CAN TUBERCULOSIS RELAPSE BE PREDICTED?

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DECLARATION

I ..... GERSHOM CHONGWE .....hereby certify that this dissertation is the product of my own work and, in submitting it for my Master of Public Health degree, further attest that it has not been submitted in part or in whole for a degree, diploma or certificate to this or another university.

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APPROVAL CERTIFICATE

This dissertation, entitled "Can Tuberculosis Relapse be Predicted?" by Gershom Chongwe is approved in partial fulfilment for the award of the degree of Master of Public Health of the University of Zambia in the year 2006.

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ABSTRACT

Objectives: The main objectives were to determine the characteristics of TB patients with relapse, identify the risk factors for TB relapse so that we can prevent future episodes.

Design/setting: This was a case control study conducted at five urban clinics in Lusaka district. We recruited 184 patients, 92 were patients who had had TB, successfully treated but relapsed (the cases), and these were compared with those who had previously been treated for TB in full but had not relapsed for at least six months (controls).

Results: The age distribution between the cases and controls was significantly different ($p = 0.048$). Older patients were less likely to relapse than younger patients. No sex difference was observed between the cases and the controls. A positive sputum smear had a high sensitivity in predicting relapse but a low positive predictive value. The sensitivity of DOTS in predicting relapse was relatively high at 70.7 percent though it also had poor positive predictive value. Having an HIV infection had a sensitivity of 64.1 with lower positive predictive value.

Conclusions: HIV infection, sex, area of residence and severity of initial illness were all poor predictors of relapse. Living in overcrowded communities and having an HIV infection are well recognised risk factors for tuberculosis aetiology but they may not be important in predicting which patients are more likely to relapse.

Recommendations: We need to do more research into more reliable and cost effective ways of identifying which patients are more likely to relapse and find better ways of preventing relapse. We also need to work towards ensuring that all centres providing tuberculosis services in this country also provide DOTS to sputum positive patients.

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LIST OF ABBREVIATIONS

TB	-	Tuberculosis
UTH	-	University Teaching Hospital
PPV	-	Positive Predictive value
NPV	-	Negative Predictive Value
HIV	-	Human Immunodeficiency Virus.
AIDS	-	Acquired Immune Deficiency Virus
AAFB	-	Alcohol Acid-Fast Bacillus
WHO	-	World Health Organisation
CD4+	-	Cluster Differentiation type 4 (type of lymphocyte)

INTRODUCTION

Tuberculosis (TB) is a specific infectious disease caused by *Mycobacterium tuberculosis*. The disease primarily affects lungs but may also affect intestines, meninges, bones and joints, lymph glands, skin and other tissues of the body. The disease is usually chronic with varying clinical manifestations[1].

Recurrence or relapse refers to a patient who returns smear and culture positive having previously been treated for tuberculosis and declared cured after the completion of his treatment[1]. It can either be due to a reactivation of endogenous infection or a new exogenous infection. In areas of high incidence, reinfection is said to be the major cause of post-primary TB[22]. It is estimated that most relapses occur within the first six to twelve months after completion of therapy[46].

There is substantial variability in the response to therapy for pulmonary tuberculosis, even in those patients with fully drug sensitive isolates. In some patients, bacilli are killed rapidly and cleared quickly from sputum. In others, viable organisms persist for many weeks or months, despite multi-drug treatment. In yet others, bacilli are cleared, only to reappear after therapy is stopped. These observations form the basis for the definitions of treatment failure and relapse, respectively. The causes of this phenomenon are not well understood, but they may involve mycobacterial and host biologic factors as well as host behavioural factors.[35]

The search for tools to monitor tuberculosis therapy and predict outcome is made particularly complex by the observation that mycobacterial killing is not a single uniform process. Most actively replicating bacilli are killed rapidly during the first one to two weeks of therapy. Prolonged treatment is required to eradicate persisting organisms with reduced or otherwise altered metabolic activity. Non-replicating bacilli show reduced susceptibility to the bactericidal activities of antimycobacterial drugs. This later sterilizing phase of therapy appears to be distinct from the first, based in part on the differential activities of antimycobacterial drugs during the two phases[35].

The global burden of tuberculosis remains enormous, mainly because of poor control in Southeast Asia, sub-Saharan Africa, and Eastern Europe, and because of high rates of tuberculosis and Human Immune-deficiency Virus (HIV) co-infection in some African countries.[22] There were an estimated 8.3 million new tuberculosis cases in the year 2000 worldwide (incidence 137/100 000 population). Tuberculosis incidence rates were highest in the WHO Africa region (290/100 000 per year), as was the annual rate of increase in the number of new cases (6%). Nine percent 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 Africa region (31%) compared to some industrialised countries, notably the United States (26%).[16]

Zambia, like many countries in Africa is in the midst of a serious TB epidemic and there are no signs that it is abating. TB case-notification data from 1964 to 2000 show a 12-fold increase over two decades; the apparent gains in controlling TB seen in the 1960s and 1970s have been reversed. A stable situation during the period 1964-1984 (case

notification rate remained around 100/100 000 population) was followed by an exponential increase since the mid-1980s[17]. The current notification rate is about 500/100 000 population. It is estimated that approximately one third of TB cases in sub-Saharan Africa after 1985 would not have occurred had pre-1985 trends continued.[18]

The tables below were extracted from the WHO report of 2005[37]. They show the estimated burden of tuberculosis in the Africa region in 1990 and 2003. The rates shown are per 100, 000 population. From table 2 we can see that the estimated burden of tuberculosis in terms of prevalence for Zambia now stands at 638 cases per 100,000 population, including those patients who are HIV positive. If we exclude HIV, we get a rate of 508 per 100,000 population. This is a significant increase in the burden compared with rates in 1990 (table 1), which stood at 492 per 100,000 and 440 per 100,000 population respectively. The death rates have also had a corresponding increase from 104 per 100,000 to 122 per 100,000 population in 1990 and 2003 respectively. These deaths are inclusive of HIV positive patients.

TABLE 1: ESTIMATED BURDEN OF TB: ZAMBIA AND SOME NEIGHBOURING COUNTRIES 1990

	INCIDENCE 1990				PREVALENCE 1990				DEATHS 1990			
Country	All cases incl HIV +ve		New ss +ve incl HIV +ve		All cases incl HIV +ve		All cases excl HIV +ve		All cases incl HIV +ve		All cases excl HIV +ve	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Zambia	24 333	297	9 987	122	40 326	492	36 042	440	8 567	104	3 904	48
Zimbabwe	13 719	131	5 507	53	24 035	230	21 984	210	4 614	44	2 381	23
Malawi	24 845	283	10 259	108	49 478	523	47 428	502	7 369	78	5 137	54
Botswana	3 266	241	1 291	95	6 711	496	6 500	480	934	69	704	52
Tanzania	47 831	183	20 294	78	96 732	371	93 199	358	13 942	53	10 095	39
Namibia	3 530	251	1 434	102	7 923	562	7 881	559	899	64	854	61
South Africa	68 593	186	27 890	76	152 637	414	151 465	411	17 682	48	16 407	45
Swaziland	2 259	267	888	105	4 724	558	4 601	543	633	75	498	59

TABLE 2: ESTIMATED BURDEN OF TB: ZAMBIA AND SOME NEIGHBOURING COUNTRIES 2003

	INCIDENCE 2003				PREVALENCE 2003				DEATHS 2003			
Country	All cases incl HIV +ve		New ss +ve incl HIV +ve		All cases incl HIV +ve		All cases excl HIV +ve		All cases incl HIV +ve		All cases excl HIV +ve	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
Zambia	70 975	656	29 130	269	68 996	638	54 954	508	13 152	122	6 584	61
Zimbabwe	85 015	659	34 126	265	85 129	660	64 474	500	19 749	153	7 869	61
Malawi	53 503	442	22 093	183	66 672	551	56 754	469	13 008	107	6 337	52
Botswana	11 307	633	4 469	250	9 202	515	6 105	342	1 530	86	610	34
Tanzania	137 260	371	58 235	157	193 610	524	175 953	476	31 745	86	19 101	52
Namibia	14 351	722	5 829	293	12 630	635	9 486	477	2 422	122	1 029	52
South Africa	241 537	536	98 208	218	206 110	458	153 694	341	32 794	73	12 459	28
Swaziland	11 666	1083	4585	426	10687	992	7361	683	2553	237	893	83

The rapid rise in the number of TB cases in the past three decades can largely be attributed to the emergence of the Human Immune-Deficiency Virus (HIV), which leads to the Acquired Immune Deficiency Syndrome (AIDS). Poor social economic status is another factor that is responsible for its spread.[2]

The Ministry of Health estimated that in the absence of AIDS the number of TB cases may have been limited to about 8,000 to 12,000 in 1996, based on case rates seen in prior years. Because of the AIDS epidemic, the additional number of annual TB cases due to HIV/AIDS could have reached about 38,000 by 2004 and 41,500 by 2014. In these years, two out of every three new cases could be attributed directly to HIV/AIDS. These projections were almost certainly under estimates. New TB cases will transmit the disease to others and emerging drug resistant strains will make it more difficult to treat cases and to limit the spread of the infection.[2]

REVIEW OF LITERATURE

Relapse Rates

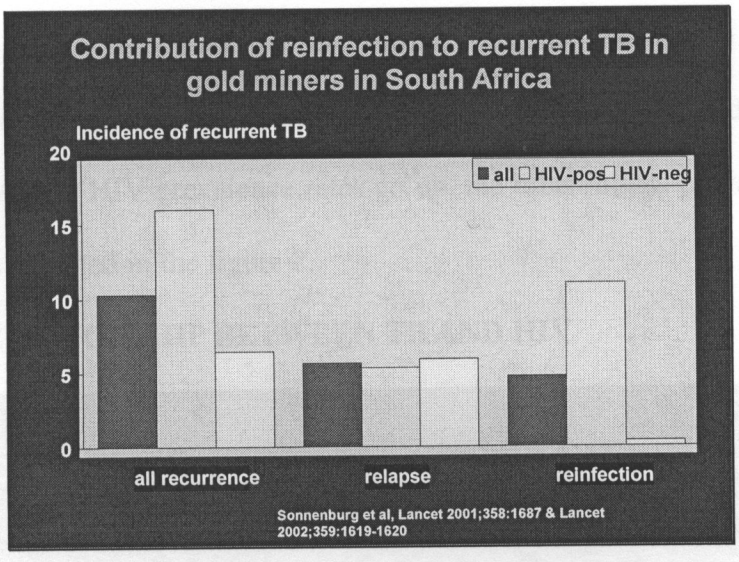
Findings in different studies are not unanimous on the question of whether rates of recurrent TB differ among patients with or without HIV infection[3, 4]. Some studies have found that the rates of tuberculosis relapse/recurrence in HIV infected patients are higher than in uninfected patients and some have even gone further to suggest extended therapy in order to prevent it [5, 12, 14, 15]. For instance, in the DR Congo a prospective randomised controlled trial of extended therapy for HIV-associated pulmonary TB had relapse rates of 1.9% after 24 months among 121 patients receiving continued therapy with rifampicin/isoniazid and 9% among 119 receiving placebo maintenance therapy. There was no relationship between relapse rates and more advanced HIV infection, and survival was not affected by increasing the duration of therapy[5]. Other studies have also reported similar rates of relapse between HIV infected and uninfected patients.[11, 13,]

Risk Factors

Before the advent of HIV/AIDS, studies on risk factors for relapse found that initial bacterial count, smear positivity, time to sputum conversion, radiological severity of disease and presence of cavitation were important risk factors for recurrence of tuberculosis[19, 24]. Recent studies have however been less likely to identify significant risk factors for recurrence, partly because of improvements in chemotherapy and low relapse rates, which result in limited statistical power[14]. Some researchers in Kenya reported that there was no significant association between recurrence among HIV-1 positive patients and initial resistance, initial treatment regimen, a diagnosis of AIDS (according to WHO

definition), or poor compliance[23]. A study among a cohort of South African mine workers identified residual cavitation as a significant risk factor for relapse but not reinfection.[14, 20]. On the other hand, HIV was identified as a significant risk factor for reinfection, as shown in figure 1.

FIGURE 1: CONTRIBUTION OF REINFECTION TO RECURRENT TB[14].



Source: Sonnenberg et al Lancet 2001;358: 1687-93

In yet another study on recurrent tuberculosis, the age-adjusted incidence rate of TB attributable to reinfection after successful treatment was four times that of new TB. People who had TB once are at a strongly increased risk of developing TB when reinfected[45].

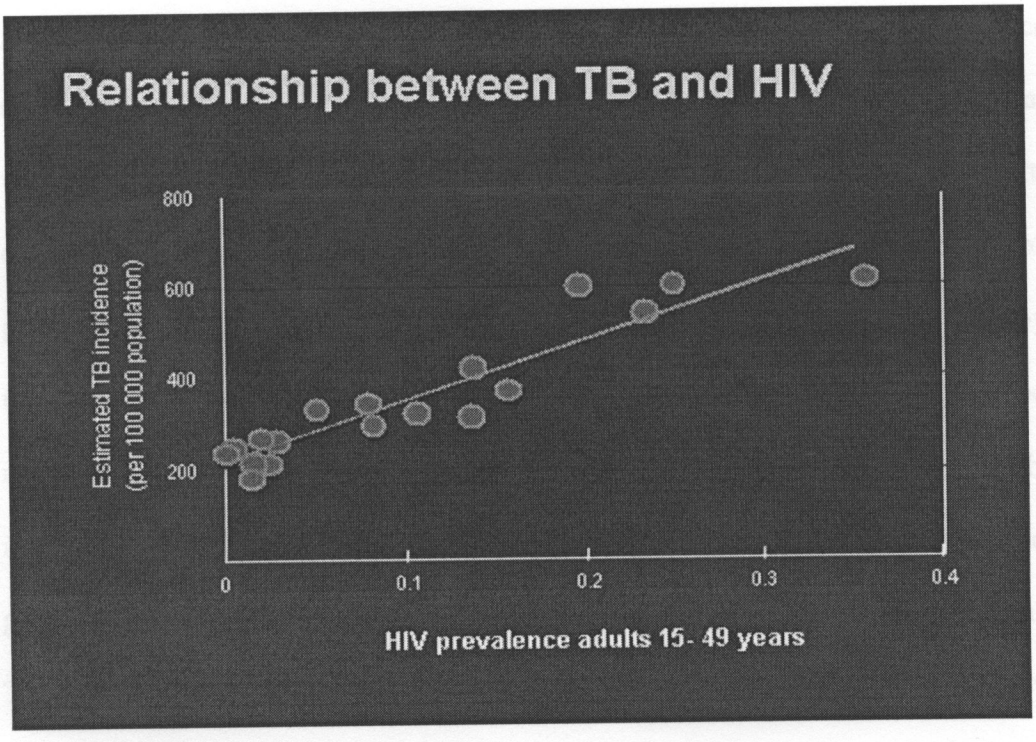
Another group of researchers writing in the Indian journal of tuberculosis reported that the pre-treatment extent of radiological lesion and extent of residual lesion had a strong association with relapse. Other risk factors such as presence of initial cavitation, irregularity of treatment, time of default and 'no weight gain during treatment' influenced the relapse in pulmonary tuberculosis. In the same study, factors such as age, sex, treatment regimens, and duration of default also influenced risk of relapse, but were not

statistically significant. The factors that did not have any effect on the occurrence of relapse in pulmonary tuberculosis were side of lesion, concurrent disease, time to sputum conversion, intermittent sputum positivity, hospitalisation of patient and initial drug resistance.[26]

Role of HIV/AIDS

Tuberculosis and HIV have been closely linked since the emergence of AIDS. HIV infection has contributed to a significant increase in the worldwide incidence of tuberculosis [36]. As the HIV prevalence rates go up, the tuberculosis prevalence rates will also rise. This is depicted in the figure 2.

FIGURE 2: RELATIONSHIP BETWEEN TB AND HIV



Source: Clydette Powell, MD. CCIH 2004

By producing a progressive decline in cell-mediated immunity, HIV alters the pathogenesis of tuberculosis, greatly increasing the risk of developing disease in co infected individuals and leading to more frequent extrapulmonary involvement and atypical radiographic manifestations[36].

At the University Teaching Hospital (UTH), Lusaka, about 70 percent of all tuberculosis cases seen are due to HIV[27]. The recurrence of TB in patients co-infected by HIV occurs in individuals with profound immuno-suppression and is associated with high mortality[25]. In a study done in Spain, the patients with recurrent tuberculosis presented a greater degree of immunosuppression, more previous complications indicative of AIDS, and greater frequency of extrapulmonary TB in the initial episode[25]. On the other hand, a study among Ethiopian children with tuberculosis found that the risk factors associated with HIV included a higher education of parents, higher income and better living conditions. The investigators went on to assert that BCG vaccination did not provide protection to children with HIV[34]. In general, early clinical response to therapy and the time in which Mycobacterium Tuberculosis sputum cultures convert from positive to negative appear to be similar for those with HIV infection and those without HIV infection[3, 4]. Current Centre for Disease Control and American Thoracic society guidelines recommend a six-month treatment regimen for patients with drug susceptible TB disease co-infected with HIV, but suggest prolonged treatment for patients who have a delayed clinical and bacteriologic response to anti-tuberculosis therapy[6]. Some experts have suggested that to ensure an optimal anti-tuberculosis treatment outcome, all patients

with HIV-related TB should be treated with longer course of therapy (i.e. 9 months), regardless of evidence of early response to therapy[7].

DOTS Strategy

According to a multi-centre group of researchers in South Africa, Directly Observed Treatment-Short course (DOTS) of tuberculosis reduces rates of TB relapse in both HIV-positive and HIV-negative patients[8] The Stop TB Initiative, a partnership hosted by the World Health Organisation, has identified five key elements for DOTS:

- Government commitment to sustained TB control;
- Detection of infectious cases using sputum-smear microscopy;
- A standardized, short-course chemotherapy of six to eight months, with direct observation of treatment;
- A reliable supply of high quality drugs;
- Information systems for monitoring and reporting of treatment outcomes.

When ministers and senior officials from 20 of the TB highest-burden countries met for the March 2000 Conference on TB and Sustainable Development, delegates committed their countries to reaching specific, time-bound global targets by 2005, namely:

- Expanding DOTS to all countries;
- Diagnosing 70 percent of all people with infectious TB; and
- Successfully treating (cure) 85 percent of those diagnosed.

Reaching these global targets by even as late as 2010 would prevent 48 million cases (23 percent of the predicted total) by 2020. The percentage of deaths averted would be even greater. Indeed, most TB deaths could be prevented immediately if all patients took a full course of anti-TB drugs now[10]. The increasing caseload, morbidity and mortality due to tuberculosis in high burden countries have become a major health challenge and threat to health systems. The escalated burden of disease and deaths due to TB has posed a great threat to the international security. In the last decade little progress has been witnessed in the implementation of WHO's recommended strategy called DOTS in the 22 high burden countries[39]. Despite its potential advantages, implementation of DOTS has been limited by its cost, which may be more than three times that of self-administered therapy[35].

Since the global TB targets were set, progress has been made. Political commitment has increased, additional financial resources mobilised, access to anti-tuberculosis drugs augmented and planning and coordination improved. Constraints remain, the most important related to human resource capacity. Although the issue is being tackled, many countries still suffer from lack of trained health care professionals. Finally, new strategies have been developed to face the current challenges such as public-private mix, community TB care, social mobilisation, TB/HIV collaborative interventions and Practical Approach to Lung Health. The current efforts should be maintained and strengthened in order to approach these targets[40].

Financial inabilities contribute greatly to the failure of respective national TB control programs. High burden countries are usually in economic recession or passing through socio-political turmoil that has further reduced spending on tuberculosis[39].

A study in Swaziland compared the outcomes of patients treated under DOTS from a community health worker and those observed by a family member. It found that the level of success was similar in both groups. They also concluded that compared with patients who have to visit a health facility daily for treatment, those whose drug-taking is supervised by a family member:

- experience fewer inconveniences
- lose less time from paid, agricultural, domestic or childcare work (hidden costs)
- place fewer demands on public health services
- Have a reduced risk of experiencing the stigma linked to visiting a TB clinic[41].

The following table is extracted from the WHO tuberculosis country report of 2005[37]. It shows the regional data for treatment outcomes of smear positive tuberculosis cases treated with DOTS in 2002. This table compares the number of cases notified with the number of the six mutually exclusive treatment outcomes. It also shows that Zambia had a treatment success rate of 83 percent (target: 85 percent by 2005) and a cure rate of 67 percent in 2002. The cure rate is way below the targeted 85 percent set by the WHO. The non-DOTS cure rates and treatment success rates were 55 percent and 71 percent respectively[37].

TABLE 3: TREATMENT OUTCOMES FOR NEW SMEAR POSITIVE CASES-DOTS

Country	Number of cases notified	Percent cured	Percent completed	Percent died	Percent failed	Percent default	Percent transferred	Not evaluated	Percent success
Zambia	11694	67	16	10	2	3	1		83
Zimbabwe	15941	62	6	11	0	7	15		67
Uganda	19088	30	31	6	0	19	7	7	60
South Africa	97656	54	14	9	1	13	9		68
Tanzania	24136	76	4	11	0	4	4	0	80

Prediction Scoring

A study to determine the efficacy of short course chemotherapy regimens used bacteriological relapse as a measure. A prediction scoring system was used to investigate the successful outcome of a short course regimen (1 SHRZ + 5H2R2) in 300 pulmonary tuberculosis patients. The prognostic factors used for this study were radiographic extent of residual lung lesions, the persistent pulmonary cavities at the end of six-month chemotherapy and the speed of sputum culture conversion. The cumulative assessment of all the three prognostic factors had determined 93 percent of the relapses (sensitivity) and 94 percent of the non-relapses (specificity) correctly.[29]

Isoniazid Prophylaxis

A study to determine efficacy of isoniazid (INH) prophylaxis in prevention of mycobacterium tuberculosis disease in adult Zambians infected with HIV-1 concluded that INH prophylaxis significantly reduces the incidence of active tuberculosis. Prophylaxis did not however delay the disease progression or reduce mortality[42]. Another study at the University Teaching Hospital (UTH) demonstrated that preventive therapy with either twice-weekly isoniazid for six months or a combination of rifampicin and

pyrazinamide for three months reduced the incidence of TB in HIV-infected persons in Zambia. It was also noticed that preventive therapy was more effective in people with less advanced immunosuppression and was of limited duration[43].

Researchers at the University Teaching Hospital (UTH) in Lusaka contend that although treatment for HIV-related TB is successful, recurrence of TB was 34 times greater in HIV-infected patients than in HIV sero-negative patients[33]. They suggested that efforts must be directed towards early diagnosis and treatment of sputum positive cases. These should be combined with studies to assess the place of preventive therapy in Africa, with an emphasis on funding preventive therapy from budgets for care of HIV-infected individuals. They further argued that prophylaxis raises the possibility that poor compliance may lead to drug resistance. Another real concern is that poor screening might allow patients with active TB to start on preventive therapy, which might still select out resistant organisms. Despite this, it may still be cost-effective to exclude active disease before initiation of preventive therapy[33]. A study in the British Medical Journal concluded that to define the efficacy and to find innovative ways of delivering preventive treatment and monitoring its cost and impact should be among the priorities of nations where the distribution of HIV infection and TB overlap[32].

STATEMENT OF THE PROBLEM

Cure rates are similar for HIV positive and negative patients (89 percent versus 88 percent), but significantly lower in those with recurrent than in those with new TB (77 percent versus 92 percent) [28]. The reported rates of recurrence of TB especially in

patients co-infected with HIV vary widely from as low as two percent to as much as 34 times as compared to those who are HIV negative [15, 20, 23, 27]. High recurrence rates pose renewed potential sources of infection and a high cost of renewed treatment [27]. Eight out of every ten patients infected with TB are in the economically productive age group of 15 – 49 years and it kills more adults than any other infectious disease [1]. It is estimated that Zambia had a tuberculosis incidence of 653/100 000 population in 2001, out of which 266/100 000 were sputum positive. The percentage of adult (15-49) TB cases that were HIV seropositive was about 60 percent.[16] Studies to investigate risk factors for tuberculosis recurrence have been done in different countries but none appears to have been done in Zambia. This study will attempt to identify those factors that may lead to recurrences/relapse and hence provide health workers with an opportunity to anticipate and where possible prevent recurrence/relapse of TB.

OBJECTIVES

General objectives

- To determine the characteristics of patients with recurrent TB.
- To Identify the risk factors for tuberculosis recurrence

Specific objectives

- To determine the association between HIV/AIDS and recurrence of tuberculosis.
- To determine whether socio-demographic factors are responsible for relapse of tuberculosis

- To investigate whether patients with severe symptoms of TB at first diagnosis are more likely to have a recurrence.
- To find out whether having a positive sputum smear is predictive of relapse/recurrence
- To determine proportion of patients put on isoniazid prophylaxis
- To determine whether DOTS reduces rates of relapse.

RESEARCH QUESTION

Can we, using socio-demographic characteristics, severity of illness at diagnosis, sputum positivity and HIV status be able to predict which patients with tuberculosis are going to have a recurrence?

METHODOLOGY

Research setting:

The project was conducted at five clinics around Lusaka namely Chawama, Chilenje, Mtendere, Kabwata and Kamwala. These areas were chosen because they serve people from low-density, medium-density and high-density areas.

Study Design:

It was a case control study. The cases were selected from patients coming to clinics with TB relapse, which was defined as smear positive TB after successful completion of anti-TB therapy. The controls were drawn randomly from patient records of people who had TB but had not relapsed for at least six months. These people were then traced by the nurses running the DOTS program at the clinic with the help of community based "treatment supporters" and a questionnaire administered. Those patients having

tuberculosis for the first time were excluded from the study. Patients who did not complete the TB therapy (defaulters) were also excluded.

Unlinked and anonymous HIV tests were done on all the cases and controls. The Determine® rapid HIV test kit was used (Abbot). Those wishing to know their results were however referred to the Voluntary Counselling and Testing centres.

Sample size:

A preliminary investigation from UTH records showed a relapse rate of about 7.5% from an estimated 2,600 cases of TB notified at UTH in the year 2002, which gives 195 cases of relapses in a year.

In order to determine the sample size an initial 30 cases and 30 controls were used and the data analysed. This pilot study showed that those who had been treated using Directly Observed Therapy short course (DOTS) had relapse rates of 61 percent versus 80 percent for those who did not receive DOTS. Then the following formula was used to calculate the actual sample size:

$$n = \frac{p_1q_1 + p_2q_2}{(p_1 - p_2)^2} \times 7.85$$

Where

$p_1 = 61$

$q_1 = p_1\text{-}100$ [39]

$p_2 = 80$

$q_2 = p_2\text{-}100$ [20] and

n is the sample size in each category, i.e. the cases and the controls.

Thus $n = \frac{61x39+80x20}{(61-80)^2} \times 7.85 = \frac{2379+1600}{361} \times 7.85 = 86.5$

The final sample was 184, i.e. 92 cases and 92 controls.

Data collection.

An interviewer-administered questionnaire was used to collect information from all patients, after obtaining consent. Most of the cases (relapse patients) were interviewed at the respective clinics as they came for collection of TB drugs. The controls were followed up and interviewed by treatment supporters or the nurses in either their homes or wherever they could be found. Data collection took three months, from September up to December 2004. Eight nursing staff in the five clinics were recruited as research assistants.

Data analysis

The data from the questionnaires and results from the lab were entered into a computer and using Epidata software for entry and analysis was done using EPI Info-statistical software. Confidence intervals were set at 95%.

In order to predict which of the patients with an initial episode of tuberculosis were more likely to relapse, we needed to calculate the sensitivity, specificity, positive predictive value and the negative predictive value of the various factors investigated. These values for each factor and/or a combination of the factors were calculated in order to ascertain the predictiveness of the variables.

Sensitivity is defined as the ability of a test to identify correctly all those who have the disease, i.e. 'true positive'. Specificity is defined as the ability of a test to identify

correctly those who do not have the disease, that is, ""true negatives".

The sensitivity and specificity are calculated as follows:

Table 3: A 2x2 table for case control studies

	Cases (Diseased)	**Controls (Not diseased)**	**Total**
Positive	a	b	a+b
Negative	c	d	a+d
Total	a+c	b+d	a+b+c+d

Thus

$$\text{Sensitivity} = \frac{a}{a+c}.$$

$$\text{Specificity} = \frac{d}{b+d}.$$

The predictive value of a positive test (the Positive Predictive Value, PPV) indicates the probability that a patient with a positive test result has, in fact, the disease in question. It is dependent on the prevalence of the illness and the sensitivity. Similarly, the Negative Predictive Value (NPV) is the probability of a patient with a negative test result being truly negative. It is a function of the specificity and the prevalence of the disease[1]. The prevalence of relapse, according to records at UTH, was 7.5 percent and this was used to calculate both the PPV and the NPV from all the variables.

$$PPV = \frac{\text{Prevalence x Sensitivity}}{[\text{Prevalence x sensitivity} + (100\text{-specifity})\ (100\text{-specifity})]}$$

$$NPV = \frac{\text{100-prevalence x specificity}}{[(100\text{-prevalence})\ (\text{specificity} + \text{prevalence})\ (100\text{-sensitivity})]}$$

ETHICAL ISSUES

Approval was obtained from the Research Ethics Committee of the University of Zambia. The Lusaka District Health Board granted permission to use their clinics. Identities of respondents were not revealed to any third parties to ensure confidentiality and all respondents were asked for their consent before participating in the study.

LIMITATIONS

A lot of people were willing to answer questions from the questionnaire but were against submitting a blood sample apparently because they feared their blood could end up being used in satanic rituals. These people were excluded from the study if they could not be convinced. This posed a challenge as it had an effect on the time it took to reach the desired sample size. In fact, an even larger sample could have been used had it not been for this problem. More than 30 people who were interviewed declined to submit a blood sample.

RESULTS:

We had 184 patients, of which 92 were cases and 92 were controls. A total of 214 patients were requested for interviews and 30 patients declined to give a blood sample, which meant that they were excluded from the study.

Sample Description

Figure 3 and table 4 show the distribution of age, sex and residential area of both the cases and the controls. The age distribution between cases and controls was significantly different ($p = 0.048$). Patients of age 35 years or more were less likely to relapse than the younger patients. No sex differences were observed between cases and controls ($p = 0.883$). Further, 28.3 percent of the cases came from high density residential areas, 38.0 percent from medium density and 33.7 percent from low density residential areas. Among the controls, there were 38.0, 33.7 and 28.3 percent patients from high density, medium density and low density residential areas respectively ($p = 0.366$).

TABLE 4: DISTRIBUTION OF SEX AND RESIDENTIAL AREA.

		CASES		CONTROLS		P- Value
		Number	Percent	Number	Percent	
SEX	Male	45	48.9	46	50.0	
	Female	47	51.1	46	50.0	**0.883**
RESIDENCE	High Density	26	28.3	35	38.0	
	Medium Density	35	38.0	31	33.7	**0.366**
	Low Density	**31**	**33.7**	**26**	**28.3**	

FIGURE 3: DISTRIBUTION OF AGE

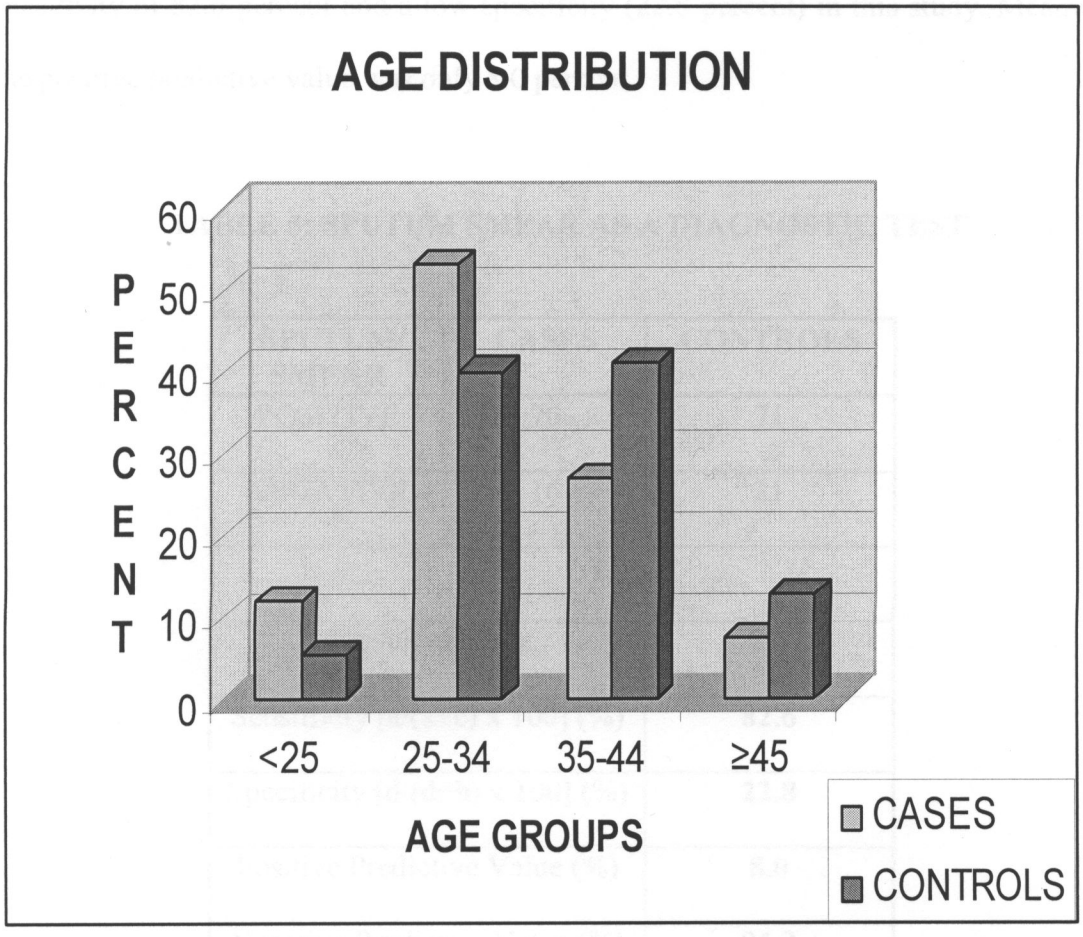


Table 5 shows the levels of diagnostic parameters for sputum smear which had a high sensitivity of 82.6 percent and a low specificity (22.8 percent) in this study. Meanwhile, the positive predictive value was only 8.0 percent.

TABLE 5: SPUTUM SMEAR AS A DIAGNOSTIC TEST

SPUTUM SMEAR	CASES	CONTROLS
POSITIVE	76	71
NEGATIVE	16	21
Prevalence (%)		7.5
Sensitivity [a/(a+c) x 100] (%)		**82.6**
Specificity [d/(d+b) x 100] (%)		**22.8**
Positive Predictive Value (%)		**8.0**
Negative Predictive Value (%)		94.2

The positive predictive value with respect to use of DOTS in the treatment of tuberculosis was only 6.3 percent. The sensitivity was 70.7 percent and the specificity was 14.1 percent. These results are shown in table 6.

TABLE 6: USE OF DIRECTLY OBSERVED THERAPY SHORT COURSE TO PREDICT RELAPSE OF TUBERCULOSIS

USE OF DOTS	CASES	CONTROLS
TREATED WITH DOTS	65	79
NO DOTS	27	13
Prevalence (%)		7.5
Sensitivity [a/(a+c) x 100] (%)		**70.7**
Specificity [d/(d+b) x 100] (%)		**14.1**
Positive Predictive Value (%)		**6.3**
Negative Predictive Value (%)		85.6

Using HIV status resulted in a sensitivity of 64.1 percent and a specificity of 27.2 percent. The positive predictive value was 6.7 percent. Table 7 shows this information.

TABLE 7: HIV STATUS AS A DIAGNOSTIC TEST

HIV STATUS	CASES	CONTROLS
POSITIVE	59	67
NEGATIVE	33	25
Prevalence (%)		7.5
Sensitivity [a/(a+c) x 100] (%)		**64.1**
Specificity [d/(d+b) x 100] (%)		**27.2**
Positive Predictive Value (%)		**6.7**
Negative Predictive Value (%)		90.3

Being HIV positive and having a sputum positive smear at the same time gave us a sensitivity of 50.0 percent and a specificity of 45.7 percent. The positive predictive value was 6.9 percent, as shown in table 8.

TABLE 8: HIV STATUS AND SPUTUM SMEAR IN PREDICTING RELAPSE OF TUBERCULOSIS

HIV POSITIVE/ SPUTUM SMEAR	**CASES**	**CONTROLS**
POSITIVE	46	50
NEGATIVE	46	42
Prevalence (%)		7.5
Sensitivity [a/(a+c) x 100] (%)		**50.0**
Specificity [d/(d+b) x 100] (%)		**45.7**
Positive Predictive Value (%)		**6.9**
Negative Predictive Value (%)		91.8

Being HIV positive and having breathlessness requiring admission to hospital was associated with a sensitivity of 18.5 percent and a specificity of 85.9 percent. The positive predictive value was 9.6 percent. These results are shown in table 9.

TABLE 9: HIV STATUS AND HAVING BREATHLESSNESS AS A DIAGNOSTIC TEST

HAVING HIV and BREATHLESSNESS	**CASES**	**CONTROLS**
POSITIVE	17	13
NEGATIVE	75	79
Prevalence (%)		7.5
Sensitivity [a/(a+c) x 100] (%)		**18.5**
Specificity [d/(d+b) x 100] (%)		**85.9**
Positive Predictive Value (%)		**9.6**
Negative Predictive Value (%)		92.9

Being HIV positive and aged over 35 years was associated with a sensitivity of 64.1 percent and a positive predictive value of 6.7 percent. The specificity was 27.2 percent, as shown in table 10.

TABLE 10: HIV STATUS AND AGE IN PREDICTING RELAPSE OF TUBERCULOSIS

AGE + HIV	**CASES**	**CONTROLS**
Above 35 years and positive	59	67
Less than 35 years old and /or negative	33	25
Prevalence (%)		7.5
Sensitivity [a/(a+c) x 100] (%)		**64.1**
Specificity [d/(d+b) x 100] (%)		**27.2**
Positive Predictive Value (%)		**6.7**
Negative Predictive Value (%)		90.3

SOCIODEMOGRAPHIC CHARACTERISTICS

We studied a number of sociodemographic characteristics and combinations with other diagnostic factors with a view to determine whether this could help predict tuberculosis relapse.

Living in a medium density residential area resulted in a sensitivity of 38 percent and specificity of 66.3 percent. The positive predictive value was 8.4 percent. These results are shown in table 11.

TABLE 11: RESIDENTIAL AREA IN PREDICTING RELAPSE OF TUBERCULOSIS; MEDIUM DENSITY HOUSING.

Area of Residence	**CASES**	**CONTROLS**
Medium Density	35	31
Other Areas	57	61
Prevalence (%)		7.5
Sensitivity [a/(a+c) x 100] (%)		**38.0**
Specificity [d/(d+b) x 100] (%)		66.3
Positive Predictive Value (%)		**8.4**
Negative Predictive Value (%)		93.0

Table 12 shows that when living in a medium density residential area was combined with sputum positivity, we got a sensitivity of 32.6 percent and a specificity of 71.7 percent. The positive predictive value was 8.6 percent.

TABLE 12: RESIDENTIAL AREA AND SPUTUM SMEAR IN PREDICTING RELAPSE OF TUBERCULOSIS.

Sputum Smear/residence	**CASES**	**CONTROLS**
Medium Density and smear positive	30	26
Other areas	62	66
Prevalence (%)		7.5
Sensitivity [a/(a+c) x 100] (%)		**32.6**
Specificity [d/(d+b) x 100] (%)		**71.7**
Positive Predictive Value (%)		**8.6**
Negative Predictive Value (%)		92.9

Living in a high-density residential area was associated with a sensitivity of 28.3 percent and a specificity of 62.0 percent. The positive predictive value was 5.7 percent. These results are shown in table 13.

TABLE 13: PREDICTING TB RELAPSE FOR PATIENTS LIVING IN HIGH DENSITY RESIDENTIAL AREAS

Area of Residence	**CASES**	**CONTROLS**
High Density	26	35
Other areas	66	57
Prevalence (%)		7.5
Sensitivity [a/(a+c) x 100] (%)		**28.3**
Specificity [d/(d+b) x 100] (%)		62.0
Positive Predictive Value (%)		**5.7**
Negative Predictive Value (%)		91.4

Being sputum positive and living in a high-density area was associated with a sensitivity of 21.7 and specificity of 73.9 percent. The positive predictive value was 6.3 percent. Table 14 is showing this information.

TABLE 14: SPUTUM SMEAR AND LIVING IN A HIGH DENSITY AREA AS PREDICTIVE FACTORS FOR TB RELAPSE

Residence and Sputum smear	**CASES**	**CONTROLS**
High density and sputum positive	20	24
Other areas/negative	72	68
Prevalence (%)		7.5
Sensitivity [a/(a+c) x 100] (%)		**21.7**
Specificity [d/(d+b) x 100] (%)		73.9
Positive Predictive Value (%)		**6.3**
Negative Predictive Value (%)		92.1

Table 15 shows the levels of diagnostic parameters for HIV status and living in a high density residential area. A combination of area of residence and HIV status gave us a sensitivity of only 17.4 percent, while the positive predictive value was 4.4 percent.

TABLE 15: HIV STATUS AND HIGH DENSITY RESIDENTIAL AREA AS PREDICTIVE FACTORS FOR RELAPSE OF TB

Area of residence and HIV status	**CASES**	**CONTROLS**
HIV positive and lives in high density area	16	28
Other areas/HIV negative	76	64
Prevalence (%)		7.5
Sensitivity [a/(a+c) x 100] (%)		**17.4**
Specificity [d/(d+b) x 100] (%)		69.6
Positive Predictive Value (%)		**4.4**
Negative Predictive Value (%)		91.2

Being HIV positive and male was associated with a sensitivity of 28.1 percent and a specificity of 64.1 percent. The positive predictive value was at 6.2 percent. These results are shown in table 16.

TABLE 16: HIV STATUS AND SEX AS PREDICTIVE FACTORS FOR TB RELAPSE; MALE PATIENTS.

SEX/HIV	CASES	CONTROLS
Male and HIV positive	27	33
Others	65	59
Prevalence (%)		7.5
Sensitivity [a/(a+c) x 100] (%)		**28.1**
Specificity [d/(d+b) x 100] (%)		64.1
Positive Predictive Value (%)		**6.2**
Negative Predictive Value (%)		91.8

In females, having HIV was associated with a sensitivity of 34.8 percent and a specificity of 63.0 percent. The positive predictive value was 7.1 percent. Table 17 is showing this information.

TABLE 17: HIV STATUS AND SEX AS PREDICTIVE FACTORS FOR TB RELAPSE, FEMALE PATIENTS

SEX / HIV	**CASES**	**CONTROLS**
Female and HIV positive	32	34
Others	60	58
Prevalence (%)		7.5
Sensitivity [a/(a+c) x 100] (%)		**34.8**
Specificity [d/(d+b) x 100] (%)		63.0
Positive Predictive Value (%)		**7.1**
Negative Predictive Value (%)		92.3

Breathlessness requiring admission to hospital in males was associated with a sensitivity of only 13.0 percent and a specificity of 93.5 percent. The positive predictive value was 14.0 percent. These results are shown in table 18.

TABLE 18: BREATHLESSNESS AND SEX AS PREDICTIVE FACTORS FOR RELAPSE OF TB; MALES

SEX AND BREATHLESSNESS	CASES	CONTROLS
Male and breathless	12	6
Others	80	86
Prevalence (%)		7.5
Sensitivity [a/ (a+c) x 100] (%)		**13.0**
Specificity [d/ (d+b) x 100] (%)		93.5
Positive Predictive Value (%)		**14.0**
Negative Predictive Value (%)		93.0

The sensitivity for a combination of being female and having severe breathlessness was only 17.4 percent. Meanwhile a high specificity of 89.1 percent was observed. The positive predictive value was 11.5 percent, as shown in table 19.

TABLE 19: BREATHLESSNESS AND SEX AS PREDICTIVE FACTORS FOR RELAPSE OF TB; FEMALES

SEX AND BREATHLESSNESS	**CASES**	**CONTROLS**
Female and Breathlessness	16	**10**
Others	76	**82**
Prevalence (%)		**7.5**
Sensitivity [a/(a+c) x 100] (%)		17.4
Specificity [d/(d+b) x 100] (%)		89.1
Positive Predictive Value (%)		11.5
Negative Predictive Value (%)		**93.0**

Table 20 shows levels of diagnostic parameters for those patients who used DOTS and had a positive sputum smear versus those who did not use it or were sputum negative. The positive predictive value was 6.7 percent, the sensitivity was 60.9 percent and the specificity was 31.5 percent.

TABLE 20: COMBINATION OF SPUTUM SMEAR POSITIVE AND USE OF DOTS IN PREDICTING RELAPSE

POSITIVE SPUTUM AND DOTS	**CASES**	**CONTROLS**
YES	56	**63**
NO	36	**29**
Prevalence (%)		**7.5**
Sensitivity [a/(a+c) x 100] (%)		**60.9**
Specificity [d/(d+b) x 100] (%)		31.5
Positive Predictive Value (%)		**6.7**
Negative Predictive Value (%)		90.9

DISCUSSION

There were 184 patients, of which 92 were cases and 92 were controls. A total of 214 patients were requested for interviews; 30 patients declined to give a blood sample, hence they were excluded from the study. This may have introduced selection bias into the study. Of the five clinics used, Mtendere provided a higher number of respondents, accounting for about one third of the total, suggesting that the results may be biased towards respondents from Mtendere.

In summary, older patients were less likely to relapse than younger patients. A positive sputum smear had a high sensitivity in predicting relapse but a low positive predictive value. The sensitivity of DOTS in predicting relapse was relatively high at 70.7 percent. Having an HIV infection had a sensitivity of 64.1 with lower positive predictive value. A combination of HIV and sputum smear, HIV and breathlessness and HIV in those over the age of 35 generally resulted in poor sensitivity. Similarly, a combination of HIV and some socio-economic variables such as sex and residential area resulted in poor sensitivity and positive predictive values. We also combined sputum smear and residential area and breathlessness and sex which also gave us low sensitivity.

A significant association between age and relapse was observed. The youngest patient was nine years and the oldest was 60 years old. Younger patients (less than 35 years) were more likely to relapse than older patients were. The reason for this may be that younger patients may be less likely to complete medication, but those less than 35 years old accounted for 53.2 percent of the HIV positive.

Having an HIV infection had a sensitivity of only 64.1 percent. The positive predictive value was only 6.7 percent. Considering that the National AIDS Council estimates that up to two-thirds of all tuberculosis patients are HIV positive[50], HIV infection did not have a significant effect on our ability to predict relapse of tuberculosis. A number of studies have concluded that HIV greatly increases the risks of relapse[5, 12, 14, 15]. A few studies however have concluded that the rates of relapse were the same between HIV infected and uninfected patients[11, 13]. This may be because HIV is common and affects all groups of tuberculosis patients.

The Zambia Demographic and Health Survey (ZDHS) in 2003 reported an HIV prevalence of 16 percent in the 15-49 year age group[51]. This age group in our study had HIV infection rates of 63.6 percent. It is important to note that while the ZDHS was a cross sectional study, our study was a case control study and thus the results may not be comparable. However the DHS is meant to highlight the exposure to HIV in this age group from the general population. Other studies have also estimated the HIV infection rate of 60 percent in this age group among TB patients.[16] Overall, 68.5 percent of the patients (cases and controls) were HIV positive. On the other hand, being above the age of 35 and HIV positive was only able to predict 64.1 percent of the relapse cases with a positive predictive value of 67.3 percent. A study conducted by the Uganda-Case Western Reserve University Research Collaboration in Kampala, Uganda among HIV-1 infected tuberculosis patients concluded that those who were 30 years and above were more likely to relapse[49]. Other studies have however found that age is not an independent risk factor for the relapse of tuberculosis[19, 48]. HIV infection considerably weakens a

person's immune system and makes them vulnerable to other illnesses. *Mycobacterium tuberculosis* has a particularly synergistic dynamic with HIV, as HIV accelerates the progression of TB infection to active TB disease. People who are infected with TB and HIV are at least 30 times more likely to progress to active TB disease than people with TB infection alone. The burden of TB greatly reduces the quality of life of people who are HIV positive. If their TB remains untreated, they have a high likelihood of dying within a few months [32]. We were able to establish that HIV is a poor predictor of recurrence of tuberculosis in the current study.

Having a positive sputum smear (alcohol-acid-fast bacillus, AAFB) was predictive of tuberculosis relapse with a sensitivity of 82.6 percent. The specificity and positive predictive value were however quite low at 22.8 percent and 8.0 percent respectively. Sputum smear remains one of the most important diagnostic tools in tuberculosis management. However, AAFB identified on smear are not diagnostic of tuberculosis, as the acid-fast stain detects mycobacteria other than *Mycobacterium tuberculosis,* including *Mycobacterium avium intracellulare* complex or *Mycobacterium kansasii*[36]. The rate of smear positivity is about 30 percent among patients in Lusaka, according to the Central Board of Health. In general, the rate of smear positivity correlates with the extent of radiographic disease. For example, patients with cavitary lesions due to active tuberculosis will almost always have positive smears, whereas a negative smear in a patient with minimal disease on chest radiograph would not be unusual, and would not rule out active tuberculosis. However in HIV-infected patients positive smears may be seen with relatively little radiographic involvement[36]. Most of the studies on prediction of

tuberculosis established that slow sputum conversion from positive to negative culture or presence of positive smear at two months was predictive of tuberculosis relapse[19, 48, 10]. Since having a positive sputum smear was predictive of relapse in our study, it would be interesting to investigate whether the relapse was as a result of drug resistance, treatment failure, reinfection or reactivation of latent infection in these individuals.

Living in high-density areas gave a sensitivity of 28.3 percent, with a positive predictive value of 5.7 percent. A similar situation was observed in patients from medium density areas, with a sensitivity of 38.0 percent and a positive predictive value of 8.4 percent. When we combined having a positive sputum smear and living in a high-density residential area we still got low sensitivity and positive predictive values (21.7 percent and 6.3 percent, respectively). Over crowding and general poor living conditions are usually cited as major risk factors in tuberculosis aetiology. However, the residential area of the patient had a poor positive predictive value for relapse of tuberculosis in our study.

When we combined living in a high-density residential area and being HIV positive we could only get a sensitivity of 17.4 percent, and a positive predictive value of only 4.4 percent. This seems to suggest that separate factors for tuberculosis aetiology and for relapse may be at play among our patients. Living in overcrowded communities and having HIV are well recognised risk factors for tuberculosis aetiology but they may not be important in predicting which patients are more likely to relapse.

Being HIV positive and being male had a sensitivity of 28.1 percent with a positive predictive accuracy of 6.2 percent. Female patients had a slightly higher sensitivity (34.8 percent) and positive predictive value (7.1 percent) than their male counterparts. These

findings suggest that sex is a poor predictive factor for relapse of tuberculosis. There was only one published trial that reported an association between the male sex and relapse[48]. Two other studies found no significant association between sex and relapse[19, 26]. These studies were however comparing three treatment regimes which we do not use here in Zambia (hence different efficacy) and all the respondents were from areas of low HIV prevalence (Hong Kong and North America), which may have impacted on the results. Sensitivity testing was not done to determine predictiveness.

Admission to hospital for breathlessness had a low sensitivity for relapse, with only 13 percent sensitivity in males. It however had a specificity of 93.5 percent. The positive predictive value was 14 percent. In females the sensitivity was 17.4 percent and positive predictive value was 11.5 percent. These low predictive values could be due to the fact that breathlessness as a symptom is present in a lot of other illnesses such as heart failure, various types of pneumonia and advanced pulmonary Kaposi's sarcoma, which may co-exist with tuberculosis. A study in Indian found that hospitalisation had no significant effect on relapse, but it did not test its sensitivity[26]. Coughing out blood and having a pleural effusion or pneumothorax also gave poor sensitivity and predictive values in our study, despite these being some of the most common presenting symptoms of tuberculosis. We speculate that the reason for this may be due to the fact that these symptoms are present in other illnesses which may coexist with tuberculosis, as already mentioned above. However, a number of studies have identified residual cavitation as a significant risk factor for relapse[14, 19, 10]. Researchers in India reported that the pre-treatment extent of radiological lesion and extent of residual lesion had a strong association with relapse[26]. Other risk factors such as presence of initial cavitation,

irregularity of treatment, time of default and 'no weight gain during treatment' were associated with relapse of pulmonary tuberculosis[26, 19, 49]. Factors such as age, sex, treatment regimens and duration of default were not associated with relapse of tuberculosis[26]. However these factors were not tested for their predictiveness. Perhaps another study would help us to investigate them.

The study established that using DOTS was associated with lower predictive values. The sensitivity of DOTS in predicting relapse of tuberculosis was 70 percent. The positive predictive value was 6.3 percent. DOTS cures active TB. It is remarkably effective. Without treatment, seven in ten people with infectious TB will die of the disease, on average within four to five years of onset, even if they are young when they contract the disease[22, 31]. A number of studies have established that using the DOTS strategy seems to reduce relapse rates[8, 37]. Another study concluded that the administration of therapy for *Mycobacterium tuberculosis* infection under direct observation leads to significant reductions in the frequency of primary drug resistance, acquired drug resistance, and relapse[9]. Despite the fact that non-DOTS TB-control programmes in low- and lower-middle income countries may decrease deaths considerably, such programmes are usually less successful at curing TB. Many sufferers remain chronically ill and continue to transmit, albeit unwittingly, the disease to family, friends, and even strangers[31]. On the other hand, good DOTS programmes rapidly reduce both death and disease, curing more than 85 percent of patients. In human terms, DOTS gives young people marked for premature TB death a chance to lead full and productive lives, raise children to adulthood, and contribute to their communities and society[31]. The World Health Organisation TB control report for the year 2004 for Zambia

stated that only 55 percent of the population live in areas nominally serviced by health facilities implementing DOTS. Increasing DOTS coverage to provide effective treatment to just 70 percent of people with active infectious TB by 2005 would save millions of lives and jump-start a decline in TB that could lead to future elimination[31]. It may be stated that the main problem of chemotherapy today is not the need to introduce new regimens or more potent drugs, but to apply the existing ones successfully[1]. Johnson and co-workers identified irregular or poor compliance as factors predictive of relapse[49]. Patient compliance is critically important throughout the prescribed period of treatment.[1] DOTS is now judged to be the standard of care by most authorities, but currently only a third of the cases worldwide are treated under this approach[44].

Development of side effects to tuberculosis drugs and subsequent discontinuation of therapy had a strong association with relapse. Poor compliance and defaulting, particularly resulting from adverse side effects of drugs, appears to be a major factor in the recurrence of tuberculosis. We did not measure the duration of interruption of therapy or which side effects were more common than others.

The generally low positive predictive values in our study were as a result of the low prevalence of relapses among tuberculosis patients, which was 7.5 percent from the records at the University Teaching Hospital. While sensitivity will tell us of those who had a disease how many will be correctly identified by our test, it does not tell us of those who test positive how many actually have the disease. Similarly, while specificity tells us of those who did not have the disease how many will test negative, it does not tell us of

those who test negative how many actually do not have the disease. The sensitivity and specificity of a test can change if the population tested is dramatically different from the population you serve and they cannot therefore be applied universally. They can also change in patients with early manifestations of a disease - just the patients that you need the test for! The positive predictive value is the probability that a person or specimen that tests positive or meets our case definition is a true case (a true positive). Thus in a situation where the prevalence is low, the probability of a patient who tests positive actually having the disease in question is low. In fact, the rarer the abnormality, the more sure we can be that a negative test indicates no abnormality, and the less sure that a positive result really indicates an abnormality[47]. From our data, the sensitivity, specificity and the positive predictive values of the various diagnostic tests were generally low. As a rule, at low prevalence rates, negative predictive value is high regardless of which data one uses, or even which test. At low prevalence rates, positive predictive value is low in all cases, even when sensitivity and specificity are relatively high.

The low positive predictive values raise questions as to the usefulness of some of the diagnostic tests used in tuberculosis relapse, because false positives are likely to be common. As an example, sputum smear had a sensitivity of 82.6 percent, specificity of 22.8 percent and a positive predictive value of only 8.0 percent. This implies that the probability of a sputum positive patient being truly positive and hence relapsing in future is only 8.0 percent and that 92 percent of those who tested positive were actually false positives. In an illness such as tuberculosis which carries with it a lot of stigma and a lengthy period of treatment, this means a lot of people having to take unnecessary drugs, at great cost to the health care system, and endure the stigma. On the other hand, if we are

to successfully control tuberculosis, putting those patients known to be high risk for relapse on prophylaxis might just be the answer. However, poor compliance to the prophylactic therapy raises the real possibility of organisms developing resistance. Further, if the screening tests are not very reliable, it may allow people with active disease to be given prophylactic therapy, which will also select out resistant organisms. Uncertainty still remains as to whether the prophylaxis would still be cost effective in the first place. Considering that the prevalence is low, the question might arise as to whether the number of people who actually get a relapse might be easily treated for their second episode at minimal cost. Thus research into not only more reliable diagnostic or screening tests but more effective and efficacious ways of preventing relapse should be encouraged. We also need to study the cost effectiveness of preventive therapy in our environment. At the end of the day, clinical judgment, coupled with a diligent search for other conditions that can present with a similar picture, should be the mainstay in the management of these patients.

Some of the possible sources of bias in this study were the varied follow up period among the controls, i.e. some patients had only completed tuberculosis treatment six months previously (and hence less time to suffer a relapse) whereas others had completed treatment and been disease free for over three years. The role of multi-drug resistant tuberculosis in treatment failure and relapse was also not studied. Further, no matching was done among the cases and the controls to remove confounding factors such as the presence of illnesses that have similar symptoms to tuberculosis (co-morbidities). We also could not differentiate between the true relapse patients and those who had a re-

infection, as we did not do DNA finger printing. Another possible source of bias could be that although all the patients were tested for HIV, we were unable to check the level of immunity of the patients (e.g. via CD4+ counts) due to financial constraints. A low level of immunity would in theory more likely cause relapse than just merely having HIV.

CONCLUSION

The mean age of the respondents was 33.9 years, with the 15-49 year age group accounting for 93.5 percent of both cases and controls. A significant association was observed between age and relapse. In general, older patients were less likely to relapse than younger patients. Being 35 years or older had a sensitivity of 64.1 percent and a positive predictive value of 6.7 percent.

A positive sputum smear had a high sensitivity in predicting relapse but low positive predictive value.

The sensitivity of DOTS in predicting relapse was relatively high at 70.7 percent. This suggests that DOTS can be used as a tool in the prediction of relapse. However, the positive predictive value was quite low at 6.3 percent, implying that there may be a lot of false positives.

Having an HIV infection had a sensitivity of 64.1 with a lower positive predictive value. HIV infection was not a good predictor of relapse in our study. A combination of HIV and sputum smear, HIV and breathlessness and HIV in those over the age of 35 generally resulted in poor sensitivity and positive predictive values. Similarly, a combination of HIV and some socio-economic variables such as sex and residential area resulted in poor sensitivity and positive predictive values. We concluded that whereas HIV and the other factors may be important in tuberculosis diagnosis and aetiology, they are not important in the prediction of relapse.

A combination of positive sputum smear and residential area and breathlessness and sex was not a good predictor of relapse.

Combining sputum smear and use of DOTS resulted in a sensitivity of 60.9 percent and a positive predictive value of 6.7 percent.

In answer to our research question, the above findings suggest that socio-demographic characteristics, severity of disease at diagnosis and HIV status are poor predictive factors. However it is important to note that these factors were not tested for association to relapse but were used as diagnostic parameters to predict relapse of tuberculosis.

RECOMMENDATIONS

Based on sensitivity findings of 70 percent or more in our study, the following were our recommendations:

1. Patients with a positive sputum smear should be monitored more closely than those who are negative and should receive directly observed therapy all the time.
2. Patients who did not use DOTS were more likely to relapse and we recommend than the country should work towards ensuring that all centres providing tuberculosis services also provide DOTS. Currently only 55 percent of the population live in areas nominally serviced by DOTS. This is according to the WHO country report for 2005.
3. A prospective study, looking at the various factors in our study should be carried out in order to remove the recall bias inherent in retrospective studies, and also to determine the role of the level of immunity (i.e. CD4+ count), the role of re-infection versus relapse and the role of multi-drug resistance in tuberculosis.
4. We need to do more research into more reliable and cost effective ways of identifying which patients are more likely to relapse and find better ways of preventing relapse.

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Appendix A

CONSENT FORM

We are carrying out research on the reasons why some patients with tuberculosis (TB) end up suffering from it again after treatment. Is there something about these patients that makes them come back with another bout of TB? Can we do something to prevent it?

We will ask you questions on tuberculosis and with your approval, we will have to do an HIV test as well. We will **not** record your name so we will not be able to tell your HIV status. However if you want to know your results you will be referred to the voluntary counseling and testing centre. The results of your tests and your answers to the questions will be kept confidential and will only be used for research purposes.

There will not be any immediate benefit to you if you choose to participate. However, any people may benefit in future if we are able to find the answers to our questions. The main risk or discomfort to you from this research will be from the needle as we collect blood.

Your participation in this study is completely voluntary. Should you choose not to participate no penalty or injury shall occur to you and you will continue to receive the same health care that you otherwise enjoy. You have the right to withdraw your participation any time you wish to do so.

If you have any doubts or you wish to seek clarification on the research please feel free to contact the researcher on the address below:

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I understand the information given to me and that my participation in this research is completely voluntary and its purpose has been fully explained to me. I also understand that my rights and privacy will be respected.

Name of participant:.....

Signature or thumb print of participant:.....

Name and signature of witness:.....

Date: .....

Appendix B

QUESTIONNAIRE Date:.....

1. group: Relapse..... 1
   Discharged..... 2
2. Patient no:
3. Age.....
4. Sex M F
5. Do you smoke? Y N
6. Do you take alcohol: Y N
7. Education attained:
   1.....none
   2.....primary
   3.....secondary
   4.....tertiary

Socio-economic status

8. What is your occupation?.....
9. Residential area
   1..... Low density
   2..... Medium density
   3..... High density
10. Made of -
    1..... mud bricks
    2..... Concrete blocks
11. House is-
    1.....rented
    2.....owned
12. Do you own a TV set? Y N
13. Do you own a DVD player? Y N

Knowledge

14. Do you know what causes TB
15. What are the signs and symptoms of TB
16. For how long is someone with TB supposed to take drugs for treatment

Medical History

17. When did you first suffer from tuberculosis:
    1..... more than 6 months ago,
    2..... 1 year ago,
    3.....More than 2 years ago

18. Initial (first episode) smear was 1..... Positive,

2..... Negative

19. How long did it take to get the second episode of tuberculosis?

1	<6 months,
2	1 year,
3	>2 years.

20. Did the initial episode involve

1	Coughing out blood
2	Removal of air, pus or fluid from chest
3	Breathlessness requiring admission to hospital
4	None of the above

21. Was sputum tested again after 2 months of treatment? Y N

22. How long did the treatment take? .....

23. If treatment took longer than 8 months what where the reasons for the extension?

.....

24. Did you ever develop side effects to the drugs causing you to stop taking the treatment? Y N

25. Was the treatment ever discontinued before completion at anytime for any reason?

Y N

26. If yes state reasons.....

27. Was Directly Observed Therapy short course (DOTs) used in the first episode o tuberculosis? Y N

28. If so who observed you during the time you were taking the drugs?

1. Health worker
2. family member
3. other

29. After completion of treatment where you put on any preventive treatment for TB (isoniazid) Y N

.....

30. HIV TEST: Positive.....1

Negative.....2