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Extrapulmonary tuberculosis in HIV-positive and HIV-negative children in Haiti: A hospital-based Investigation

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Extrapulmonary Tuberculosis in HIV-Positive and HIV-Negative Children in Haiti:

A Hospital-Based Investigation

by

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Dedication

This thesis is dedicated to the children of CHOAIDS (Caring for Haitian Orphans with AIDS, inc.) and the USF College of Public Health. In the fall of 2000, I started the Community of Family Health Program with the desire to serve; a little over a year into the program, I decided to get a master's degree in Epidemiology. I had no idea that in early 2004 I would start an orphanage in my homeland, Haiti, to provide care to HIV-positive AIDS orphans. As a Christian, I believe that God appointed me to do this work. I have learned so much from these children, but most of all, they have taught me to appreciate the simple things about life. Living with this virus has not been easy for my angels, but I do hope that God will continue to provide for them through me so that I can continue to help in the alleviation of their pain by caring for them. Haiti is an impoverished country plagued by civil unrest and disease; my goal is to help shape these young lives and others to become responsible adults who will contribute toward the building of the "new Haiti." Eleanor Roosevelt once said "do the thing that you think you cannot do." That's my motto!

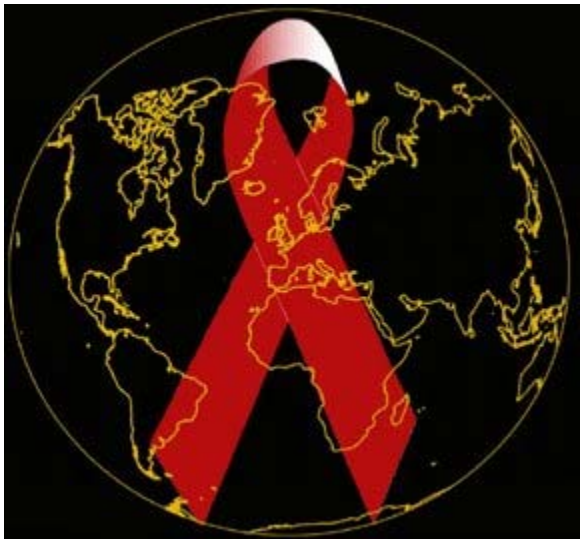

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Table of Contents

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ABSTRACT

Introduction: Globally, one in four persons infected with the human immunodeficiency virus (HIV) who are living with the acquired immunodeficiency syndrome (AIDS) will die of tuberculosis (TB). The estimated number of HIV-infected children who die of tuberculosis, especially extrapulmonary TB (EPTB), in Haiti, is only loosely based on facts or investigation. This study proposes to describe demographics of children with EPTB in a pediatric TB hospital in Haiti. The objectives are two-fold. The first objective is to describe the population of children discharged from Grace Children's Hospital with a confirmed diagnosis of tuberculosis overall, and broken down by whether or not the child had an extrapulmonary manifestation of the TB disease. Specifically, we describe the demographic characteristics and the prevalence of HIV and other co-morbidities of the children, in-hospital mortality, and the diagnostic tools used to determine TB infection including the sputum test, and the documentation of family members also infected. As part of the descriptive process, by examining those with only pulmonary TB (PTB) and EPTB separately, we investigate if they appear to be different sub-populations based on demographic characteristics and clinical measures. The second objective of this work is to determine if there is a positive association between HIV infection and the EPTB manifestation in children with a confirmed diagnosis of TB, both crudely and after adjusting for demographic variables and co-morbidities.
Methods: A cross-sectional study design was used to review medical charts of clinically diagnosed pediatric TB cases for a five-year period (January 1, 1999 – December 31, 2003). This included 492 pulmonary TB and 210 extrapulmonary TB cases. Variables measured included clinical measures and demographic characteristics.
Results: Data for 615 hospitalized, clinically diagnosed pediatric TB cases were reviewed. There were 315 (51.4%) males and 298 (48.6%) females with a mean age of 5.40 years (range 0.17 - 14 years), with 214 (37.9%) of the patients aged 0-2 years. Percent males were 47.8% and 57.9% in PTB and EPTB groups respectively ($p<0.05$). One hundred and seven (17.4%) of patients were HIV positive. Three hundred eighty-eight (63%) of the patients had one or more additional co-morbidities: [anemia 299 (48.6%), intestinal parasites 93 (15.1%), malaria 58 (9.4%) and gastroenteritis 19 (3.1%)]. Nearly 85% of the children were undernourished. Eighty-three child patients (13.5%) died in the hospital. Children with EPTB were much more likely to be over the age of two (74% vs. 56% in PTB group), resulting in a highly significant Chi-square

statistic. The overall difference in mean age, however, was only borderline significant with children with EPTB being slightly older [p=0.059] and age was only weakly associated with TB group. They were much less likely to be HIV positive (8.6% vs. 22%, p<0.01). Children in the EPTB group were somewhat less likely to die in the hospital (10.0% vs. 15.4%, p=0.066). The OR was greater than 4 for HIV and was greater than 2 for poor nutrition status [p<0.01 for each].

Conclusion: There was no association in this model between EPTB and mortality. The apparent univariate association between EPTB and reduced mortality can be explained by lower prevalence of HIV and poor nutrition status in this sub-sample. This study has implications for hospital-based pediatric TB diagnosis and epidemiology in resource-poor countries.

CHAPTER I INTRODUCTION

Haiti's children are suffering. There is an urgent documented need to augment the present health system, which lacks the capacity to diagnose, treat, or provide adequate preventative measures designed to improve the health of the general population, and especially, children. This research will address the problems of TB and AIDS in children, and argue for increased resources to offset the loss of life resultant from the epidemic spread of TB and HIV/AIDS in Haiti.

Tuberculosis is a global health problem. In 1993, the World Health Organization (WHO) declared it a global health emergency, and in 1999, estimation of global *mycobacterium tuberculosis* infection was approximated at two billion (Centers for Disease Control & Prevention, 1999; Houghton, 2002).[1] According to WHO, tuberculosis kills approximately three million people and sickens eight million worldwide each year (Basel, 1998). Every 15 seconds, one of every three persons to die from TB is a child (Mwinga, 2005).

Children with HIV-infection are between five to ten times more likely to develop tuberculosis than HIV-negative children. One-third of the increased number of TB cases is attributed to the spread of the human immunodeficiency virus (HIV) epidemic (UNAIDS, 2004a).[2] Worldwide TB is the leading cause of death in HIV-infected persons, especially in developing countries. In addition, among infectious diseases,

[1] The infectious bacterium that causes TB.
[2] There are two types of HIV: HIV-1 and HIV-2 (Centers for Disease Control & Prevention, 1998).

tuberculosis is the second leading cause of mortality worldwide (CDC, 1999; Houghton, 2002).[3] Since one in four persons infected with HIV and living with the acquired immunodeficiency syndrome (AIDS) will die of TB disease and the leading cause of death in Haiti is AIDS-related, the estimation of the number of HIV-infected children who die of TB disease in Haiti has not been investigated.

Haiti has both a high prevalence of HIV and a high endemicity of TB. HIV infection damages the immune system and therefore compromises immune functions. As the infection progresses to AIDS, EPTB becomes as frequent as PTB in patients, and adults with AIDS are known to have increased susceptibility to develop TB disease and for their TB disease to quickly progress to EPTB (Chan, Birnbaum, Rao, & Steiner, 1996; Yang et al., 2004). Children and adults with AIDS are known to have similar AIDS-related opportunistic infections. The majority of HIV transmission occurs through heterosexual contacts in Haiti. This is directly related to the increase in the nation's infant mortality rate.

Accurate measures of HIV-infection and death occurring due to HIV-infection among Haitian children is very difficult to determine because of the lack of diagnostic tests for HIV in children, and incomplete definition of pediatric HIV clinical manifestations (Jean et al., 1997). Just as it is for adults, HIV-infected children are at a greater risk of becoming infected with TB and thereby developing TB disease.

Morbidity, mortality, and infection of others in the community with TB are minimized when symptoms are diagnosed and treatments are initiated early. Antiretroviral therapy became available to a select few of those with AIDS in Haiti in late 2002, and identifying and treating HIV co-infected will reduce the transmission of the

[3] The third infectious disease and leading cause of death worldwide is malaria

tubercle bacilli to infants, children, and other vulnerable persons in the population. Although pediatric EPTB is common, it is unresearched in Haiti because physicians lack basic resources to diagnose TB disease; thus they treat TB based on clinical suspicion or possible contact to an active TB case, rather than chest radiographs and bacteriologic tests.

Isolating the *mycobacterium tuberculosis* in suspected pediatric cases (particularly infants) is very challenging because of the lack of sputum production and the atypical presentation of TB disease. Misdiagnosis of TB infection in children is common because some patients are asymptomatic and those with symptoms are nonspecific. Decreasing the number of misdiagnoses among these cases will require clinicians in resource-poor areas to receive updated data including instructions on other AIDS-related lung diseases.

This chapter begins with a review of the literature relating to studies of TB diagnosis, with an emphasis on pediatric cases. Next, the background and significance of TB and HIV/AIDS is discussed in reference to the Caribbean. The following section situates the problem of these diseases in Haiti and highlights key country indicators. The second part of this chapter introduces the history and pathomechanics of TB and HIV/AIDS with a discussion of TB transmission, tuberculous meningitis, osteomyelitis TB, and lymph node TB.

Studies of TB Diagnosis

In a cross-sectional study conducted in a pediatric referral center in a TB endemic area of Peru, the investigators sought to provide a description of the epidemiology and clinical features of pulmonary TB in children. Clinical features of manifested or suspected TB cases in children include the presentation of cough, a history of contact case, characteristic of chest radiographs, and purified protein derivative (PPD) reaction. With a sample size of 135 suspicious cases of pediatric TB, of patients aged 1 month to 17 years, the researchers formed the following 3 groups: definitive TB, probable TB, and no TB. *Mycobacterium TB* was isolated from sputum of 50 children and these children were considered to have TB; 35 children among that group were shown to have acid-fast bacilli (AFB) in sputum smear. Probable TB cases were classified as those who met at least two or more of the Migliori clinical diagnostic criteria for pulmonary TB; 55 children met the criteria; 30 children negative for TB. Patients' age, sex, BCG immunization and PPD reaction, the presence of extrapulmonary TB, and socioeconomic status were not significant in all the groups.

Extrapulmonary TB (lymphadenopathy, miliary disease, intestinal-intraperitonial TB, intra-abdominal, meningitis, and optic involvement) was present in 21 children (16%); characteristics of children with EPTB and those with PTB were similar with both groups including malnourished children. Children with EPTB were younger than those children without signs and symptoms of EPTB. In this study, the researchers determined children diagnosed with PTB were more likely to be symptomatic, without a positive skin test and specifics in chest radiographs. Additionally, in infants, it was less likely that they will have a positive smear culture. Improvement in diagnostic tools for pediatric TB

is necessary because historical and clinical data, which are currently considered as the gold standard used in developing countries, only comprise part of the diagnosis (Salazar et al., 2001).

HIV is a known risk factor that further complicates the treatment of the diagnosis of tuberculosis in children, especially infants. Tuberculosis and HIV further aggravate diagnosis-related issues including, the absence of alternative sensitive diagnostic TB tests, lack of production of sputum samples in small children, the inconsistency of symptoms presentation in children, the lack of a standardized case definition used specifically for diagnosing TB in children, and the inclusion of small or limited number pediatric TB cases included in studies in the developed world.

In a two-design study conducted at two ambulatory centers in Abidjan, Cote d'Ivoire, investigators sought to present the importance of HIV infection as an independent risk factor for developing TB in children. In a sample of 161 cases, of children aged 0-9 years who had already begun TB treatment, data collected included socioeconomic and demographic status, household environment, risk factors for TB, and the children's medical history. Clinical examination performed was chest radiograph, tuberculin skin test, sputum smear and culture, HIV antibody test and lymphocyte phenotype. The cases were gender and aged-matched to 161 controls of healthy siblings referred to the hospitals for tuberculin skin tests. Among the 161 cases, 39 had confirmed pulmonary TB, 80 with clinical PTB, and 42 with clinical EPTB. Moreover, 31 children in that group were found to be HIV-positive, with 129 HIV-negative with no available HIV serologic result in 1 child. HIV prevalence among all the three TB groups was not significant. None of the controls were HIV-positive.

Risk factors included, children with TB were more likely to be HIV-positive and to have had at least one contact with a TB patient, and to be living in very low socioeconomic status housing. Clinical presentation of TB in both HIV-positive and HIV-negative children was also not significant, with confirmed clinical TB being lower in children with HIV-infection. HIV-positive children in all three groups were less likely to have an induration of tuberculin skin test of greater or equal to 5mm and their results were similar to that of the control group. It was suggested that the tuberculin skin test might not be a useful tool to diagnose TB in HIV-infected children. This study shows that the *manifestation* of TB does not significantly differ between children who are HIV-positive and those who are HIV-negative (Mukadi et al., 1997).

Because there are limited published data on pediatric HIV-infection and EPTB, the following point to the necessity and urgency for these studies. In a retrospective study conducted in Malawi using national TB data, 11.9% of the sample size was pediatric cases. This number represented 1.3% of all the reported cases; of those, 15.9% of the pediatric cases were EPTB. Children between 1 to 4 years old were more likely to have EPTB than those less than one year and between 5 to 14 years old (88/ 100,000, 78/ 100,000 and 33/ 100,000) (Harries et al., 2002).

A Ugandan study showed EPTB occurred in 50% of patients under 14 years old in hospitalized cases for a five-year period (1985 - 1989) (Okot-Nwang, Wabwire-Mangen, & Kagezi, 1993). HIV disease associated with EPTB constitutes 50% of all TB disease and includes lymphadenopathy, pleural effusion, pericardial disease, miliary, and meningitis (H. Hausler, 2000; Sharma & Mohan, 2004).

A study conducted in India among AIDS patients found that between 56% of TB disease cases were EPTB (Sharma & Mohan, 2004). Another such study there, determined that nearly 55% of the HIV-infected children with EPTB had the disease in one or more sites, of those, 78% had both PTB and EPTB (Shahab, Zoha, Malik, Malik, & Afzal, 2004).

Since the inception of the HIV epidemic in the United States, AIDS-related EPTB cases rose from 16% in 1991 to 20% in 2001 (Jones et al., 1993). A study conducted in Ethiopia determined that HIV-positive patients with PTB were less likely to have smear-positive, and HIV-infection patients developed EPTB later than PTB (Yassin et al., 2004). A study conducted in Tennessee to ascertain the effect of the AIDS epidemic on EPTB determined that the epidemic did not affect the number of cases reported, however, EPTB was more frequent in non-white children 0-14 years and the most common forms of EPTB were miliary, lymphatic, and meningeal TB (Mehta, Dutt, Harvill, & Mathews, 1991).

Extrapulmonary TB is a common phenomenon among HIV-infected and AIDS patients; the prevalence increases as HIV progresses to AIDS (Berenguer et al., 1992; Shafer, Kim, Weiss, & Quale, 1991).[4] However, the specific profile of extrapulmonary TB in HIV-infected children is not recognized. In children four years old and younger, TB is typically disseminated into the body through the bloodstream thus increasing the risk for tuberculous meningitis.

[4] Although extrapulmonary TB is stated to be common, no exact rate is published.

Study Objectives

The objectives of this study are two-fold. The first objective is to describe the population of children discharged from Grace Children's Hospital with a confirmed clinical diagnosis of tuberculosis overall, and broken down by whether or not the child had an extrapulmonary manifestation of the TB disease. Specifically, we describe the demographic characteristics, and the prevalence of HIV and other co-morbidities of the children, in-hospital mortality and the diagnostic tools used to determine TB infection including the sputum test, and the documentation of family members also infected. As part of the descriptive process, by examining those with only pulmonary TB (PTB) and extrapulmonary TB (EPTB) separately, we investigate if they appear to be different sub-populations based on demographic characteristics and clinical measures. The second objective of this work is to determine if there is a positive association between HIV infection and the EPTB manifestation in children with a confirmed diagnosis of TB, both crudely and after adjusting for demographic variables and co-morbidities.

Background and Significance

Tuberculosis is a very contagious, but curable disease. The tubercle bacilli primarily affect the lungs in approximately 75% of sufferers to give rise to pulmonary TB; it can also involve other parts of the body and produces extrapulmonary TB (Houghton, 2002). Extrapulmonary areas typically include the lymph nodes, pleura, bones and joints, meninges, genitourinary tract and kidneys (DHPE, 2004; Houghton, 2002; WedMD Health, 2001).

Tuberculosis infection does not unvaryingly result in disease. Ninety percent of immunocompetent persons infected with TB do not develop the disease; although people with weakened immune systems are at higher risk of developing TB disease (DHPE, 2004). This population includes infants, children, the elderly, and those with immunocompromising diseases, particularly HIV infection. The human immunodeficiency virus disease is very complex and its natural history can be further complicated by a myriad of factors: mode of transmission, the prevalence of opportunistic infections, the availability of anti-HIV therapy, host genetics, and the viral strain (Deschamps, Fitzgerald, Pape, & Johnson, 2000). Infection with HIV causes destruction of the cell-mediated immunity in infected patients, which increases susceptibility to both pulmonary and extrapulmonary TB.

Among children, HIV and TB are closely related and the presence of tuberculosis in the pediatric population of a given area is used as a measuring instrument to determine the prevalence of TB in the adult population (Mwinga, 2005). Although HIV co-morbidity is found in more than 50% of pediatric TB cases, children seldom present for a primary diagnosis of HIV. More than 25% of infants born HIV-positive developed TB within the first two years of life (Chintu & Zumla, 1995). At this time, no specific or definitive diagnostic tool to diagnose TB in infants and young children exists. Further, these cases may be very difficult to identify due to lack of specificity in signs and symptoms and complications in acquiring samples for bacteriologic confirmation (American Lung Association, 2003; Chintu & Zumla, 1995; Vallejo, Ong, & Starke, 1994).

Infection with HIV progresses more rapidly to AIDS in children because of the inability of the underdeveloped immune system to fight the maturation of the virus. According to Bartlett (2004), 20% of children with HIV develop serious and recurrent bacterial infections, which include meningitis and pneumonia. Dependent on the damage done by the virus on the immune system, HIV-infected children are prone to develop disseminated TB: tuberculous meningitis, miliary TB, and tuberculous lymphadenopathy (WHO, 2000a).

Recent data complied by the UNAIDS estimates the worldwide number of people living with HIV to be 37.8 million, among them two million children and 17 million women (UNAIDS & HIV/AIDS, 2004). Global HIV infection has increased in both adults and children but this increase has been mostly seen in countries where heterosexual intercourse is the most common mode of transmission. In the Caribbean and sub-Saharan Africa, heterosexual intercourse is the primary mode of transmission for HIV. In these countries, the number of women and men infected with HIV and AIDS reached a 1:1 ratio in 2002 (UNAIDS, 2004a). In the Caribbean and Central America, the HIV epidemic is focused among heterosexuals, especially commercial sex workers who are predominately women. In contrast, in South America, HIV infection is generally characterized by intravenous drug users and men who have sex with men (UNAIDS, 2004a).

In Latin America and the Caribbean alone, over two million people are estimated to be living with HIV. In 2003, there were 250,000 new HIV infections in these regions with 120,000 AIDS deaths. In Haiti, 280,000 people are living with HIV, a rate that ranks higher than any other country in Latin American or the Caribbean (UNAIDS,

2004a; UNAIDS & HIV/AIDS, 2004).[5] At the end of 2003, more women than men were living with HIV in the Caribbean (UNAIDS, 2004a).[6] The following are estimates for the year 2003 and the first quarter of 2004, based on published data for the years 1999 and 2001 and most recent trends from a national surveillance system: the total number of people infected with HIV/AIDS in Haiti is 260,000 (range 120,000 - 560,000), and the number of children is estimated to be 19,000 (range 7,900 - 45,000) (UNAIDS/WHO, 2004).[7]

Country Profile

Haiti shares the Island of Hispaniola with the Dominican Republic; Haiti is on the west and the Dominican Republic is on the east. Haitians are descendants of mostly West African slaves and Europeans. Two languages are spoken in Haiti: French and Creole; the former is the official and the latter the maternal language.[8] Haiti is the first black republic and the second oldest republic in the New World after the United States. The population of Haiti for the year 2004 is estimated at 8,437,000 with an annual growth rate of 3.0; 43% of Haiti's population is under 14 years old (CIA, 2005).

Although Haiti is mostly rural, the greater part of its health resources are located in the capital city, Port-au-Prince, which constitutes slightly over one-third of the population (EarthTrends Country Profiles, 2003). Its past and present is plagued with political upheavals at the hands of its governments. In the past 18 years, Haiti has suffered several political crises and has had a total of 13 governments (UNAIDS,

[5] Adults and children (0-49 years).
[6] Ratio of 3:1.
[7] The definition used for adult and children can be simplified as, men and women aged 15 to 49 years for the former, and 0 to 15 years for the latter.

2004b).[9] Since the country does not have a stable economy, it lacks the infrastructure, effective manpower, and resources to provide basic care to its people.

Health care services are not free in Haiti; they are mostly an out-of-pocket service. According to PAHO/WHO, in 2002, Haiti spent no more than one percent of its gross domestic product on health expenditures, with only 60% of the population benefiting from these services (PAHO, 2003). Over two-thirds of the country is rural, and while there are a total of 371 health posts, 217 health centers, and 49 hospitals, they are divided into Haiti's nine departments. Forty percent of the population is estimated to rely on traditional medicine for health care (PAHO, 2003). Economic, social, and cultural factors heavily influence how and when individuals seek medical care. With over 60% unemployment and under-employment, most people are not able to afford basic health care and therefore rely on traditional medicine.

Tuberculosis is among the many infectious communicable diseases that afflict people globally, especially in countries like Haiti. The World Health Organization declared TB an important global health problem in 1991 and devised strategies for its control. In 2002, there were an estimated 370,000 new cases of TB and 53,000 deaths in the Americas. In that same year, Haiti had 12,066 reported TB cases with the highest rate of cases in the Americas (147 cases per 100,000 people) (WHO, 2005).

Since the HIV epidemic began in Haiti in the early 1980s, life expectancy at birth has dramatically decreased by six years. Life expectancy for men is 50.2 years and 56.5 years for women (EarthTrends Country Profiles, 2003).[10] In 2002, the infant mortality rate per 1000 live births was 138 deaths for males and 128 deaths for females. The

[8] Creole became official in 1987.
[9] Eighty percent of people in Haiti live in poverty.

mortality rate for under-fives for that same year was estimated to be 103.7 per 1000 live births (PAHO/WHO, 2003; WHO, 2004). Since 1997, the cause of death data has been collected from hospital death certificates (UNAIDS/WHO, 2004). The acquired immunodeficiency syndrome is the leading cause of death among the adult population and is suspected to be the primary cause of death in children in Haiti. The 2003 data indicated the estimated number of adults receiving anti-HIV therapy was 1,370 while the estimated number of patients in need of anti-HIV therapy was 40,000 (WHO, 2004).

The prevalence of HIV in Haiti has neared six percent and is among only three other countries in the region with a prevalence rate above three percent (UNAIDS, 2004a).[11] A study conducted at a prenatal clinic in Port-au-Prince indicated that HIV prevalence was almost ten percent among pregnant women (DHPE, 2004). In Haiti, as in other developing countries, heterosexual intercourse is the most common mode of HIV transmission. Many infected women, unaware of their status, become pregnant and give birth to infected babies (Jean et al., 1997; UNAIDS, 2004a). The majority of infected children in Haiti acquire HIV through vertical (mother-to-child) transmission. The increase in HIV-infected newborns is believed to have had a direct impact on the nation's infant mortality rate (Jean et al., 1997). However, an accurate measure of HIV infection and HIV-related deaths among Haitian children is difficult to determine for two main reasons: (1) there is a lack of diagnostic tests for HIV in children; and (2) there are no complete definitions in existence for pediatric HIV clinical manifestations (American Lung Association, 2003). Nevertheless, AIDS-related infant mortality in Haiti is estimated to be 20% (Jean et al., 1997).

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[10] 2000-2005 projections.
[11] Bahamas and Trinidad & Tobago are the other countries.

Historical Perspective and Pathomechanics of TB and HIV/AIDS

Tuberculosis is an infectious communicable and curable disease caused by the tubercle bacillus. There are three major tubercle bacilli that can cause disease in humans: *Mycobacterium tuberculosis, Mycobacterium bovis,* and *Mycobacterium avis* (Houghton, 2002). Tuberculosis existed in animals in the Paleolithic Period (*Mycobacterium bovis*), prior to becoming a threat to humans (Bates & Stead, 1993; Kime, 2002).[12] The pathogenicity of *M. tuberculosis* threatens humans, other primates, and guinea pigs, while *M. bovis* is dangerous to many other animal species, most specifically, cattle (Daniel, 2000). The first human infections are theorized to have occurred through *M. bovis* during the inception of the horticultural period, through the ingestion of contaminated meats and/or milk from infected animals. However, *M. bovis* is no longer a threat to humans since the introduction of pasteurization of milk (Houghton, 2002).

Evidence suggests tuberculosis in Europe in the Neolithic Period was common, but was largely absent at this time in Asia (Daniel, 2000; Kime, 2002). According to a number of hypotheses (archeological, linguistic, and scientific evidence), the existence of mycobacterium in pre-colonial America first occurred 30,000 to 35,000 years ago through two major movements of migration from Asia. However, the type of mycobacterium transported to the Americas is still heavily debated. Although mycobacterial DNA was extracted from a 1000 year-old Peruvian mummy by Salo and colleagues, the species of mycobacterium was not identifiable (Daniel, 2000). Unfavorable climates prevented the preservation of human remains in other locations in

[12] *M. tuberculosis* and *M. bovis* are two different species, which are closely related genetically; both are members of M. tuberculosis complex.

the Americas, and as a result, only speculative inference can be made about the existence of *M. tuberculosis* in other settlements (Daniel, 2000).

While TB devastated the American Indians in North America, evidence shows it was not known in sub-Saharan Africa and in certain areas of North Africa. Furthermore, TB was not known in areas of Africa that were not colonized, or in remote villages that were isolated from the spread of the tubercle bacillus. Other studies (Cummins, 1920; Hirsch, 1886; Linchenstein, 1928; Livingston, 1857) carried out in that region did not find evidence of TB until the first half of the 19th century (Africans were TB-free when they were brought to the U.S). When the Africans became exposed to the disease either from the Europeans or Egyptians, they developed the violent form that is sometimes referred to as sub-acute TB (the sub-acute typhoidal illness), and experienced a high mortality rate.

Several other studies (Grigg, 1958; McCarthy, 1912; Yandell, 1831) show that African Americans are less resistant to TB than are whites. Investigators found that HLA-DR expression by monocytes, which provide innate resistance to TB, are twice as common in European Americans as in African Americans (McPeek, Salkowitz, & Laufman, 1992). Another study among 41,000 nursing home residents determined that African Americans were less resistant to infection with *M. tuberculosis* (Bates & Stead, 1993).

Scientific Discoveries and Anti-TB Therapy

Hippocrates (460 – 370 BCE), the famed physician of Ancient Greece, referred to tuberculosis as *phthisis*, which is the Greek term for consumption (Basel, 1998;

Houghton, 2002). He was the first to observe tubercles, then called *phymata*, in animal tissues (cattle, sheep, and pigs) (Basel, 1998). At the time, TB or *phthisis* was considered a hereditary non-infectious disease. Aristotle was the first to believe that *phthisis* was contagious. Francastorius of Verona (Girolamo Fracastoro) (1478 – 1553), was the first to suggest that *phthisis* was transmitted by an invisible "virus" and also that the "virus" could live on the garments of the infected person for as long as two years.

Most notably, the evolutionary scientific work on TB over the centuries has proven the existence of the disease in many different parts of the world. Preliminary efforts were focused on the identification of the microorganism, then on the containment of the disease. Epidemics of tuberculosis or the "White Plague" caused countless deaths over the centuries.[13] There were many debates and uncertainties among scientists on the mode of transmission, the many forms of TB, its pathogenesis, and etiologic nature. In 1834, Johann Lukas Schonlein developed the term 'tuberculosis' to describe affliction with tubercles, but he did not recognize the similarity between scrofula and *phthisis*.[14]

> In an effort to prove the infectious nature of tuberculosis, in 1840, Jakob Henle presented the following postulates:
>
> *1) The causative agent must be found in every case of a disease; 2) it must not occur in another disease; and 3) its application must always provoke the same disease* (Basel, 1998; Loffler, 1958).

Jean Antoine Villemin (1865) discovered the disease was caused by a specific airborne microorganism. Then, in 1882, microscopist Robert Koch (who trained under Henle), produced irrefutable evidence that tuberculosis was caused by a specific microbe

[13] Other referent names for TB disease: scrofula, king's evil, Pott's disease, military TB, *tabes mesenterica,* and *lupus vulgaris* (Houghton, 2002).

- *Mycobacterium tuberculosis*. He also developed the tuberculin skin test that is still in use today in the identification of those who are infected with TB. Another milestone in the history of tuberculosis was the discovery of x-rays by the physicist Wilhelm Conrad von Rontgen, in 1895. X-rays are used to determine severity and to monitor TB (Basel, 1998).

Some efforts of the early treatment methods for tuberculosis included the promotion of self-healing in sanatoria, and lung collapse therapy (pneumothorax and thoracoplastic). These methods were considered to be applicable to strengthen the human body against the tubercle bacilli. There were different forms of sanatoria and they were all situated in elevated locations where those suffering with TB or consumption went to seek treatment. A typical treatment regimen included strict rest cure and sensible diet. The pneumothorax therapy was first created by Carlo Forlanini of Pavia, in 1888, and consisted of filling the pleural cavity with nitrogen. Thoracoplastic, an extrapulmonary procedure, was another method used and was developed in Germany by Max Schede. It is a surgical procedure of unilateral partial rib resection to reduce the volume of the thoracic cavity (Schede, 1890). Among all the treatment methods listed above, the latter was the most effective with only a 20% rate of case-fatality. Other forms of treatments used included many complicated intrapulmonary operations such as lobectomy, segmentectomy, and decortication.

Vaccination against the mycobacterium predates antibacterial treatment regimens. The Bacille Calmette-Guerin vaccine (BCG) was developed in 1906 from attenuated bovine strain of tuberculosis by Albert Calmette and Camille Guerin (Basel, 1998; Houghton, 2002). It was first administered in France, in 1921, among children who were

[14] Scrofula is also known as *Tuberculous lymphadenitis.*

at high risk of becoming infected with TB. Vaccination continued thereafter throughout Europe. The most lethal form of TB, miliary, and meningitis were thought to have been eliminated among BCG vaccinated children but the benefits of BCG vaccination in adults is not considered beneficial (eCureMe, 2003).[15]

The development of antibacterial treatments against tuberculosis with low toxicity levels was very challenging. In 1939, Selman Waksman of the University of California, successfully isolated an antibiotic (actinomycin), which was very toxic in both human and animal (Basel, 1998). Later, in 1942, he also isolated cultures of another streptomycete (streptomyces griseus), which ultimately gave rise to streptomycin. Streptomycin was used alone as a successful treatment regimen against TB until scientists detected resistance to the drug. Other antibiotics for TB treatment regimens used in combination with streptomycin and their date of discoveries are as follows: p-aminosalicylic acid (1949), isoniazid (1952), pyrazinamide (1954), cycloserine (1955), ethambutol (1962), and rifampin (rifampicin 1963). Treatments used in situations where drug resistance to TB has been developed are referred to as aminoglycosides and quilolones. Aminoglycosides include capreomycin, viomycin, kanamycin, and amikacin. Quilolones include ofloxacin and ciprofloxacin (Basel, 1998).

In recent years, TB among African Americans has followed a different pattern than when it was first introduced in that population.[16] The presentation of TB in African Americans today takes the same chronic form as in European Americans. This is an indication for the selection of TB resistance, which dates back 15 to 20 generations.

[15] The BCG is used in most developing countries where TB prevalence is high. It has shown to help reduce the risk of the development of tuberculosis (Bates & Stead, 1993).

Transmission

Tuberculosis is transmitted through person-to-person close contact. The droplet nuclei gain entry into the body through contact with a symptomatic individual's bodily aspirant.[17] Tuberculosis is not transmittable through shaking hands with or touching the clothes of the infected person (Houghton, 2002).

Infants can acquire the tubercle bacilli through aspiration or ingestion of their mother's infected amniotic fluid either before or during pregnancy (eCureMe, 2003). *Mycobacterium tuberculosis* is among the many bacteria that affect AIDS patients, and TB is known to accelerate the progression of HIV infection to AIDS (Bartlett, 2004; H. Hausler, 2000). Pulmonary TB occurs in 70 to 90 % of HIV-infected patients; moreover, its spreading is related to the patients' CD4+ T-lymphocyte cells. Infection with HIV is one of the major risk factors for patients to become infected with TB. Though the lifetime risk for the general population or immunocompetent persons to develop TB disease after *M. tuberculosis* infection is only ten percent, TB infection tends to be reactivated in HIV-infected patients very early and at a higher rate because of immunosuppression (Marques, Rioja, Oliveira, & Santos, 1996).[18]

Children with HIV infection are faced with increased frequency of childhood diseases such as ear infections and pneumonia. In addition to the previously mentioned illnesses, children in developing countries are further faced with chronic gastroenteritis, tuberculosis, and enlargement of the lymph nodes and liver. The majority of these children have neurological implications, which involve infection in the brain and/or developmental delay. Response to standard treatment for infections in HIV-positive

[16] It was frequently expressed in extrapulmonary disseminated form.
[17] Sneezing, singing, talking, coughing, and spitting (Board of Health, 2004; Houghton, 2002).

children is often not successful and these children often face severe complications that are life-threatening (F. Thomas, 2004; WHO, 2000a).

In HIV-infected persons, the clinical presentation of TB often depends on the amount of damage measured by the immune system; the amount of harm the virus has done to the person's CD4+ T-lymphocyte cells. In patients with HIV infection CD4+ T-lymphocytes 200 per microliter counts or above, sputum smear examinations for acid-fast bacilli (AFB) are often positive for this population. Patients with CD4+ T-lymphocyte counts below 200 are characterized by clinical symptoms including extrapulmonary TB diseases (Prasad et al., 2004). According to Marques (1996), diagnosing TB in AIDS patients should be different from that of non-AIDS patients. Marques (1996) suggests blood cultures, biopsy of organs (i.e., the liver), and aspirates of bone marrow and lymph nodes. In addition, in TB endemic areas or where HIV is also endemic or has high prevalence, urine, sputum, and blood cultures should be routine tests in AIDS patients suspected of having tuberculosis.

Tuberculous Meningitis

Meningitis is an inflammation of the membranes that cover the brain and spinal cord and can be caused by either viruses or bacteria (Board of Health, 2004; IDPH, 2004; F. Thomas, 2001). Analysis of a sample spinal fluid is used to determine which germ has infected the patient. Both viral and bacterial meningitis are contagious and are spread through person to person casual contacts (Board of Health, 2004).[19, 20, 21] Viral meningitis

[18] Each year, HIV-positive persons have a 7% chance increase of developing TB (eCureMe, 2003).
[19] Aseptic meningitis (DHPE, 2004).
[20] Sharing a glass, cup, eating utensils, and respiratory secretions (Board of Health, 2004).
[21] In addition, viral meningitis is said to be transmittable through fecal contamination.

is more prevalent, less severe than bacterial meningitis, and has an incubation period of three weeks (Board of Health, 2004; Irishhealth, 2004).[22, 23] Viral meningitis is most frequently caused by enteroviruses that affect the stomach and small intestine. Others are caused by mosquito-borne viruses or arboviruses (IDPH, 2004).[24] Conversely, bacterial meningitis can be serious, causing brain damage or death, and has an incubation period of ten days (IDPH, 2004).[25] Furthermore, bacterial meningitis requires the intervention of a clinician to determine which type of antibiotics should be administered.

Meningeal TB infection is very serious in children. Internationally, bacterial meningitis is a major cause of death and disability in children. A modest annual estimation of childhood deaths due to bacterial meningitis is 125,000 (Duke, Curtis, & Fuller, 2003; H. Hausler, 2000; Molyneux et al., 2003).[26] Studies of HIV-positive children with meningitis are limited but the most common cause of meningitis in this group is S. pneumonia and H. influenzae. Meningitis infection in HIV-positive children has a higher mortality rate than in HIV-negative children; moreover, it is among the top ten killers of children worldwide. In children with HIV, meningitis is a common cause of death, which is further complicated with pneumonia and other forms of bacterial sepsis. This often creates additional difficulties, causing chronic failure to thrive, and increases the incidence of diarrheal disease.

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[22] Viral meningitis has no known treatment; it is a mild infection and often clears up in one week or less than ten days.
[23] Treatment involves hydration of the patients and reduction of the fever.
[24] At least 80 different types found in fecal excretion of persons infected with viral meningitis.
[25] There are at least 50 types of bacteria that cause meningitis, but there are only two types that are worth mentioning: meningococcal and pneumococcal. The bacteria that cause these two types of meningitis live in the upper respiratory tract (throat, nose, sinuses or larynx) (Irishhealth, 2004).
[26] The case-fatality rate of bacterial meningitis is much higher in children in developing countries than in children in the developed countries.

Patients with HIV infection are at higher risk (than the general population) of acquiring the many different types of meningitis, which also include TB meningitis associated with HIV infection (Yechoor, Shandera, Rodriguez, & Cate, 1996). During the earlier phase of HIV infection, patients develop what is often referred to as a mononucleosis type illness, which is not known to be associated with encephalitis (F. Thomas, 2001).[27] In pediatrics, TB meningitis most frequently occurs in children aged six months to four years. It progresses much quicker in infants than in young children, and experts recommend initiation of treatments for TB meningitis before results of required examinations are known (eCureMe, 2003).

In HIV-positive adults, at least 25% of the meningitis cases are caused by *M. tuberculosis*; 25% are due to acute bacterial meningitis; viral meningitis accounts for approximately 15%; and cryptococcal meningitis between 10 to 15% of cases (Duke et al., 2003). Furthermore, *S. pneumoniae* is often the most common cause of meningitis in HIV-positive adults.

Osteomyelitis TB

The definition of osteomyelitis is an infection of the bone and bone marrow that is caused by bacteria, fungi, and AIDS-related opportunistic infections (Gunja, 1997).[28] The infection occurs elsewhere in the body, most frequently in the lungs, but is spread throughout via the bloodstream. This is referred to as haematogenous osteomyelitis. Osteomyelitis usually occurs after an open injury where there was contamination of the

[27] Usually within days or weeks.
[28] About 60% of all the cases are caused by Staphylococcus aureus. Others include *E. coli, Salmonella, Strep. Pneumonia, H. influenzae, Brucella,* and *tuberculosis bacilli.*

bone. Due to extensive blood circulation, children are more prone to becoming infected than are adults (Gunja, 1997; Health24, 2003).[29]

Lymph node TB

The lymphatic system is attacked by HIV upon entrance in the body. Typically, an HIV-infected person develops the acute retroviral syndrome within one to three weeks of infection.[30] These symptoms are not specific to HIV but necessary for the replication of the virus. The duration of these symptoms is between one and four weeks. The infected individual becomes asymptomatic thereafter, but is infectious for a period that could be ten years or longer before AIDS-related symptoms develop (Bartlett, 2004). Tuberculosis lymphadenitis occurs when *M. tuberculosis* infects the lymph nodes. It causes the lymph nodes to enlarge and form masses in the neck, which may sometimes drain in the skin. Tuberculosis lymphadenitis is the second most common type of TB in children (eCureMe, 2003). A study conducted in India found that among 1616 HIV-positive patients with known CD4+ counts, tuberculous lymphadenitis was present in 41% (Shobhana et al., 2002).

In Hochedez et al. (2003), lymph node TB was found to be more common in HIV-positive patients. However, it was also found among HIV-negative patients because of immunosuppression.[31] The characteristics of the lymph node TB in HIV-infected patients were more prominent. The study was conducted in France among a sample of 32 patients with lymph node TB: 13 HIV-positive and 19 HIV-negative.[32] The median time

[29] The lower leg or tibia.
[30] Fever, sore throat, headache, skin rash, tender lymph nodes and malaise.
[31] Intravenous drug use.
[32] The average age of these patients was 36.5 years for HIV-positive and 38.5 non-HIV patients.

spent before seeking care after the appearance of signs and symptoms related to lymph node TB in the two groups was one month for the non-HIV group and two months for the HIV-positive group. The tuberculin skin test produced a positive reaction in 63% of HIV-negative and 15% in the HIV-positive patients. The manifestation of lymph node TB among the HIV-positive patients was more disseminated and affected the abdomen more frequently.

In this chapter we discussed the past research and findings of studies on TB disease and HIV infection in both adults and children, and the complications of diagnosing TB in both HIV-positive and HIV-negative children, with an emphasis on resource-poor countries. In Chapter Two, we provide a global overview of HIV/AIDS and tuberculosis and its transmission and diagnosis in children. Moreover, the basics of tuberculin skin tests and BCG examination are discussed. In Chapter Three, we present the research design, study site and population, and statistical methods and data analysis. Next, in Chapters Four and Five, we present the results of the investigation and discussion of the findings, respectively.

CHAPTER II HIV & AIDS

The human immunodeficiency virus is the causative agent of AIDS (Rambaut, Posada, Crandall, & Holmes, 2004). Because of lack of accurate data, the determination of HIV-1 geographic origin is notional. Scientific evidence has documented the introduction of the HIV epidemic to be of zoonotic sourcing, particularly that of multiple species transmission among simian species (Lemey et al., 2003). Other scientific and non-scientific postulates on the origin of HIV have been attributed to some of the following: vaccines HIV-contaminated polio, smallpox, hepatitis and tetanus; the African green monkeys; African people, their cattle, pigs, and sheep; and the CIA (Lemey et al., 2003; Stine, 2003).

HIV-1 like symptoms or AIDS-related opportunistic infections (OIs) were first discovered among gay men in Los Angeles, California, in 1981; chronological data suggest symptoms seen among gay men in the U.S. were discovered among previously healthy Haitian men in Haiti in 1979 (CDC, 1998b). The French physician Luc Montagnier, co-discoverer of HIV, first heard of the "gay disease" in 1982 after Robert Gallo, of the United States, found the retrovirus that caused AIDS in patients in Los Angeles. At the time, there were only a small number of patients in France with the disease in question (Montagnier, 2002). Then, the retroviruses were known as the human T cell leukemia viruses, HTLV-1 and HTLV-2, and the process of identifying the virus in the blood was identical to that of today (Montagnier, 2002). In 1984, the collaborative

efforts of two groups of scientists, led by Luc Montagnier and Robert Gallo, discovered that HIV causes AIDS.

The chronology of the first few global AIDS cases is as follows: in 1959, scientists found evidence of HIV in blood samples collected from a patient in a malaria endemic town in Kinshasa, Zaire; the individual later died of AIDS. Evidence of HIV antibodies was found in a frozen sample of a 15 year-old male prostitute with the manifestation of Kaposi's sarcoma who died in 1969 (Stine, 2003). In 1976, a Danish surgeon who had worked in Zaire died of an AIDS-related illness. Another AIDS case with highly controversial results was presented in 1999 at the 11th International Congress of Virology.

Transmission and Diagnosis of TB and HIV in Children

HIV Transmission in Children

Vertical transmission is the most common mode of HIV transmission in children. The neonate can become exposed to maternal infected birth fluid during the birthing process; furthermore, post-partum HIV infection poses a 30% risk of transmission in infants through breast milk (WHO, 2000b). Other sources of HIV infection in infants and children include sexual abuse, transfusion with HIV-contaminated needles, blood or blood products, and child prostitution (WHO, 2000b). Research has not yet shown the determinant stage in which HIV infection occurs (in utero, during delivery, or postpartum), moreover, it is difficult to pinpoint the exact stage the virus starts depleting the immune system (F. Thomas, 2004).

Diagnosing HIV in Infants, Children, and Adolescents

There is great similarity in childhood related illness regardless of HIV status. In general, most of the pathogens that cause illness in children also cause illness in HIV-positive children but at a higher rate.[33] Though both HIV-positive and HIV-negative children are often affected by similar pathogens, there are some illnesses that occur more frequently in HIV-positive children than in their HIV-negative counterparts (WHO, 2000a).

The presentation of HIV-related infections in children varies. Some HIV-infected children develop severe clinical signs and symptoms very early after becoming infected with the virus, some may develop signs and symptoms within a year, while others can remain asymptomatic until teenage years.[34] According to WHO (2004), healthcare providers are to suspect HIV in infants or children who have recurring infections of pneumonia, meningitis, sepsis, and cellulitis in a period of 12 months; the presence of oral thrush that lasts more than one month after the neonatal period; chronic parotitis either with or without pain or fever for more than 14 days; generalized lymphadenopathy; the presence of hepatospenomegaly without any viral infections (i.e., cytomegalovirus); the persistence of or recurrent fever that lasts more than 7 days; neurological dysfunction; HIV dermatitis; and herpes zoster (shingles).[35] Further, there are signs and conditions that are specific to children with HIV: pneumocystic carinii pneumonia (PCP),

[33] e.g., pneumococcal infections and pulmonary tuberculosis.
[34] During their first year of life.
[35] Progressive neurological impairment, microcephaly, delay in achieving developmental milestones, hypertonia, or mental confusion.

oesophageal candidiasis, lymphoid interstitial pneumonia (LIP), and shingles across several dermatomes or Kaposi sarcoma.[36]

In settings where resources are limited or where testing for HIV in children is unavailable, diagnosing AIDS in children is done through observation for at least two major and two minor signs. The major signs include: weight loss or abnormal slow growth; chronic diarrhea for more than one month; and prolonged fever for more than one month. The minor signs are: generalized lymph nodes enlargement; recurrent common infections of the mouth and/or throat; persistent cough; generalized rash; confirmed HIV infection in the mother; and fungal infections.[37] The following criteria are used to diagnose HIV in infants, children, and adolescents:

1. Diagnosis: HIV-infected

    a) A child less than 18 months of age who is known to be HIV seropositive or born to an HIV-infected mother and: i) has positive results on two separate determinations (excluding cord blood) from one or more of the following HIV detection tests: HIV culture, HIV-DNA-PCR or HIV-P24 antigen; ii) meets criteria for AIDS diagnosis based on the 1987 AIDS surveillance definition.

    b) A child 18 months of age born to an HIV-infected mother or any child infected by blood, blood products, or other known modes of transmission (e.g. sexual contact) who: i) is HIV-antibody positive by repeated reactive EIA and confirmatory test; or ii) meets any of the criteria in one of the previously mentioned.[38]

2. Diagnosis: perinatally exposed

    a) A child who does not meet the criteria above who: i) is HIV seronegative by EIA confirmatory test (WB or IFA) and is <18 months of age at the time of the test; or ii) had unknown antibody status, but was born to a mother known to be infected with HIV.

3. Diagnosis: seroreverter (SR)

[36] Common in infants aged six months or younger.
[37] Ear and throat.
[38] Western blot or immunofluorescent assay.

a) A child who is born of an HIV-infected mother and who: i) has been documented as HIV-antibody negative;[39] and ii) has had no other laboratory evidence of infection;[40] and iii) has not had an AIDS-defining condition.

4. Criteria for HIV infection for persons >13 years:

a) Repeat reactive screening test for HIV antibody with specific antibody identified by the use of supplemental test (e.g. WB, IFA);[41] i) direct identification of the virus in the host tissues by virus isolation; ii) HIV antigen detection; iii) a positive result on any other highly specific licensed test for HIV (Foshee, 2004).

Diagnosing TB in Infants, Children, and Adolescents

Tuberculosis diagnosis in the adult HIV-positive patient is more straightforward than the child, secondary to the clinical presentation of adult TB.[42, 43] Misdiagnosis and over-diagnosis of TB disease is common in children due to the fact that some patients are asymptomatic or some of the symptoms are nonspecific. In resource poor settings, diagnosing TB in children employs a combination of clinical and epidemiological methods, but the diagnosis relies heavily on clinical suspicion (Chintu & Zumla, 1995; eCureMe, 2003; Salazar et al., 2001).[44] Because of their immature immune systems, children who are infected with TB are more likely to progress to TB disease. Tuberculosis infection in children usually indicates recent exposure rather than the reactivation of latent TB. While children are at increased risk of developing TB disease, most signs and symptoms of tuberculosis are not obvious. Most often, two main

[39] Two or more negative EIA tests performed at 6-18 months of age or one negative EIA test after 18 months of age.
[40] Has not had two positive viral detection tests, if performed.
[41] Enzyme Immunoassay.
[42] For instance, a typical case might include an individual who does not produce sputum, or when sputum is produced, it is more likely not to contain a large quantity of the mycobacterium, sputum cultures are often negative, chest x-rays may appear atypical and the patient is more likely to manifest extrapulmonary TB.
[43] Particularly infants.

diagnostic tools are important: AFB smears and cultures.[45] A spinal tap is recommended as in inclusion for meningeal TB diagnosis.

The Basics on Tuberculin Skin Tests and BCG Immunization

There are three types of tuberculin skin tests**:** Mantoux, Monotest, and TINE test. These tests are used to measure the body's immune response to the purified protein derivative (PPD) injection. The Mantoux test is an intradermal injection of PPD.[46] TINE/MONO tests are instruments that are impregnated with PPD, and these are pressed into the skin of the forearm. The reaction of the Mantoux and Mono tests are measured between 48 and 72 hours and results are recorded in millimeters. Using a similar time interval, the TINE test results are measured based on the amount of blistering on the skin.

Results of tuberculin skin tests are dependent on several factors, which include exposure to TB, contact case, HIV status, country of origin, BCG vaccine, and lifestyle.[47] A positive test indicates TB infection, not disease. Conversely, a negative skin test does not eliminate TB disease. A TB skin test may be negative yet the disease may still be present if the individual has HIV infection, malnutrition, severe viral infections, severe disseminated TB, cancer, and use of immunosuppressive drugs.

The Bacille Calmette Guerin immunization (BCG) is given at birth to children born in hospital. Now, this practice is strictly limited to developing countries. In 2001, the immunization rate for children under one year in Haiti was 49% (PAHO, 2001). Immunization with BCG may cause a positive reaction tuberculin test several years after

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[44] The vagueness in symptoms is common with TB; some of these symptoms include, weigh loss, night sweats, fatigue, loss of appetite, and low-grade fever.
[45] Help determine which drugs will work against the organism.
[46] Into, not below, the skin.

the vaccination, but this reaction is often weaker and is referred to as a natural infection with *M. Tuberculosis* (H. Hausler, 2000). In diagnosing TB in children with HIV infection, the interpretation of the tuberculin test is even more difficult and should be followed by radiographic analysis and other applicable examinations.[48]

[47] IDU, homelessness, alcoholism and malnutrition.
[48] Follow recommendations for the necessary extrapulmonary TB.

CHAPTER III METHODS

Research Design

This is a retrospective chart review of all children aged 14 and younger with TB disease admitted to Grace Children's Hospital. There are two objectives: (1) describe the cases in terms of clinical measures and demographic characteristics; and (2) use a cross-sectional design to analyze the data.

Study Population

The data set for this exploratory study is based on a chart abstraction form developed in accordance with medical chart forms the investigator obtained from the hospital on a previous trip. At GCH, all children hospitalized for TB disease are screened for HIV, except in August of 2002 and the year of 2003, when, due to lack of funding, only suspected HIV cases were tested. Inclusion criteria include all confirmed hospitalized pediatric TB cases aged 14 years and younger between January 1, 1999 and December 31, 2003, and were reviewed and separated by outcome status: extrapulmonary TB and non-extrapulmonary TB.

The previously stated five-year period was arbitrarily chosen with no preliminary pilot study done. Pregnant teens, prior treatment and hospitalization for TB, and Haitian children born in the U.S. were excluded. Pregnant teens were excluded because we wanted to minimize the possibility of including children who may have acquired HIV

infection through sexual contact; children with prior hospitalization and treatment for TB were excluded to minimize the potential bias of MDR-TB because GCH does not do drug-susceptibility testing; and Haitian children who were born in the U.S. were excluded because they may have a better health profile (e.g., access to primary health care, better nutrition) than the average child hospitalized at GCH.

Study Site

This study was conducted at the Grace Children's Hospital (GCH), a referral pediatric TB hospital and the only pediatric TB hospital in Haiti. GCH was founded by Jim and Virginia Snarley in 1967. The hospital is financed and operated by a Christian service organization, the International Child Care. It has been in operation for 37 years and provides additional services, especially primary health care, general pediatric clinic services, eye care to adults and children, adult TB treatment, reproductive health services, and HIV/AIDS counseling and testing to the community. In August of 2004, GCH added antiretroviral therapy to its list of services. Grace Children's Hospital oversees the majority of TB cases in Haiti and operates mostly on an outpatient system; it is the only tertiary pediatric hospital that dedicates over 80% of its facility to treat urgent pediatric TB cases and other various diseases.[49]

[49] Malnutrition, severe diarrhea, and upper respiratory infections.

Statistical Methods and Data Analysis

Objective 1: Descriptive Study

To assess if there is a relative association between the manifestation of EPTB and HIV infection in children hospitalized for TB treatment, variables will include clinical measures and demographics characteristics. The available sample size of 615 pediatric TB cases included 492 PTB and 210 EPTB. Data collection was based on a chart abstraction form developed with information compiled from the hospital on a previous visit by the principal investigator. Age groups were created to measure the number of cases per group, EPTB types, and HIV status including those patients who were not tested, gender, mortality data, co-morbidity, nutrition status, TB contact, BGC vaccination, and bacteriologic examinations (Table 1). The co-morbidities at time of TB diagnosis included anemia, gastroenteritis, intestinal parasite, malaria, sickle cell anemia, typhoid, and meningitis. The nutrition status had two levels: under-five and older children. The under-five group had *degrees* of undernourishment. TB contact included, mother, father, grandmother, a deceased parent (mother or father), neighbor and other relatives (cousin, aunt, brother, sister and/or uncle). We created a variable called Tbgroup, which included both PTB and EPTB; all the necessary information was recorded based on TBgroup status (Table 2).

Objective 2: HIV and EPTB manifestation in TB-infected children

Statistical analysis was conducted using SAS statistical software package version 9.1. Logistic regression procedure was used to compute the univariate and multivariate analyses. The variables included were TBgroup (PTB vs. EPTB), gender, age, HIV

status, nutrition status, and only co-morbidities that were greater than 5% (anemia, intestinal parasite, and malaria). Descriptive statistical measurements were done on the following variables: age, gender, patient weight, nutrition status, immunization for the BCG vaccine, TB contact, sputum culture examination, co-morbidities, and mortality.[50, 51] In the univariate portion of the analysis, we determined the probability of patients with pulmonary TB on the basis of age, gender, HIV status, nutrition, anemia, malaria, and intestinal parasite. Adjusted values for EPTB were obtained for the following: age, gender, and nutrition status. Though both are valid in measuring the level of association, Chi-square rather than odds ratio measures was preferred for this study to indicate statistical significance. The default alpha ($\alpha = 0.05$) was used for Chi-square and p-value.

[50] Children under-five are assigned degrees of malnutrition (primary, secondary, and tertiary), marasmus, and kwashiorkor; older children do not have degrees of malnutrition, they are reported as either malnourished or normal.

[51] Anemia, malaria, intestinal parasites, gastroenteritis, typhoid, sickle cell anemia and a combination of two, three or four of the previously mentioned conditions.

CHAPTER IV RESULTS

Objective 1: Descriptive Results

This study sought to describe the demographics of children with pulmonary TB (PTB) and extrapulmonary TB (EPTB) in a pediatric TB hospital in Haiti. Data for 615 hospitalized, confirmed pediatric TB patients were collected for a five-year period from January 1, 1999 to December 31, 2003. These included 492 cases with only pulmonary TB and 210 whose TB infection had progressed to extrapulmonary (EPTB). Eighty-eight of the extrapulmonary cases also had a concurrent diagnosis of pulmonary TB. The most common sites of EPTB included lymph node, pleura, bone and joint, and peritoneal (Table 1).

There were 315 (51.4%) males and 298 (48.6%) females with a mean age of 5.40 years (range 0.17 - 14 years), with 214 (37.9%) of the patients aged 0-2 years.[52] One hundred and seven (17.4%) patients were HIV-positive. Three hundred eighty-eight (63%) patients had one or more additional co-morbidities. These included anemia 299 (48.6%), intestinal parasites 93 (15.1%), malaria 58 (9.4%) and gastroenteritis 19 (3.1%). Nearly 85% of the children were undernourished. Eighty-three patients, 13.5 percent of the children, died in the hospital.

Four hundred-eighteen (68.0%) of the patients lived in the major metropolitan area.[53] BCG vaccination status of 294 (59%) patients was reported, and BCG vaccination

[52] Two of the records reviewed did not have documentation of patients' gender.
[53] One hundred-two (16.5%) of the residential data were missing.

percentage for both the under-five and older than five years population was 151(51.5%) and 143 (48.6%), respectively. Two hundred fifty-five (48.3%) of the total population had a positive PPD with 5 (1%) of that population having a PPD reaction that is referred to as phlyctenulaire.[54]

Two hundred fifty-two (41%) of the patients had a contact source for TB [65 (25.8%) had a mother who was an active TB case, 25 (10%) had a father who was an active TB case, 61 (24.3%) had at least one relative with active TB (i.e., uncle, aunt, and cousin), 50 (19.8%) had a neighbor with TB, and 31(12.3%) had parent who died of TB disease (mother/father)] **(Table 1)**. One hundred-twenty (19.5%) of the AFB sputum examination data were missing, however, AFB sputum culture was positive for 79 (16%) and the tubercle bacilli was detected in 483 (97.6%). Sputum smear data are not considered reliable because they were found on different parts of the charts. In other words, it was very difficult to determine if the tests were requested or done.

Objective 2: Association of HIV with EPTB manifestation in TB-infected children

Tables 2 through 4 highlight differences between children with localized pulmonary TB and children whose TB had progressed to extrapulmonary locations. Percent males were 47.8% and 57.9% in PTB and EPTB groups respectively ($p<0.05$, Table 2). Children with EPTB were much more likely to be over the age of two (74% vs. 56% in PTB group), resulting in a highly significant Chi-square statistic. The overall difference in mean age, however, was only borderline significant with children with

[54] It is an inflammation of the injection site that may contain pus or other types of fluid; this reaction occurs as a result of the Mantoux test.

EPTB being slightly older [p=0.059] and age was only weakly associated with TB group. **(Tables 3, 4)**.

Children in the EPTB group were somewhat less likely to die in the hospital (10.0% vs. 15.4%, p=0.066). They were much less likely to be HIV-positive (8.6% vs. 22%, p<0.01). Seventy-seven (12.5%) of the patients' HIV status were unknown. The proportion of patients with unknown HIV status in both PTB and EPTB were equivalent, 50 (12.4%) and 26 (12.4%) respectively. Although HIV-negative co-morbidities were not found to be significant at any level, patients with EPTB also had a lower proportion of anemia, malaria, sickle cell anemia, and typhoid than did PTB patients **(Table 2)**.

Patient body weights were recorded in kilograms. The mean weight for 450 patients was 20.16 kg [range 1.00 – 56.50]; however, 165 (26.8%) of patients' weight data are missing. The percentage of undernourished children in the EPTB and PTB groups were 74.4% and 86.6% [p<0.01]. In those under-five for whom the degree of undernourishment was recorded, the *degree* of undernourishment was significantly less severe for the EPTB group [p<0.0006] **(Table 2)**.

Following multivariate adjustments, the negative association between EPTB and HIV status remained statistically significant as well as the negative association between EPTB and malnutrition; gender was still borderline significant [p=0.062] **(Table 4)**.

Table 5 combined the two groups and assessed risk factors for mortality in the sample. The OR was greater than 4 for HIV and was greater than 2 for poor nutrition status [p<0.01 for each]. There was no association in this model between EPTB and mortality. The apparent univariate association between EPTB and reduced mortality can be explained by lower prevalence of HIV and poor nutrition status in the sample.

CHAPTER V DISCUSSION

Objective 1: Descriptive results

The initial research question to determine if there would be a positive association between extrapulmonary TB (EPTB) and HIV infection in the children hospitalized at Grace Children's Hospital was not borne out by the reviewed data. Instead, we had the surprising results that among TB-infected children, children with EPTB were less likely to be HIV-positive than children without EPTB. Over 50% of the EPTB compared to 48% of the PTB cases were males. Contrary to adult studies, EPTB rather than PTB was found to be associated with being female, non-Hispanic black, and HIV-positive (Antony, Harrell, Christie, Adams, & Rumley, 1995; Yang et al., 2004).

In terms of undernourishment, co-morbidities and HIV-infection, PTB patients were sicker than the EPTB patients (**Table 2**). There are two possible explanations for this finding: the potential for misclassification or diagnosis bias (e.g., differential diagnostic practices for HIV-positive children that may be related to lack of laboratory resources), and the natural history of TB disease. The diagnosis of TB at the Grace Children's Hospital is based on its basic examination for TB (e.g., clinical signs and symptoms, PPD, chest radiograph, sputum tests for older children, and contact case investigation), but relies on two principle factors: clinical signs and symptoms, and TB contact case. The physicians often do not rely on chest radiographs because they are not considered to be reliable in diagnosing many types of EPTB and are sometimes

impossible to acquire (i.e., cost, problems with the hospital's machine or political unrest that often causes businesses to close). Bacteriologic examination is necessary to diagnose EPTB.

When it comes to children with HIV infection, the potential for diagnosis bias, especially differential diagnostic practices, is suspected to be involved. In these HIV-positive children, physicians may be less likely to request laboratory examination to confirm TB diagnosis, but are more likely to request these examinations for HIV-negative children.

While HIV-positive patients were two to three times more likely to have not had sputum culture documentation on their medical records, the total number of patients with PTB without a sputum culture was 88 (21.8%). To verify this fact, we excluded the PTB patients with negative sputum culture and created two sets of contingency tables.[55] We first focused on the PTB patients with positive sputum culture and all the patients with EPTB to calculate the odds ratio. Though this caused a decrease in the number of PTB patients with HIV-infection, the negative association between EPTB and HIV-infection observed was even weaker (OR = 0.89 vs. 0.431). Then, when we combined the PTB patients with sputum culture positive with the PTB patients without sputum culture documentation, and included all the EPTB patients, we determined that the association between EPTB and HIV-infection increased (OR= 0.26 vs. 0.431).

Among the HIV-infected patients with PTB, 50 (56.2%) had a negative sputum culture, but were treated for TB disease. With more than 50% of the patients with negative sputum culture, it is suspected these patients could have had some other HIV

[55] Sputum culture is not necessary for the diagnosis of EPTB.

disease associated pneumonia (e.g., lymphoid interstitial pneumonia), and that their disease was not at all TB-related.

Tuberculosis is very difficult to diagnose in children with HIV as it is seldom confirmed by culture. This may sometimes lead to over-diagnosis of PTB or could also be mistaken for other HIV-related opportunistic infections. In a study investigating the outcome of tuberculosis in children with AIDS in a culture positive sample, the study found that 25% of the patients had lymphocytic interstitial pneumonia (LIP), and 42% had pneumonia. It is documented that both adult and pediatric AIDS patients have chronic lung diseases together with atypical x-rays presentation, which may often lead to a misdiagnosis of tuberculosis (Chan et al., 1996).

In another pediatric study of 14 HIV patients with culture confirmed TB, five of these patients were found to have EPTB in conjunction with PTB involvement with two children with central nervous system TB. Four of the patients had positive culture for *M. tuberculosi*s between 4 to 10 months after the initial diagnosis of TB; three of these patients were found to have drug-resistance to TB, and the fourth patient had a source case with TB drug-resistance (Schaaf, Geldenduys, Gie, & Cotton, 1998). Furthermore, BCG vaccination data was reported for nearly 60% of the patients with 52% of the reported data being in the under-five population. It is reported that BCG vaccinated children with compromised immune systems (e.g., most of our population) are known to develop local reactions and disseminated disease (Khouri, Mastrucci, Hutto, Mitchell, & Scott, 1992).

Objective 2: Association of HIV with EPTB manifestation in TB-infected Children

In all TB cases, the lungs are the portal of entry for the bacilli. The natural history of TB in children is very complex because many of the clinical manifestations are non-specific to TB infection or disease. Children aged 3 years and younger are more susceptible to TB and are more likely to develop EPTB (W. Hausler & Sussman, 1998). Because of immature immune systems, children are more vulnerable to becoming infected through an adult (sputum smear-positive) with active TB disease (Coberly & Chaisson, 2001). In our study, children with EPTB were more likely to be over the age of two (74% vs. 56% in PTB group). The overall difference was only slightly significant with children with EPTB being slightly older [p=0.059] and age only weakly associated with TB group **(Table 3, 4)**.

The prevalence of HIV in Haiti neared six percent, and although TB is endemic in the population, there is no published statistical measurement of pediatric TB in that population.[56] Jacobs (1997) states that HIV infection in the adult population has a direct effect on TB infection and disease in children. In other words, TB disease in young children is used as a measurement of TB in the general population in an area (H. Hausler, 2000). Forty-one percent of the children had a TB contact source with 50% having a parent or close family member as their contact, and over 12% lost a parent to TB disease **(Table 1).**

This study shows that among all the TB cases admitted at GCH between 1999 and 2003, patients with EPTB were less likely to die in the hospital (10.0% vs. 15.4%, p=0.066) and much less likely to be HIV-positive (8.6% vs. 22.0%, p<0.01). Although 12.5% of the patients were not tested for HIV infection, the proportion of non-tested

patients for both groups was equivalent in both PTB and EPTB **(table 2)**. In other words, regardless of age, patients with HIV were more likely to have pulmonary rather than EPTB. While co-morbidities among the HIV-negatives did not prove to be significant at any level (anemia, malaria, intestinal parasite, gastroenteritis, sickle cell anemia, and typhoid), patients with EPTB had lower proportion of co-morbidities.

Patients with EPTB had a better risk profile than did PTB patients. Patients with EPTB were more likely to survive. Extrapulmonary TB patients seen at GCH may have been those who survived the disease while others with EPTB compounded by HIV-infection died prior to coming to the hospital. In other words, the observed cases can be said to be a selected number of children with fewer number of those with HIV-infection. Moreover, the children with EPTB were less likely to have nutritional deficiencies; this also supports the fact that they would have died if they were malnourished in addition to HIV infection and EPTB.

A study conducted in New York City found EPTB was more common among HIV-positive rather than the HIV-negative cases reviewed (38% vs. 13%) (P. Thomas et al., 2000). In this case, the conclusion drawn from these data are correct, which is, children with EPTB seen at GCH are probably a false representation of pediatric EPTB and HIV-infection in Haiti. Based on these results, this study is not an accurate representation of pediatric EPTB in Haiti.

Grace Children's Hospital is a tertiary referral hospital that is often the last facility patients are referred to for TB treatment. This means, by the time these patients arrived at this hospital, they had already been to many other centers, clinics, and other hospitals, and that their cases had already advanced to the critical stage of TB disease.

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[56] Rate for 2002 was 147 cases per 100,000 persons.

Potential biases involved are referral, detection, and selection biases. Patients were referred to GCH by other institutions based on treatment failure and lack of accurate diagnosis. During a 10-month period, GCH lacked the resources to test all patients for HIV, and therefore, those tested were based on clinical suspicion. Children with HIV-infection were less likely to have had laboratory confirmation for TB disease (Table 6).

As is the case in many resource-poor settings, diagnosing pediatric TB is difficult and it is often primarily focused on clinical signs and symptoms, and TB contact case investigation. In addition to the potential for misclassification or diagnosis bias and natural history of TB, the divergent findings can further be explained by the fact that GCH physicians lack some of the basic diagnostic tools in diagnosing EPTB. Since both types of TB are treated with similar antibiotics, physicians may treat patients regardless of which types of TB disease they present. In other words, there may be an under-reporting of EPTB cases in patients with HIV infection since the treatment regimen for both PTB and EPTB is similar (except in cases of miliary TB, bone and joint TB, or TB meningitis where the length of treatment is longer).

Haiti is an impoverished nation plagued by political violence and lacks the resources and infrastructure to provide adequate primary and basic healthcare to the majority of its citizens. It is estimated that 40% of the population uses traditional medicine not by choice, but because it is the only option open to them. These treatments may last from several weeks to months, and only when progress in their treatment fails, patients may seek care from the local health center, which may be located far from their homes.[57]

[57] Rate for 2002 was 147 cases per 100,000 persons.

Many obstacles may keep patients from acquiring the necessary healthcare, such as cost, sporadic political violence, and transportation. Transportation is a major issue, not only due to cost, but also because merely 13% of the roads in Haiti are covered with asphalt and accessible for public buses (CDC, 2004). In rural Haiti, most people have to walk for hours before boarding public buses. Once they arrive at the local health center, tests may be requested based on clinical presentation and history. The individual is provided with a prescription to fill or may possibly be referred to the regional hospital. In the case of tuberculosis, GCH is the only pediatric TB hospital in the country serving all Haiti's nine departments. According to information in the medical charts and the physicians at GCH, it is the teaching hospital, *L'Hôpital Universite d'Etat d'Haiti (HUEH)* that often referred parents to GCH after they were referred to the general hospital by other facilities.

Some of the limitations of this study include a significant amount of missing data (e.g., age, HIV status, sputum culture), and records for sputum smear were not consistently reported in one area of the charts and therefore were not usable because we could not differentiate between requesting the specimen examination and test performed. CD4+ cell counts and viral loads data were not reported, thus patients with HIV-infection could not be differentiated from those with AIDS. Based on previous studies, it was assumed that the patients contracted HIV from their mothers, because there was no record on route of transmission.

According to the Centers for Disease Control and Prevention, 90% of pediatric HIV infection occurs through perinatal (vertical) transmission (CDC, 1998a). Haiti has a high illiteracy rate (48%) and over 80% of the population lives in poverty. Its people

suffer from some of the most curable disease. Our recommendation is for policy-makers, non-governmental agencies, and both international and national charitable organizations to work with churches and grassroots organizations to institute TB and HIV screenings.

Further, it is necessary to provide training to these local facilities to help communities in identifying the common symptoms of TB disease and refer these individuals to a healthcare facility for treatment. There is a stigma attached to both TB and HIV in Haiti, which plays a direct role in delaying medical attention. TB and HIV screening and education should be part of pre-natal care, so that pregnant women can be treated and educated on identifying signs and symptoms of both diseases.

Tuberculosis and HIV are both prevalent in Haiti. The task of combating both infectious diseases will involve the concerted efforts of all parties. This includes allocation of necessary resources, updated information so that health care providers can be knowledgeable on both TB and HIV to minimize misdiagnosis, and ultimately, patients need to seek care much earlier in the disease process.

TABLES

Table 1: Descriptive Statistics	N= 615
	n(%)
Gender **(% Males)**	315(51.4)
Age Group	
0-2 years	214(37.9)
3-5 years	103(18.2)
6-8 years	87(15.3)
9-11 years	78(13.8)
12-14 years	83(14.7)
Age not recorded in chart	50(8.1)
Mean Age	5.4
HIV Status	
HIV+	107(17.4)
HIV-	431(70.1)
Not Tested	77(12.5)
Pulmonary TB	492(80.0)
Extrapulmonary TB	210(34.2)
EPTB Types	
Bone and Joint	21
Intestinal	1
Lymph node	62
Miliary	4
Meningitis	6
Pericarditis	1
Peritonitis	12
Pleurisy	35
Pleuropulmonary	51
Skin	1
Lymph node and Peritonitis	4
Lymph node and Pleurisy	4
Lymph node and Bone & Joint	2
Lymph node and Meningitis	1
Lymph node and Skin	1
Peritonitis and Pericarditis	1
Peritonitis and Pleuropulmonary	3
Pleurisy and Pericarditis	1
Percent Died	83(13.5)

Co-morbidity	
Anemia	299(48.6)
Gastroenteritis	19(3.1)
Intestinal Parasite	93(15.1)
Malaria	58(9.4)
Meningitis	1(0.16)
Sickle Cell Anemia	13(2.1)
Typhoid	5(0.81)
Nutrition Status	
All Children	
Normal	96(15.6)
Undernourished	518(84.4)
Under-5	
Normal	35(11.2)
Undernourished: primary	69(22.0)
Undernourished: secondary	96(30.7)
Undernourished: tertiary	79(25.2)
Undernourished degree unknown	16(5.1)
Marasmus	11(3.5)
Kwashiorkor	7(2.2)
TB Contact Case	
No TB Contact	103(16.7)
Contact unknown	260(42.3)
TB Contact	252(41)
Mother	65(25.8)
Father	25(10)
Deceased Mother/Father	31(12.3)
Grandmother	29(11.5)
Neighbor	50(19.8)
Other Relatives	61(24.2)
Sputum Culture	
Sputum Culture (+)	79(12.8)
Sputum Culture (-)	416(67.6)
Culture not done	120(19.5)

§ **Percentages of characteristics are based on non-missing values**

Table 2: Pulmonary and Extrapulmonary Tuberculosis				
	PTB n(%)	EPTB n(%)	Chi Square	p-value
Gender (% Male)	193(47.8)	121(57.9)	5.5131	0.0189
Age Group			25.3586	<0.0001
0-2 years	165(43.9)	49(25.9)		
3-5 years	51(13.6)	52(27.5)		
6-8 years	56(14.9)	31(16.4)		
9-11 years	53(14.1)	25(13.2)		
12-14 years	51(13.6)	32(16.9)		
Mean age	5.16	5.84		
Sputum Culture not done	88(21.8)	32(15.2)	17.7739	0.0001
Percent Died	62(15.4)	21(10.0)	3.3786	0.066
HIV Status			17.9242	0.0001
HIV+	89(22.0)	18(8.6)		
HIV-	265(65.6)	166(79.1)		
Not Tested	50(12.4)	26(12.4)		
Co-morbidity N= 388				
Anemia	206(51.0)	92(43.8)	2.8512	0.0912
Malaria	42(10.4)	16(7.6)	1.2457	0.2644
Gastroenteritis	15(3.7)	4(1.9)	1.5064	0.2197
Intestinal Parasite	55(13.6)	38(18.1)	2.1591	0.1417
Typhoid	4(1.0)	1(0.5)	0.4518	0.5015
Sickle Cell Anemia	10(2.5)	3(1.4)	0.7304	0.3931
Meningitis	1(0.25)	0	0.5206	0.4706
Nutrition Status N=313				
All Children n(%)			23.5174	<0.0006
Normal 96(15.6)	50(13.7)	46(23.6)		
Undernourished 518(84.4)	314(86.6)	149(74.4)		
Under-5			23.8516	0.0006
Normal	16(7.8)	19(17.6)		
Undernourished: primary	39(19.0)	30(27.8)		
Undernourished: secondary	65(31.7)	31(28.7)		
Undernourished: tertiary	64(31.2)	15(13.9)		
Undernourished degree unknown	7(3.4)	9(8.3)		
Marasmus	10(4.8)	1(0.93)		
Kwashiorkor	4(2.0)	3(2.8)		

§ **Percentages of characteristics are based on non-missing values**

Table 3:Crude Association of HIV with the EPTB Manifestation in TB-Infected Children			
Odds Ratio Estimates			
Effect	Point Estimates	95% Wald Confidence Limits	
HIV Status	**0.323**	**0.188**	**0.555**
Gender	0.668	0.477	0.936
Nutrition Status	0.781	0.689	0.884
Anemia	0.749	0.536	1.048
Malaria	0.711	0.39	1.297
Intestinal Parasite	1.402	0.892	2.203

Table 4: Adjusted Association of HIV with EPTB Manifestation in TB-infected Children			
Odds Ratio Estimates			
Effect	Point Estimates	95% Wald Confidence Limits	
HIV Status	**0.431**	**0.228**	**0.749**
Gender	0.689	0.467	1.018
Age	0.967	0.913	1.025
Nutrition Status	0.774	0.651	0.921
Anemia	1.05	0.709	1.557
Malaria	0.815	0.407	1.632
Intestinal Parasite	1.216	0.736	2.007

§HIV association is adjusted for all other covariates in the table

Table 5: Multivariate odds ratio for association of tabled characteristics with mortality			
Odds Ratio Estimates			
Effect	Point Estimates	95% Wald Confidence Limits	
HIV Status	**4.179**	**1.625**	**10.751**
PTB vs. EPTB	1.068	0.379	3.008
Gender	0.478	0.194	1.178
Age	0.93	0.792	1.091
Nutrition Status	2.139	1.492	3.065
Anemia	0.899	0.344	2.352
Malaria	1.436	0.454	4.537
Intestinal Parasite	1.736	0.504	5.981

Table 6: TB*HIV*Sputum Indicator n(%)		
	PTB	EPTB
HIV+	33(37.1)	7(38.8)
HIV-	44(16.6)	21(12.7)
Not Tested for HIV	11(22)	4(15.4)

§ Patients with no sputum record examination, n=120

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APPENDIX A

Table A-1

Timetable for Development of TB in HIV-Negative Cases	
Form of tuberculosis	Time from infection to onset
Immune conversion	4-8 weeks
Primary complex	1-3 months
Local lung complications	3-9 months
Pleural effusion (usually teenagers)	3-12 months
Miliary/meningeal	3 months onwards
Bone	10-36 months
Skin	5 years onwards
Renal	10 years onwards
Secondary breakdown	5 years onwards

(Hoskyns, 2003)