committee, and written consent was obtained from each of the study subjects.

3.8.1 Permission to Conduct Data Collection

Permission to conduct the study was obtained from respective authorities (Municipal Medical directors and Medical Officers In charge) at the three Municipals hospitals, IDC and MNH.

3.9 STATISTICAL ANALYSIS

Collected data was checked twice for completeness and consistency, and errors or discrepancies found were promptly corrected. Data was entered into computer using EPI info version 6, and data entry errors were checked by the study investigator.

The data analysis was performed using SPSS version 10. Univariate analyses of the association of socio-demographic and clinical variables of household contacts and of Index cases with those of household contacts' MST positivity were performed using Pearson's χ^2. Odds ratio (OR) and their 95% confidence intervals (CI) were determined. When the Pearson's χ^2 was not applicable due to less than 5 numbers in the cell, a Fisher's exact test was used instead. ANOVA test for comparison of the means of continuous variables was used. The two-tailed p value of 5% was regarded as significant.

Multivariate logistic regression models were used to identify independent predictors associated with Tb infection among household contacts, with all variables that were statistically significant in the Univariate analysis ($p < 0.05$).

CHAPTER 4

4.0 RESULTS

This study recruited index cases from the Muhimbili National Hospital, Infectious Diseases Control Center (IDC) and the three municipal hospitals in Dar es Salaam between 16th April 2007 and 12th October 2007. Having screened a total of 93 patients, 57 of them fulfilled the inclusion criteria of an index case and were enrolled into this study. These index cases were newly diagnosed with pulmonary tuberculosis (PTB) on the basis of positive sputum microscopy for acid fast bacilli. Their mean (SD) age was 34.8 (± 1.42), and it ranged from 20-70 years. However, 70.0% had their age ranging between 25 - 44 years. The proportion of males among the index cases was 56.0% (32/57), and 9 (36.0%) of them were HIV positive.

Table 1 compares the socio-demographic, behavioral and clinical characteristics of the index cases by HIV serostatus. The proportion of females among the HIV positive index cases was 64.0% (16/25), which was significantly higher than that of 28.1% (9/32) among the HIV negative index cases, (p=0.007). The mean (SD) age of male index cases was 35.3 (± 11.4) while that of females was 34.2 (± 10.0), (p=0.719).

Otherwise, the HIV positive and HIV negative index cases did not differ with regards to the remaining evaluated socio-demographic and behavioral characteristics as well as the clinical presentation features.

Of particular importance also was the fact that the distribution of sputum smears AFB densities did not significantly differ between the HIV positive and HIV negative index cases, although there was a tendency for a higher (59.3%) proportion of HIV negatives having +3 sputum smear AFB density compared to a proportion of 40.7% in the HIV positive group.

Furthermore, among the HIV positive index cases, the sputum AFB densities were not different when these were segregated by the degree of immunedeficiency. However, there was a statistically insignificant observation that 75.0% of those Index cases with CD4

count levels below 200 cells/μL had fewer (+1 and +2) sputum AFB densities compared to 38.5% of those having CD4 ≥ 200 cells/μL, (p=0.111).

Table 1: Socio-demographic, behavioral and clinical characteristics of the Index cases by HIV serostatus (**N=57**).

	Sputum smear positive Index cases			
Characteristics	**HIV Positive N=25 (%)**	**HIV Negative N=32 (%)**	**Total N=57 (%)**	**P value**
Sex				0.007
Male	9 (36.0)	23 (71.9)	32 (56.0)	
Female	16 (64.0)	9 (28.1)	25 (44.0)	
Age distribution (years)				0.181
20-34	12 (48.0)	21 (65.6)	33(57.9)	
≥35	13 (52.0)	11 (34.4)	24 (42.1)	
Mean Age (SD)	36.6 ± 9.3	33.4 ± 11.7	34.8 ± 10.7	0.262
Marital status				0.426
Single/Divorced/widow	12 (48.0)	12 (37.5)	24 (42.1)	
Married/cohabit	13 (52.0)	20 (62.5)	33 (57.9)	
Cigarette smoking				0.094*
Yes	2 (8.0)	8 (25.0)	10 (18.0)	
No	23 (92.0)	24 (75.0)	47 (82.0)	
Illicit drugs				0.260*
Yes	1 (4.0)	4 (12.5)	5 (9.0)	
No	24 (96.0)	28 (87.5)	52 (91.0)	
Number (%) who knew of TB & HIV diagnosis during current Tb Diagnosis	21 (84.0)		-	-
Number (%) who knew of TB & HIV diagnosis < 5 yrs ago	4 (16.0)		-	
Duration of constitutional Symptoms prior to Tb Diagnosis				0.776
< 4 weeks	10 (40.0)	14 (43.8)	24 (42.0)	
≥ 4 weeks	15 (60.0)	18 (56.3)	33 (58.0)	
BMI				0.421
Underweight	6 (24.0)	9 (28.1)	15 (26.0)	
Normal weight	15 (60.0)	16 (50.0)	31 (55.0)	
Overweight + Obese	4 (16.0)	7 (21.9)	11 (19.0)	
Sputum smear density				0.477
+1	9 (56.3)	7 (43.8)	16 (28.0)	
+2	5 (35.7)	9 (64.3)	14 (25.0)	
+3	11 (40.7)	16 (59.3)	27 (47.0)	

P-value denotes differences between the HIV positive and HIV negative index cases,
*Fisher's Exact Test,

A total of 237 household contacts participated into the study, of whom 125 were the contacts of HIV positive index cases (mean 5 contacts per patient) and 112 were the contacts of HIV negative index patients (mean 3.5 contacts per patient).

The overall mean (SD) age of household contacts was 20.5 (± 16.1) years. Contacts of HIV positive index cases had their ages ranging from 1- 82 years with a mean (SD) age of 22.0 (± 18.1) years, whereas the age range for contacts of HIV negative Index cases was 1- 60 years, with a mean (SD) age of 18.8 (± 13.3) years, p=0.124. 58% of the contacts were females, who had a higher mean (SD) age of 22.0 (± 16.4) years compared to the age of 18.5 (± 15.4) years among male contacts, (p=0.102).

BCG scars were found among 80.0% (100/125) contacts of HIV positive index cases, and 86.6% (97/112) contacts of HIV negative index cases. However, this difference was not statistically significant, with a p-value of 0.175.

As shown in table 2, the proportion of contacts who reported to be staying with their respective index case for one or more years was 63.0% among contacts of HIV positive cases, and 76.0% among contacts of HIV negative index cases, (p=0.035). On the other hand, the respective proportions who reported staying with their index cases for less than one year were 36.8% and 24.1% for contacts of HIV positive and HIV negative cases respectively [odds ratio 0.55 (95% CI 0.3 – 0.96)].

A total of 55 (23.0%) household contacts gave a history of being in contact with a case of Tuberculosis other than the index case, among whom (25/55) 45.5% recalled of an exposure from a case with sputum smear positive tuberculosis. These were 11 and 14 contacts of the HIV positive and HIV negative index cases respectively, **table 2**.

Table 2: Socio-demographic, clinical characteristics & mantoux reactivity of Household contacts of PTB Index cases (**N=237**).

Characteristics	Contacts: Index case HIV Positive n = 125 (%)	Contacts: Index case HIV Negative N = 112 (%)	Total N= 237 (%)	P value
Contacts per index case	5 (125/25)	3.5 (112/32)		
Sex				0.749
Male	51 (40.8)	48 (42.9)	99 (42.0)	
Female	74 (59.2)	64 (57.1)	138 (58.0)	
Age range (years)	1 - 82	1 - 60		
Mean Age				
Overall	22.0 ± 18.1	18.8 ± 13.3	20.5 ± 16.1	0.124
Male	19.4 ± 16.9	17.5 ± 13. 9	18.5 ± 15.4	0.558
Female	23. 9 ± 18.9	19.8 ± 12.9	22 ± 16.4	0.145
Age distribution (years)				0.857
1 – 4	23 (18.4)	19 (17.0)	42 (18.0)	
5 – 14	27 (21.6)	29 (25.9)	56 (24.0)	
15 – 24	28 (22.4)	26 (23.2)	54 (22.0)	
≥ 25	47 (37.6)	38 (33.9)	85 (36.0)	
BCG Scar				0.175
Present	100 (80.0)	97 (86.6)	197 (83.0)	
Absent	25 (20.0)	15 (13.4)	40 (17.0)	
Duration of living with index case prior TB diagnosis was:				0.035
Number (%) whose duration of living with index case prior TB diagnosis was < 1 year	46 (36.8)	27 (24.1)	73 (31.0)	
Number (%) whose duration of living with index case prior TB diagnosis was ≥ 1 year	79 (63.2)	85 (75.9)	164 (69.0)	
Exposure to Tb patient other than Index case				0.646
Yes	27 (21.6)	28 (25.0)	55 (23.0)	
No	98 (78.4)	84 (75.0)	182 (77.0)	
Contacts' HIV status				0.992
HIV Positive	10 (8.0)	9 (8.0)	19 (8.0)	
HIV Negative	115 (92.0)	103 (92.0)	218 (92.0)	
Degree of closeness				0.011
Sharing room	41 (32.8)	55 (49.1)	96 (40.5)	
Sharing house	84 (67.2)	57 (50.9)	142 (59.5)	
Range of mantoux induration (mm)	0 – 23	0 -22		
Overall Mean (SD) MST (mm)	9.9 (± 6.7)	10.1 (± 6.4)	10.0 (± 6.6)	0.790
Mean (SD) MST (mm) by contacts' serostatus				0.792
HIV positive contacts	8.4 (± 7.0)	12.6 (± 7.7)	10.4 (± 7.4)	0.233
HIV negative contacts	10.0 (± 6.7)	9.9 (± 7.0)	10.0 (± 6.5)	0.896
Mantoux response				
Positive	77 (61.6)	70 (62.5)	1.04 (0.61-1.76)§	0.887
Negative	48 (38.4)	42 (37.5)	1	

P-value denotes differences between the household contacts of HIV positive and HIV negative index cases
§- Univariate Odds Ratio (95% CI)

None of the household contacts had Mantoux skin test before, and all of them consented and underwent ELISA test for HIV antibodies. 19 (8.0%) of the household contacts were found to be HIV positive. The respective HIV prevalence among the household contacts of HIV positive and HIV negative index cases were 8.0% (10/125) and 8.0% (9/112), p=0.992.

Interestingly, the degree of closeness of household contacts with the index cases differed significantly, between the contacts of HIV negative and those of HIV positive index cases. 49.1% of contacts of HIV negative index cases shared a room with their index case, whereas the proportion was 32.8% among contacts of HIV positive index cases, (p = 0.011).

Risk of Infection among Household Contacts

As shown in table 2, the overall mean (SD) diameter of mantoux skin test (MST) induration was 10.0 (± 6.6) mm. The mean MST induration diameter among contacts of HIV negative index cases was 10.1 (± 6.4) mm, whereas that among contacts of HIV positive Index cases was 9.9 (± 6.7) mm, p=0.790. The distributions of MST responses are shown in **figure 1** in which MST anergy was seen among 27% and 25% of HIV positive and HIV negative index cases' contacts respectively. Majority of HIV positive index cases' contacts had mantoux positive responses ranging 15 – 19 mm (33%), whereas contacts of HIV negative index cases had their most frequent MST induration sizes ranging between 10 -14 mm (30%). The MST induration size ranging 20 – 23 mm was less seen in contacts of both HIV positive and HIV negative index cases, the proportions with such a range being 2% and 4% respectively.

The mean MST induration size among HIV positive contacts was 10.4 (±7.4) mm and that among HIV negative contacts was 10.0 (± 6.5) mm, p=0.792. The distribution of MST responses among the household contacts in relation to their HIV serostatus is shown in **figure 2**, in which MST anergy was seen among 26.0% of the HIV positive contacts and among 26.0% of the HIV negative contacts. 37.0% of the HIV positive contacts and 30.0% of the HIV negative contacts had a MST positive response ranging between 15 – 19 mm.

Overall, a positive mantoux skin test (MST) response was seen in 61.6% (77/125) of the household contacts of HIV positive Index cases and in 62.5% (70/112) of the household contacts of HIV negative Index cases (odds ratio 1.04 [95% CI 0.61–1.76], p=0.887) (**table 2**).

In order to minimize the influence of environmental Mycobacteria on mantoux skin test response, an analysis confined to the age group 1-14 years was performed and it showed no statistically significant differences between contacts aged 1-14 years of HIV positive index cases and similarly aged contacts of HIV negative index cases (odds ratio 1.39 [95% CI 0.63-3.07], p=0.419).

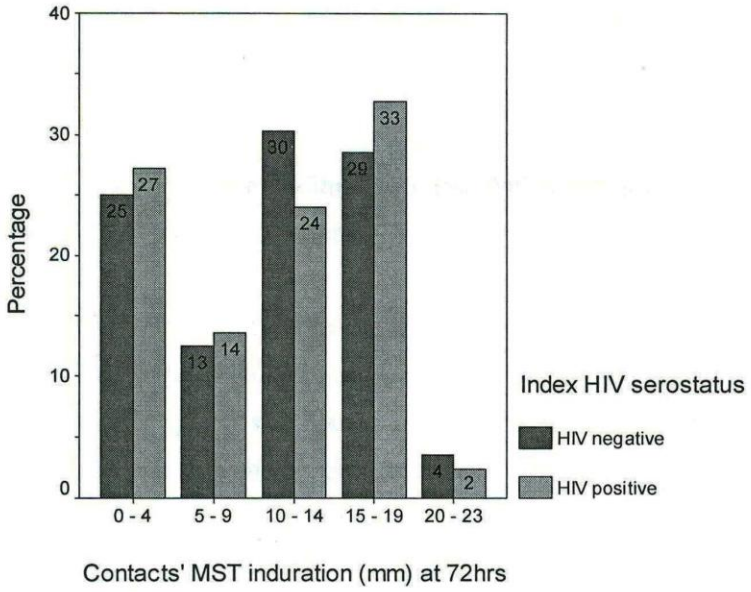


Fig 1: Distribution of MST induration size among household contacts of HIV positive and HIV negative index cases.

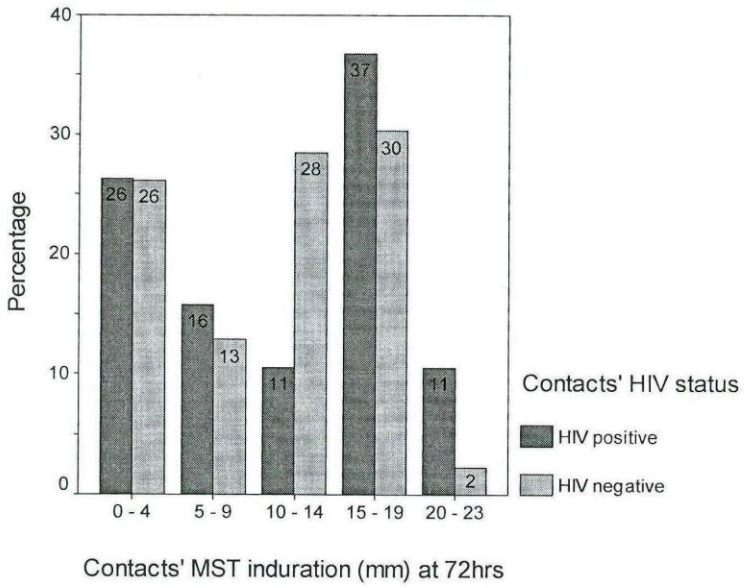


Fig 2: Distribution of MST induration size among HIV positive and HIV negative household contacts.

Risk factors for a positive Mantoux skin test (MST) response

Household Contacts characteristics:

Age group:

Table 3 and 4 shows the contact's characteristics associated with Mantoux skin test positivity among household contacts of HIV positive and HIV negative index cases respectively. Age group was found to be associated with a positive MST response. Household contacts of both HIV positive and HIV negative Index cases aged 25 years and more were found to have a higher risk of a positive MST compared to those aged 24 years and below. The odds ratio (OR) for a positive MST response among the 80.9% of household contacts of HIV positive index cases who were ≥25 years was 5.49 [95% CI 1.83-16.5], (p=0.002). On the other hand, the OR among the 84.2% of household contacts of HIV negative index cases who were ≥25 years was 4.80 [95% CI 1.37-16.80], (p=0.014).

HIV serostatus

Although the overall prevalence of infection with *Mycobacterium tuberculosis* (on the basis of a positive MST) among HIV positive household contacts was 73.7%, it was found

that there was no significant difference in the proportions with a positive MST between HIV positive household contacts of HIV positive index cases and HIV positive household contacts of HIV negative Index cases. These were 70.0% (7/10) among HIV positive contacts of HIV positive Index cases and 77.8% (7/9) among HIV positive contacts of HIV negative Index cases, p=0.740.

Duration of contact with index case

As shown in tables 3 and 4, among contacts, the duration of living with an HIV positive or an HIV negative index case prior to TB diagnosis that was a year or more was found to be significantly associated with *Mycobacterium tuberculosis* infection. 73.4% of such contacts of HIV positive index cases were found to be infected, and had an OR of 3.93 [95% CI 1.82-8.48], p=0.0005, when compared to the risk among the 41.3% of those whose duration of contact was less than a year. On the other hand, 69.4% of contacts of HIV negative index cases found to be infected had an OR of 3.30 [95% CI 1.35-8.08], p=0.007, of being infected when compared with the risk among the 40.7% of those who had a contact duration of less than a year.

Degree of closeness with index case

Sharing a room was also found to be a statistically significant contributory factor to a higher MST positivity in household contacts of both HIV positive and HIV negative Index cases. The prevalence of Tb infection (MST positivity) was 78.0% among contacts who shared a room with the HIV positive index case. When compared to those who did not share a room, the OR for a positive MST response was 3.08 [95% CI 1.31-7.24], p= 0.008. On the other hand, the prevalence of a positive MST was 81.8% among contacts who shared a room with the HIV negative index cases, and their OR for such a positive MST response was 5.76 [95% CI 2.43-13.64], p= 0.0001, when compared to those who did not share a room. These are shown in tables 3 and 4.

BCG scar

The presence or absence of BCG scar among household contacts was not found to have any influence on the prevalence of the MST response among household contacts of either HIV positive or HIV negative Index cases.

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Table 3: Contacts characteristics associated with Mantoux positivity among household contacts of HIV positive index cases (N=77).

Contacts' characteristics	Contacts of HIV +ve index cases and Mantoux +ve n=77 (%)	Univariate Odds Ratio (95% CI)	P value
Sex			
Male	32/51 (62.7)	1	
Female	45/74 (60.8)	0.92(0.44-1.92)	0.827
Age group (years)			0.006 t
1-4	10/23 (43.5)	1	
5-14	17/27 (63.0)	2.21 (0.71-6.88)	0.171
15-24	12/28 (42.9)	0.98 (0.32-2.97)	0.945
≥25	**38/47 (80.9)**	**5.49 (1.83-16.5)**	**0.002**
BCG scar			
Present	61/100 (61.0)	0.88 (0.35-2.19)	0.783
Absent	16/25 (64.0)	1	
HIV status			
Positive	7/10 (70.0)	1.50 (0.37-6.10)	0.740*
Negative	70/115 (60.9)	1	
Duration of living with the Index case prior to Tb diagnosis			
< 1 year	19/46 (41.3)	1	
≥ 1 year	**58/79 (73.4)**	**3.93 (1.82-8.48)**	**0.0005**
Degree of closeness			
Sharing room	**32/41 (78.0)**	**3.08 (1.31-7.24)**	**0.008**
Sharing house	45/84 (53.6)	1	

*Fisher's exact test, t- χ^2 test for trend

Table 4: Contacts characteristics associated with Mantoux positivity among household contacts of HIV negative index cases (N=70).

Contacts' characteristics	Contacts of HIV –ve index cases and Mantoux +ve n=70 (%)	Univariate Odds Ratio (95% CI)	P value
Sex			
Male	29/48 (60.4)	1	
Female	41/64 (64.1)	1.17 (0.54-2.53)	0.693
Age group (years)			0.001 t
1-4	10/19 (52.6)	1	
5-14	12/29 (41.4)	0.64 (0.20-2.04)	0.445
15-24	16/26 (61.5)	1.44 (0.44-4.77)	0.551
≥25	**32/38 (84.2)**	**4.80 (1.37-16.80)**	**0.014**
BCG scar			
Present	60/97 (61.9)	0.81 (0.26-2.56)	0.721
Absent	10/15 (66.7)	1	
HIV status			
Positive	7/9 (77.8)	2.22 (0.44-11.24)	0.480*
Negative	63/103 (61.2)	1	
Duration of living with the Index case prior to Tb diagnosis			
< 1 year	11/27 (40.7)	1	
≥ 1 year	**59/85 (69.4)**	**3.30 (1.35-8.08)**	**0.007**
Degree of closeness			
Sharing room	**45/55 (81.8)**	**5.76 (2.43-13.64)**	**0.0001**
Sharing house	25/57 (43.9)	1	

*Fisher's exact test, p value, t- χ^2 test for trend

Index cases characteristics:

As shown in table 5, among the investigated HIV positive index cases' characteristics that were associated with a higher likelihood of a positive mantoux reactivity response among their household contacts were the female gender and sputum AFB density of 3+. The proportion of females among household contacts of HIV positive index cases was 70.1%, while the proportion of males was 32.1%. The OR for a positive MST among female index cases compared to male index cases was found to be 4.52 [95% CI 1.80-11.3], (p = 0.000). Similarly, the proportion among contacts of HIV positive index cases with sputum density of 3+ was 73.1%, while the proportion with sputum density of +1 or +2 was 53.4%. The OR for a positive MST among index cases with sputum AFB 3+ was 2.37 [95% CI 1.10-5.09], (p=0.028) when compared to that among those with a sputum density of +1 or +2.

Table 5: Index cases characteristics associated with Mantoux positivity among household contacts of HIV positive index cases (**N=77**).

Index cases' characteristics	Contacts of HIV +ve index cases And Mantoux +ve n=77 (%)	Univariate Odds Ratio (95% CI)	P value
Sex			
Male	9/28 (32.1)	1	
Female	**68/97 (70.1)**	**4.52 (1.80-11.3)**	**0.000**
Age distribution (years)			0.887 t
20-34	31/51 (60.8)	1	
≥35	46/74 (62.2)	1.06 (0.51-2.21)	0.876§
Sputum AFB densities			0.026
+1 and +2	39/73 (53.4)	1	
+3	**38/52 (73.1)**	**2.37 (1.10-5.09)**	**0.028**
Duration of constitutional Symptoms prior to Tb diagnosis			
< 4 weeks	35/55 (63.6)	1.17 (0.56-2.42)	0.678
≥ 4 weeks	42/70 (60.0)	1	
Crowding (persons per house)			
< 4 persons	9/16 (56.3)	1	
≥ 4 persons	68/109 (62.4)	1.29 (0.45-3.73)	0.638

*Fisher's exact test, t- χ^2 test for trend

On the other hand, female gender and sputum AFB density of 3+ of HIV negative index case was not found to be associated with a significantly increased risk of a positive MST among their household contacts (**table 6**).

It should also be noted that age of the Index case; duration of constitutional symptoms prior to pulmonary tuberculosis diagnosis, and the degree of household overcrowding were

found not to be associated with an increased likelihood of transmission of *Mycobacterium tuberculosis* infection to the household contacts of both HIV positive and HIV negative Index cases.

Table 6: Index cases characteristics associated with Mantoux positivity among household contacts of HIV negative index cases (**N=70**).

Index cases' characteristics	**Contacts of HIV –ve index cases and Mantoux +ve n=70 (%)**	**Univariate Odds Ratio (95% CI)**	**P value**
Sex			
Male	49/84 (58.3)	1	
Female	**21/28 (75.0)**	**2.36 (0.89-6.21)**	**0.115**
Age distribution (years)			0.800 t
20-34	58/92 (63.0)	1	
≥35	12/20 (60.0)	0.88 (0.33-2.37)	0.799
Sputum AFB densities			0.807
+1 and +2	35/55 (63.6)	1	
+3	**35/57 (61.4)**	**0.91 (0.42-1.96)**	**0.492**
Duration of constitutional Symptoms prior to Tb diagnosis			
< 4 weeks	31/46 (67.4)	1.43 (0.65-3.15)	0.372
≥ 4 weeks	39/66 (59.1)	1	
Crowding (persons per house)			
< 4 persons	23/33 (69.7)	1	
≥ 4 persons	47/79 (59.5)	0.64 (0.27-1.52)	0.309

*Fisher's exact test, t- χ^2 test for trend

Multivariate logistic regression analyses

Contacts' characteristics

In order to find the predictors of tuberculosis infection, a multivariate analysis was performed. The factors that emerged to be significantly associated with a positive MST response among household contacts of HIV positive and HIV negative index cases were age of 25 years or above; duration of the contact living with the index case of one year or more, and sharing a room with a Tb patient (**table 7**).

Index cases' characteristics

On the other hand, following a logistic regression analysis of HIV positive and negative index case's characteristics, only female gender among HIV positive index cases was found to be a predictor of infectiousness to their respective household contacts (OR 4.95 [95% CI 2.0-12.23], p=0.0005) (**table 8**).

Table 7: Multivariate analysis of contacts' characteristics associated with Mantoux positivity response in HIV positive and HIV negative index cases' contacts.

Characteristics	Multivariate Odds Ratio (95% CI)	P value
Household contacts of HIV positive Index cases		
Age distribution (years)		0.007
1-4	1	
5-14	3.27 (0.91 – 11.77)	0.069
15-24	1.72 (0.49 – 6.02)	0.393
≥25	**7.37 (2.18 – 24.97)**	**0.001**
Duration of living with the Index case prior to Tb diagnosis		
< 1 year	1	
≥ 1 year	**4.49 (1.88 – 10.71)**	**0.0007**
Degree of closeness		
Sharing room	**3.23 (1.23 – 8.51)**	**0.018**
Sharing house	1	
Household contacts of HIV negative Index cases		
Age distribution (years)		0.0017
1-4	1	
5-14	0.97 (0.24 – 3.94)	0.961
15-24	**4.97 (1.02 – 24.12)**	**0.047**
≥25	**10.88 (2.31 – 51.17)**	**0.0025**
Duration of living with the Index case prior to Tb diagnosis		
< 1 year	1	
≥ 1 year	**4.10 (1.21 – 13.87)**	**0.023**
Degree of closeness		
Sharing room	**7.76 (2.72 – 22.09)**	**0.0001**
Sharing house	1	

Table 8: Multivariate analysis of Index cases' characteristics associated with Mantoux positivity response in household contacts of HIV positive index cases.

Characteristics	Multivariate Odds Ratio (95% CI)	P value
HIV positive Index cases		
Sex		
Male	1	
Female	**4.95 (2.0 – 12.23)**	**0.0005**
Sputum AFB densities		
+1 and +2	1	
+3	-	0.364

CHAPTER 5

5.0 DISCUSSION

This study was aimed at determining whether HIV infected individuals who are also sputum smear positive for AFB are as or more infectious than HIV un-infected patients with positive sputum smears.

In this study, the proportions of contacts with a positive MST response were similar among contacts of both HIV positive and HIV negative index cases signifying a similar risk of infection with *Mycobacterium tuberculosis*. This finding agrees with the previous studies from Kenya and Zaire reporting no differences in the prevalence of *Mycobacterium tuberculosis* infection among household contacts of HIV positive and HIV negative Index case [23, 24].

Similarly, the prospective cohort study done in Brazil found that contacts of HIV sero-positive persons with PTB were less likely to have a positive TST response than contacts of HIV- seronegative persons after analysis with TST conversion (second TST) at one year follow-up, but when TB infection was analyzed by the first tuberculin response no statistically significant difference was found between contacts of HIV positive and HIV negative Index cases [26]. The first Tuberculin response analysis results for TB infection of the Brazilian study were similar to the results of this cross sectional study.

However, a study from Philippines did find a higher prevalence of *M tuberculosis* infection among contacts of HIV positive than those of the HIV negative tuberculosis patients [22], On the other hand, studies in Zambia suggested that the infectiousness of HIV positive patients with tuberculosis is lower than that of HIV negative patients with tuberculosis [25]. It would appear that a generalization of the mantoux skin test positivity response cut-off level in household contacts of HIV positive and HIV negative index cases with no regards to the HIV serostatus of the respective household contacts in the above quoted studies could explain the difference with the present study. The study done in Philippines used MST positive response of 10 or more mm and the ratio of the HIV positive index case was 3.6 higher than that of the HIV negative index cases; while in the Zambian study, the MST

positive response used was 5 or more mm and the ratio of contacts of HIV positive index case was 1.5 times higher than that of the contacts of HIV negative index cases. In this study the ratio of contacts of HIV positive index cases to that of HIV negative index cases was 1.06 and the HIV status of the household contact was considered on the interpretation of the MST positivity response.

Since this study was conducted in Tanzania which is in Sub-Saharan Africa, the region with high prevalence of HIV infection, testing for HIV infection among household contacts was done in order to be aware of the cause of anergy or lower sensitivity to the Mantoux test [70]. Furthermore, in this study the HIV serostatus of the contact was taken into account. All those contacts who were HIV and their MST positivity response was 5 mm or more were regarded as mantoux positive and they contributed about 9.5% (14/147) of all Mantoux positive results.

The longer duration of contact with an infectious source, the higher the likelihood of acquiring the Tb infection [68], and into this account women are the ones who have longer duration of contact with their respective family members unlike men [71], therefore female sex of the index case has been reported to be the best predictor of tuberculosis transmission to their respective contacts [23]. This is also confirmed in this study, particularly among the HIV positive female index cases. This could in part be explained by a larger proportion of female HIV positive index cases in this study that actually amounted to 64.0% of all the 25 female index cases. It is also known that the majority of people living with HIV in Sub-Saharan Africa, about 61.0% are indeed women [7].

The age and sex distribution of the sputum smear positive index cases in this study showed an age ranging from 20 – 70 years, and that the most affected age group was 25-34 years age group among both males and females, with prevalences of 43.8% and 44.0% respectively. This finding is similar to that reported by the Tanzania's MOH, NTLP annual report of 2004 that showed the most affected age group to be 25-34 years among both males and females with prevalence of 32.2% and 36.6% respectively [6].

Factors associated with the likelihood of *M tuberculosis* transmission were analyzed in this study, including the degree of closeness of contact to the index case, contact's age and sputum smear AFB density of the Index case as these had been demonstrated before that they were associated with high tuberculosis infection transmission [31]. In this study, the degree of closeness was defined by either a contact sharing the same room or just sharing a house with the Index case. This factor was strongly associated with a higher prevalence of Tb infection among all household contacts (even to contacts aged 1-14 years) of both HIV positive and HIV negative index cases as had been seen in a study from Kenya [23].

It was found in this study that increasing age among contacts of both HIV positive and HIV negative index cases was associated with a higher likelihood of Mantoux positivity, suggesting that the response was attributed by infection with M tuberculosis rather than BCG immunization. Similar effect was also seen in a study among contacts who had been vaccinated with BCG as evidenced by the presence of BCG scar and those not having BCG scar [23,24,72].

It has been proposed that the higher the bacillary load, the better the efficiency of transmission [31] and a study done in the USA showed that patients with greater bacterial loads in sputum were associated with a higher prevalence of infection in contacts. Indeed following adjustment, HIV status of the index patient did not explain the differences [28]. Similarly, in this study the presence of smear density +3 in the sputum of the Index cases was only associated with a higher risk of Tb infection among contacts of HIV positive index cases, and when a logistic regression analysis was done the association was not sustained.

A reduced risk of transmitting *M tuberculosis* by the HIV infected patients is correlated by the known fact that tuberculosis patients with HIV infection more frequently have atypical findings in their chest radiographs, or have normal radiographs, facts that could represent a reduced burden of bacilli, rather than a reduced immunologic response to a mycobacterial infection [73]. In fact, some studies have even indicated that HIV positive patients with pulmonary TB may be less infectious due to low bacillary load in the sputum, particularly when the CD4 count is still relatively high [22]. However, a study done in Tanzania which

analyzed 844 patients, 433 (51.3%) of whom were HIV-positive reported that a high bacillary density was significantly less common among HIV positive (39%) than among HIV negative (75.7%%) patients ($p < 0.0001$); and the proportion of those with high bacillary density increased progressively with CD4 cell counts ($P = 0.003$), while the AFB density fell with falling CD4 cell count [74]. In the present study, HIV positive patients with CD4 counts of 200 cells/µl or more were found to be relatively more infectious to their household contacts than those with CD4 counts less than 200 cells/ µl. However, this finding did not show a statistical significance, probably as a result of the small number of the index cases which were only fifty seven. Furthermore, this study relied on the already available sputum smear densities and CD4 count levels without regarding the respective Tb laboratory clinics' personnel skills. It had previously been documented in study done in Dar es salaam comparing microscopy and culture sputum smear results from the thirteen peripheral tuberculosis diagnostic centers (PDCs) including Muhimbili National Hospital, IDC, Amana, Mwananyamala and Temeke Hospitals (the centers where this study recruited its index cases) and the results from Central Reference Tuberculosis laboratory (CTRL) that PDC had inadequate performance in diagnosis of TB using smear microscopy and there is need for immediate and rigorous measures to improve the quality of smear microscopy and to strengthen the capacity of laboratory personnel microscopy technique through supportive supervision and training [75].

The health seeking behavior among Tb patient is low and most of them, reported late to the hospital. A finding that in this study 58.0% of sputum smear patients sought medical advise during the fourth week and above after onset of Tb constitutional symptoms emphasizes the point. This may be explained by the fear or discrimination faced by Tb patients from their relatives and friends as shown in a study done in Amana municipal hospital, Dar es Salaam, Tanzania [76].

In this study, the duration of constitutional symptoms of tuberculosis presented by the HIV positive and HIV negative patients prior to hospital Tb diagnosis was found not to differ between these two groups and this could explain as to why the prevalence of Tb infection among their household contacts was also found to be almost equal. A study done in USA found that HIV positive tuberculosis patients who presented with symptoms were

diagnosed earlier with tuberculosis than immunecompetent patients and thus remained infectious for a shorter period than HIV negative. Therefore contacts of HIV positive Tb patients had lower prevalence of Tb than contacts of HIV negative patients [28]. However, other studies insisted that the reduced risk of *M tuberculosis* transmission was associated with a shorter period of infectiousness of the HIV infected Tb patients [31,77,78].

STUDY LIMITATIONS

Due to financial constrains, this study had to rely on the already available sputum smear for AFB densities results which were obtained from the respective TB clinics and for the HIV positive Index cases. Similarly, their results for HIV test and CD4 count levels were obtained from the respective Tb/ HIV CTC. Apart from that, short duration for conducting study was another limitation that forced the investigator to collect only the required calculated Index cases' sample size. The integrity of such results were thus out of the control of the investigator.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 CONCLUSION

It is therefore concluded from this study that patients with pulmonary tuberculosis and HIV co-infection have the same likelihood of infectiousness to their contacts as those who are not HIV infected. Mantoux skin test (MST) positivity response among household contacts of HIV positive and HIV negative index cases increased with contact's age, duration of living with the Index case, and the degree of closeness; especially by sharing a room with an index case. Female HIV positive Index cases were more infectious than their male counter-parts. Indeed some of these factors are potentially modifiable.

The HIV serostatus of contacts and BCG vaccination as evidenced by the presence of BCG scar did not influence the acquisition of *M. tuberculosis* infection.

6.2 RECOMMENDATIONS

There is a need for prospective studies with larger sample size using rapid test (interferon-gamma assay) which has better indicator for detecting risk of Mycobacterium tuberculosis infection than MST in order to define better the infectiousness of HIV infected cases with pulmonary tuberculosis.

Policies should be made on contact tracing and screening of the close contacts of smear-positive pulmonary TB patients, independently of the HIV serostatus of index case.

Imposition of strategies to identify and treat close contacts that were recently infected with TB could have a positive impact on TB prevention and control in the near future.

CHAPTER SEVEN

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