

APPROVAL PAGE

This dissertation of CAROLINE MALIBATA has been approved as fulfilling the requirements or partial fulfilment of the requirements for the award of Master of Medicine in INTERNAL MEDICINEby the University of Zambia.

Examiners

1. Signature.....  Date..... 1/06/05
- 2.. Signature.....  Date..... 1/6/05
3. Signature.....  Date..... 01/06/05

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SCHOOL OF MEDICINE
DEPARTMENT OF INTERNAL MEDICINE

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AUTHOR: BY CAROLINE MALIBATA B.Sc. Hb (UNZA) MBChB (UNZA)

TITLE: THE PREVALENCE OF MYCOBACTERIUM TUBERCULOSIS IN
PATIENTS WITH A SHORT HISTORY OF COUGH (LESS THAN
THREE WEEKS AT KAMWALA, CHILENJE AND KABWATA
CLINICS, LUSAKA, ZAMBIA


A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR DEGREE OF MASTER OF MEDICINE (INTERNAL
MEDICINE) OF THE UNIVERSITY OF ZAMBIA


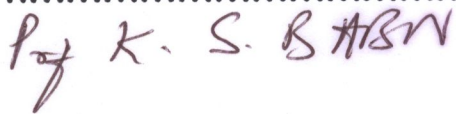


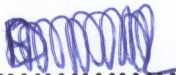
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DECLARATION

I hereby declare that the work presented in this dissertation has not been presented either wholly or in part for any degree and is not currently submitted for any degree.

Signed..... .....
(Candidate)

Signed..... .....
(Supervisor) 

Signed..... .....
(Supervisor)

DEDICATION

My husband, Charles Chipalo

And my daughters Chomba and Cholwe Chipalo.

My mother Mrs. Lucy Malibata.

YOU GIVE ME THE REASON TO WORK HARD

ACKNOWLEDGEMENTS

I will always remember the following for their support and encouragement

Dr. P. Mwaba, Head of Department, Internal Medicine.

Professor K.S. Baboo, Department of Community Medicine.

Dr. A. Mwiinga, Lecturer, University of Zambia.

All the staff at Kamwala, Chilenje and Kabwata clinics.

ABBREVIATIONS:

UTH- University Teaching Hospital

TB- Tuberculosis

AAFB- Acid Alcohol Fast Bacilli

HIV- Human Immunodeficiency Virus

ZN- Ziel Nielsen

CT- Computed Tomography

PCR- Polymerase Chain Reaction

PPD- Purified Protein Derivative

BCG- Bacille Calmette-Guerin

DOTS- Directly Observed Therapy

MDR- Multi-Drug Resistant

CDC- Center for Disease Control

AIDS- Acquired Immunodeficiency Syndrome

CNS- Central Nervous System

WHO- World Health Organization

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ABSTRACT

Tuberculosis continues to be the leading cause of death from an infectious disease. It poses a serious threat to the health of the human population. Two problems threaten the eventual conquest of tuberculosis: the human immunodeficiency virus and the emergency of multi-drug resistant Tuberculosis.

Aim:

The prevalence of pulmonary tuberculosis (PTB) in patients with a short duration of cough was determined at 3 urban clinics of Lusaka.

Hypothesis:

A significant proportion of patients with pulmonary tuberculosis present with cough less than 3 weeks duration.

Methodology:

Two hundred and four (204) out-patients (125 males and 84 females; mean age 34 years) at Kamwala, Chilenje and Kabwata clinics, Lusaka, Zambia who had a cough less 3 weeks were screened by microscopy and culture of 3 sputum samples and chest radiographs; 54 (26.5%) had PTB. There was no difference in the age and gender between patients with PTB and those with no evidence of PTB. Twenty-nine patients (53%) with microbiologically confirmed tuberculosis had chest radiographs suggestive of TB. Fifty-nine patients with no microbiological evidence of TB had chest x rays suggestive of TB. Some patients with short history of cough would benefit from PTB screening strategies with emphasis on sputum examination rather than chest x-rays which are unreliable. They include patients with other features of TB and those who are very sick.

Conclusion:

A significant proportion of patients presenting with short duration of cough who were screened (26%) had pulmonary tuberculosis, which was proven microbiologically by sputum smear examination.

In addition chest xray alone should not be used as the sole tool for the diagnosis of pulmonary tuberculosis.

As is seen by the study 47% of patients with bacterial logical evidence of PTB had non suggestive chest xrays sputum smear examination should be mandatory at all health centers in patients presenting with cough whatever the duration.

CHAPTER 1

BACKGROUND INFORMATION AND REVIEW OF LITERATURE.

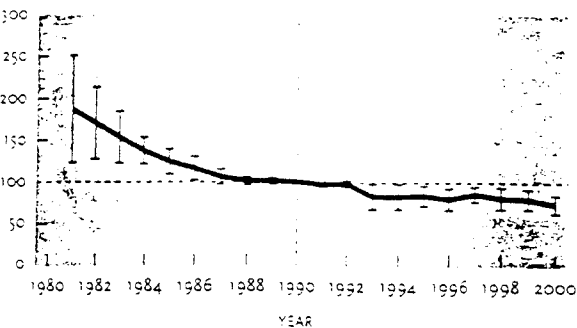
Tuberculosis continues to be a devastating disease worldwide and is believed to be present in about one third of the world population .It remains the leading cause of death from infectious diseases .The World Health Organisation has declared that 24th march each year should be designated 'World TB Day, to mark the anniversary of the discovery of mycobacterium tuberculosis by Robert Koch in 1882 (WHO 1997). The reason for focusing attention on tuberculosis is that this disease poses a very serious threat to the health of the human population worldwide .So threatening is the situation that in 1993,the World Health Organisation took the unprecedented step of declaring tuberculosis a global emergence (WHO 1994). Two serious problems that threaten the eventual. Conquest of tuberculosis has arisen in recent years: the Human Immunodeficiency Virus (HIV) pandemic and multi-drug-resistant tuberculosis and at present around 10 percent of patients worldwide with tuberculosis are HIV positive, but this percentage is rising daily. It is estimated that 8 million new cases of TB and 2.6 to 2.9 million deaths from this disease occur annually around the world (Martin et al, 1977). The World Health Organisation predicts continued increase in TB and an estimated worldwide increase of nearly 12 million cases each year by the year 2005 (WHO, 1988, Ravigilion et al, 1995).

On a global profile, Africa has been hit badly by the TB epidemic. In the period between 1981 and 2000, different regions of the world have shown variable patterns in TB notification rates (WHO 2002). African countries with low HIV burden (Algeria, Benin, Comoros, /Guinea, Madagascar, Mali, Mauritania, Mauritius) have not shown much change in the case notification rates in the period 1981 to 2000.

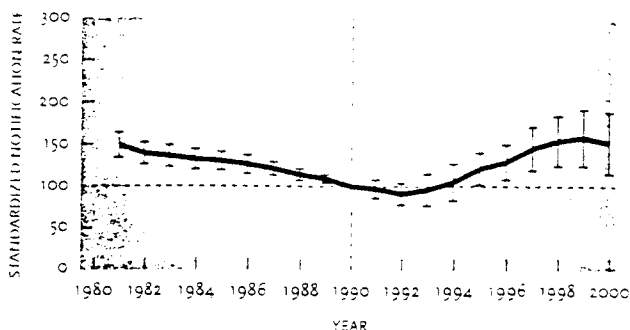
Trends in case notification rates for selected countries in different regions, 1981–2000

To highlight trends in notifications within regions, the rates for all countries have been expressed relative to an arbitrary standard of 100 in 1990. Error bars are 95% CL on the standardized (unweighted) rates. Countries selected in each region are those for which case notifications were judged to represent trends in incidence over the period 1981–2000.

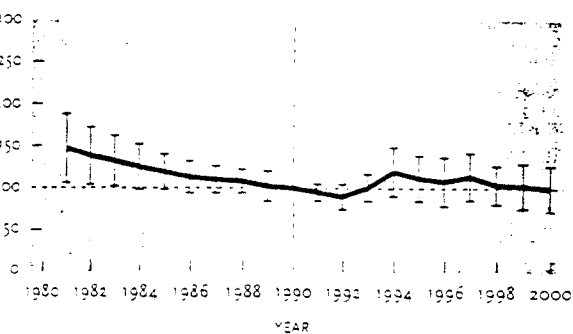
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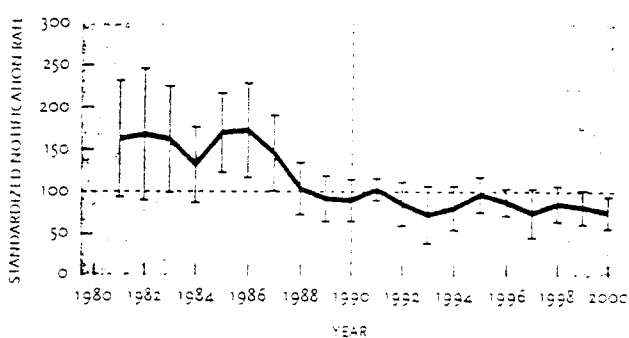
EASTERN EUROPE



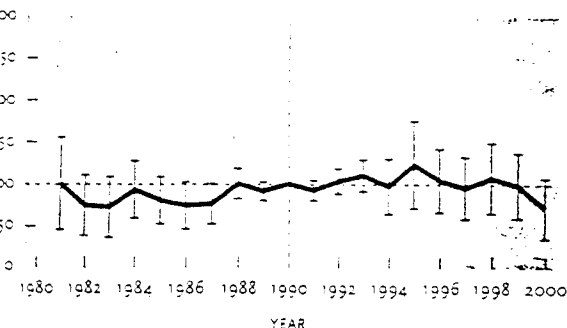
LATIN AMERICA



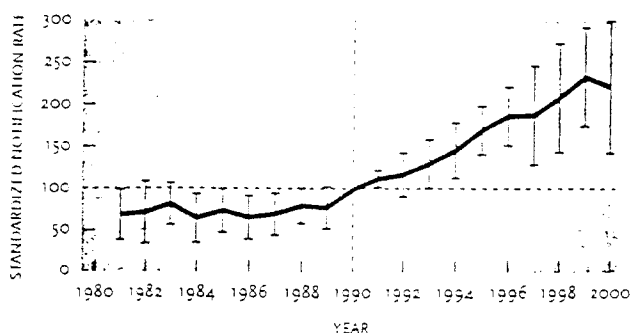
EASTERN MEDITERRANEAN



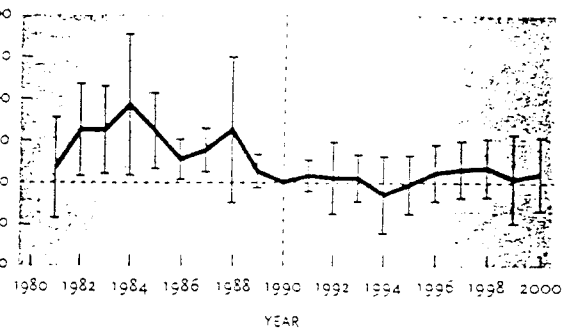
AFRICA – LOW HIV



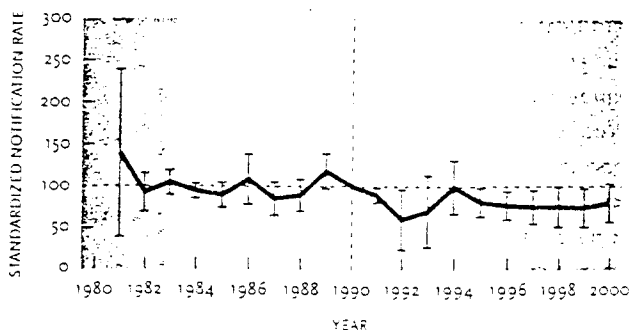
AFRICA – HIGH HIV



WESTERN PACIFIC (excluding Established Market Economies)



SOUTH-EAST ASIA



Established Market Economies: Australia, Austria, Belgium, Canada, Czech Rep., Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Japan, Netherlands, New Zealand, Norway, Portugal, Singapore, Spain, Sweden, Switzerland, United Kingdom, United States. Eastern Europe: Albania, Armenia, Belarus, Estonia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Poland, Romania, Russia, Slovakia, Slovenia, Tajikistan, Turkmenistan, Ukraine, Uzbekistan, Yugoslavia. Eastern Mediterranean: Cyprus, Jordan, Lebanon, Morocco, Oman, Qatar, Syria, Tunisia. Latin America: Argentina, Chile, Cuba, Ecuador, El Salvador, Guatemala, Honduras, Jamaica, Mexico, Nicaragua, Peru, Puerto Rico, Uruguay, Venezuela. Africa - low HIV: Algeria, Benin, Comoros, Guinea, Madagascar, Mali, Mauritania, Mauritius. Africa - high HIV: Botswana, Central African Republic, Côte d'Ivoire, DR Congo, Kenya, Lesotho, Malawi, Uganda, Zambia, Zimbabwe. South-East Asia: Bhutan, India, Maldives, Sri Lanka. The Western Pacific: Cambodia, China Hong Kong SAR, China Macao SAR, Indonesia, Rep. Korea, Viet Nam.

In the year 1981, for these countries the rate was about 100, and remained 100 in 1988 and 1994; and fell to between 50 and 100 in the year 2000. On the other hand, African countries with a high HIV burden (Botswana, Central African Republic, Ivory coast, DR Congo, Kenya, Lesotho, Malawi, Uganda, Tanzania, Zambia, Zimbabwe) showed steady rates of between 50 and 100 in the period 1981 to 1990. After 1990, the rates began to escalate year after year (see graphs) with a high rate of close to 200 in the year 2000. These changes have been closely related to HIV epidemic (WHO 2002). In countries with established market economies (figure 1) the rates show a steady decline from 1981 to 1988, falling from 200 to 100. There was stabilization at 100 from 1988 to 1992 after which they fell further to about 80 in 1992 and remained so up to the year 2000 (WHO 2002). Eastern Europe showed a steady decline from a rate of 150 in 1981 to 100 in 1992. In 1994 the rates began to rise gradually reaching 150 in 2000 (WHO 2002). In Latin America, there was a gradual decline from 150 in 1981 to just below 100 in 1992 (figure 1). In 1992-1994, there was a rise to about 120 and remained more or less steady up to the year 2000 (WHO 2002). The Eastern Mediterranean had a rate of 150 in 1981 and remained steady up to 1986. From 1986-1989 the rates fell to between 50 and 100 and fluctuated between these until 2000 (figure 1).

The Western Pacific (excluding established market economies) showed a steady rate of about 150 with mild fluctuations between 1981 and 1988 when the rate fell to about 100 and remained steady up to the year 2000 (WHO 2002). In Southeast Asia, the rates have remained steady between 75 and 100 from 1981 to 2000 (figure 1).

In Zambia the rates are similar to those of the countries in Africa with a high HIV burden. Between 1964 and 2000 there are three discernable periods (Mwaba P, et al, 2003).

1. A relatively stable situation during the period 1964 to 1984. In this period the total number of cases increased from 4,572 in 1964 to 7,272 in 1984 reflecting an increase of the population with an average of about 3% per year. During this period the case notification rate remained relatively constant (99/100,000 in 1966 113/100,000 in 1984)
2. A gradual increase in number of tuberculosis cases in the period 1985 to 1989. During this period the case notification rates increased steadily from 113/1000 in 1984 to 189/100,000 in 1989.
3. A sharp increase of cases and notification rates during the period 1990- 2000 .In this period, the absolute number of notified new cases increased from 21,530 in 1991 to 52,000 in 2000. The case notification rates increased nearly fourfold during this period and coincides with the rise in the number of HIV and AIDS cases.

In a study done in Malawi to determine the prevalence of mycobacterium tuberculosis in patients with a cough less than 3 weeks it was found that 35% had PTB (Harries et al. 1998).

Ninety-eight adult outpatients at Queen Elizabeth Hospital who had cough for 1-3 weeks were successfully screened by microscopy and culture of 2 or 3 sputum specimens and chest radiographs; 34 (35) % had PTB. Ten patients were sputum smear-positive and 24 were smear-negative and culture positive. There was no difference in age, gender or clinical features of general illness

between patients with PTB and those with no evidence of TB. Nine patients (26%) with microbiologically confirmed tuberculosis had chest radiographs consistent with TB compared with 5 (8%) with no microbiological evidence of TB. The conclusion was that certain classes of patients with short history of cough would benefit from PTB screening strategies with emphasis on sputum examination rather than chest radiography, which is unreliable in such patients. The classes include patients in high-risk institutions like prisons and refugee camps.

This is a significant finding and attracts the need for a high index of suspicion. Other parts of the world do not have information concerning similar studies. Similarly, no study has been done in the Zambian set up to find prevalence in patients with the same duration of cough.

However, in a study done at the UTH in the department of obstetrics and gynaecology, it was found that out of 251 maternal deaths, 58% were due to non-obstetric cases and tuberculosis accounted for 25% of these deaths (Zumla et al, 1999).

BACKGROUND ON TUBERCULOSIS: DIAGNOSIS OF TB:

Traditionally diagnosis of TB is made based on clinical findings and chest radiographs and confirmed by sputum or tissue smears that show TB bacilli. These methods remain the "gold standard" for diagnosis. Polymerase Chain Reaction (PCR) allows more sensitive and rapid diagnosis. A study at the UTH found that PCR did not identify all smear positive cases and was not sustainable for routine use at a rural site (Needham et al. 1998)

PATHOGENESIS AND CLINICAL FEATURES:

Primary TB infection causes bacteremia and can affect any organ. In most patients, primary infection is asymptomatic or minimally symptomatic. Clinical pneumonia is seen in 5% to 10%.

Secondary TB (reactivation TB) is responsible for 90% of TB in patients not infected with HIV. The manifestations of TB are protean, especially if extrapulmonary involvement is present. Therefore TB should be considered in differential diagnosis of all patients with fever of unknown origin, night sweats or unexplained weight loss.

PRESENTATION OF TB IN HIV INFECTION

Unlike other opportunistic infections, TB can occur in persons with early-stage HIV infection (CD4 count > 300 cells/mm) and is similar to that in healthy hosts with reactivation disease (Chaisson RE et al. 1997). Typical symptoms include fever, weight loss, productive cough of several weeks duration and hemoptysis with less extrapulmonary disease and chest radiographs with focal infiltrates and/or cavitation involving the upper lobes.

In advanced HIV disease, TB may present atypically and extrapulmonary TB is more common. (Moreno. S. et al, 1997, Chaisson RE et al, 1987). Chest radiographs may be normal or show evidence of perihilar or mediastinal lymphadenopathy without parenchymal lung involvement. It may mimic

community-acquired pneumonia or *Pneumocystis carinii* pneumonia. Cavitation is unusual with diffuse or interstitial infiltrates. One third have positive blood cultures (Shafer W. et al, 1989).

RADIOGRAPHIC FINDINGS

Primary TB can present as lobar or segmental infiltrate, hilar adenopathy, Ghon focus, pleural effusion or bronchopneumoma. Reactivation TB can show upper lobe fibrosis, cavitations, or (less often) lower lobe fibrosis, adenopathy, pleural effusion, pneumothorax and alveolar filling pattern. (Woodring J.H et al 1986, Leung A.N 1999). A study done at 3 hospitals (Zambia and Zaire) showed that the HIV-infected patients had significantly higher proportion of lymphadenopathy, pleural effusion, miliary shadowing, an interstitial pattern, and consolidation. There was significantly less cavitation and atelectasis seen (Pobee J O et al 1997).

IMAGING TECHNIQUES:

Computerized tomography (CT) is more sensitive than chest radiographs (Im GH et al 1993)

MYCOBACTERIAL DETECTION AND ISOLATION:

Acid Fast Smear:

The Ziehl-Nielsen Carbol-fuchsin stains are less sensitive than culture but rapid and inexpensive and very specific for mycobacteria. A single sputum smear has a sensitivity of 8% to 22% but yield is improved when multiple sputum specimens are examined (NotteFSetal1995).

A UTH study showed that the use of sodium hypochlorite and not auramine increased the sensitivity from 43 % to 76.3 % with 100 % specificity (Fleming AF et al 1998).

Fluorochrome stains:

Use fluorochrome stains such as auramine-rhodamine stain. Mycobacteria fluoresce with a bright orange colour and can be seen easily with lower power microscopy, increasing the sensitivity of the smear.

Nucleic Acid Amplification:

These are rapid, widely available and can be performed in a day. The U.S Food and Drug has only approved two of three:

Gene probes: these target mycobacterial ribosomal RNA by transcription-mediated amplification.

Use of DNA probes is highly specific for *m. tuberculosis* species. It is best in patients in who acid-fast are positive and cultures are in process. Specificity is less than 100% and occasional false positive results occur in patients with non-tuberculous mycobacterial infections (MMWR Morb wkly Rep 1996, MMWR Morb wkly Rep 1993)

PCR Testing:

Amplifies a very small portion of predetermined region of *m tuberculosis* complex DNA. Can detect as few as one organism from a sample. False positive reactions from carry-overs of previously amplified DNA or from cross-contamination by the positive samples are a major draw back necessitating meticulous laboratory techniques.

Firefly Luciferase:

Uses the fluorescent capabilities of fireflies genetically implanted in *m tuberculosis*. It is in the developmental stage.

CULTURE TECHNIQUES:

The ability to culture mycobacteria is the "gold standard" in the diagnosis of TB. Cultures are more sensitive than smears but less sensitive than nucleic acid amplification.

SEROLOGICAL ASSAYS:

Development of sensitive and specific serological assays for *m* tuberculosis has been attempted for several decades but remains elusive.

TUBERCULIN SKIN TESTING:

Involves injection of 0.5 ml purified protein derivative (PPD) and assessed at 48 to 72 hours. About 20% of patients with active TB may have negative skin tests. False negatives of up to 50% have been reported in patients with advanced HIV infection.

BCG VACCINE AND SKIN TESTING:

The skin test reactivity associated with BCG in childhood usually diminishes in 5 years. A positive skin test in a person vaccinated with BCG more than 5 years should be considered as caused by *m* tuberculosis and not the BCG.

In a study done at the UTH, to determine the effects of childhood BCG immunizations and HIV infection on dual skin reactions to purified protein derivative, it was found that childhood BCG immunization is associated with PPD reactions ≥ 10 mm among adults. Reduced PPD reaction rates in HIV positive adults appear to be due to loss of BCG-induced PPD reactivity (Zumla A, Chintu C et al. 1999).

MANAGEMENT OF TUBERCULOSIS:

An effective anti-TB regime must contain multiple drugs to which the organism is susceptible and must be continued for a sufficient period of time.

The drugs streptomycin sulfate, isoniazid, ethambutol hydrochloride, rifampicin and pyrazinamide form the foundation of oral treatment. With emergence of resistance, a four drug initial regime using DOTS is recommended as standard (Bastian I and Colebonders R 1999). In general a 6-month regime

with four of the first line drugs is recommended for adults and children (American Thoracic Society 1994).

- (i) Induction phase: isoniazid + rifampicin + pyrazinamide + ethambutol for 2 months (or daily for 2 weeks and then 2 or 3 times a week for 6 months or 2 or 3 times a week for 2 months, (ii) Continuation phase: isoniazid and rifampicin daily or twice a week for 4 months In Zambia, the continuation phase is with isoniazid and ethambutol for 6 months

MULTIDRUG RESISTANT TB (MDR-TB):

This refers to resistance to at least 2 drugs, usually isoniazid and rifampicin. The most common cause of emergence of drug resistance is inadequate or incomplete treatment (Bradford WZ and Paley C L 1998). Programmes should, therefore, ensure prompt diagnosis of TB and adequate treatment (Mwinda A 2001). Treatment of MDR-TB should contain multiple bactericidal drugs to which the organism is sensitive and not previously used (Moore M et al 1997). Recommended second line drugs are capreomycin, amikacin sulfate and kanamycin sulfate. Quinolones are weakly bactericidal — ofloxacin, ciprofloxacin, sparfloxacin and levofloxacin. Ethionamide is also bactericidal. Bacteriostatic agents are cycloserine and para-aminosalicylic acid. The duration of treatment of MDR-TB depends on the response. In general treatment with at least 3 effective drugs should be continued until the cultures become negative and then a regime of at least 2 drugs for 12 to 24 months (Moore M et al 1997).

DIRECTLY OBSERVED THERAPY (DOT):

DOT means patients receive prescribed medications under direct observation of health care personnel. The decreasing incidence of MDR-TB in the United States has been attributed to successful completion of regimes by directly observed therapy (Chaulk CP and Kazandjian 1998).

EVALUATING RESPONSE TO TREATMENT:

The efficacy of a regime is determined by the rate of bacteriological conversion during therapy and the rate of relapse during or after completion of therapy (WHO 1988). Patients should be observed closely during therapy and for the first 12 months after completion (Dobos RJ 1952, WHO 1988).

TREATMENT FAILURE:

A finding on acid-fast smear or culture of m tuberculosis after 5 months of treatment is considered as treatment failure. Failure can result from prescription of inappropriate dosage or inadequate number of drugs, patient non-compliance, malabsorption or organism resistance (American Thoracic Society 1994).

RELAPSE

Active TB develops within the first 2 years after successful completion of treatment. In such cases of relapse the organism often has a susceptibility pattern similar to that of the initial infection. The possibility of new infection with m. tuberculosis should be considered.

USE OF CORTICOSTEROIDS IN TB

The addition of systemic corticosteroids has been shown to reduce morbidity in patients with high fever, severe paradoxical response, miliary TB, pericarditis and CNS TB (Dooley D P et al 1997)

PARADOXICAL RESPONSE

In the first 3 to 12 weeks after starting an apparently adequate regime, old lesions may enlarge or new ones develop - high fever, lymphadenopathy, and worsening pulmonary or extra pulmonary lesions. Recognition of this rare occurrence is important because lesions regress without change in the initial regime. Severe lesions can be treated with a short course of oral corticosteroids (Smith H 1987).

RECENT ADVANCES

Several established drugs are being evaluated as possible second line drugs for TB. They include isoniazid in high doses (16 to 20 weeks), clarithromycin, metronidazole, and amoxicillin-clavulanate potassium (augmentin). Use of fluoroquinolones has increased in treatment of MDR-TB.

Studies of alternative therapy include gene therapy and immunotherapy with aerosolized interferon-gamma or mycobacterium vaccae at initiation of treatment. A study done at the UTH showed that M. vaccae may be candidate for prevention of tuberculosis (Chintu C, Zumla A et al).

JUSTIFICATION

The standard way of diagnosing TB is to carry out sputum smear and culture examinations in patients who have been coughing for more than 3 weeks. Those with cough less than 3 weeks duration are usually put on a short course of antibiotics and only if they do not respond are they further investigated for tuberculosis. Although health workers are discouraged from investigating patients with cough less than 3 weeks (mostly due to lack of facilities), those who are HIV positive or appear chronically ill looking are sent for sputum examination. Sometimes they are just sent for routine sputum examination. Little is known about the amount of tuberculosis there is in these patients. There is need to know the extent of the problem and possibly revise the diagnostic criteria.

OBJECTIVES

General objective

To determine the prevalence of PTB in patients with a short history of cough (< 3 weeks)

Specific objectives

1. To describe the clinical features in patients with cough less than 3 weeks.
2. To describe the laboratory features in patients with cough less than 3 weeks.
3. To describe the radiological features of patients with cough less than 3 week.

CHAPTER 2

RESEARCH METHODOLOGY

Study design

This was a cross-sectional descriptive study.

Study site

The study was conducted at Kamwala, Chilenje and Kabwata Clinics, Lusaka. The reason for choosing urban clinics was that it would increase the number of patients recruited to the study including those who would not have reached a tertiary center such as the UTH therefore making the study more representative. A tertiary center tends to receive patients who have complications and by the time the patients are referred they may already have been coughing for more than 3 weeks. Moreover, those with cough but not considered to have complications are unlikely to reach the UTH and these form an important part of the study.

Adult patients were systematically recruited after getting consent on prescribed consent form. The principal investigator visited the clinic on Mondays, Wednesdays and Fridays. The study period was approximately 6 months.

Sample size

209 patients were recruited into the study (sample size determined using EPI-INFO)

INCLUSION CRITERIA:

1. Adult aged 15 years and older
2. Cough less than 3 weeks
3. Not previously treated for TB in the last one year.
4. Cough free for at least one month prior to onset of cough under investigation.
5. Written consent.

EXCLUSION CRITERIA:

1. TB treatment
2. History of TB in the last 1 year.
3. Serious associated illness e.g. hepatitis, meningitis.
4. Failure to submit sputum.
5. Extra-pulmonary tuberculosis.

CLINICAL METHODS

All patients in the study underwent a thorough clinical evaluation. This included a history and physical examination. Medical history included reviewing past medical history i.e. medical records of patients. Physical examination included general examination, respiratory system examination and examination of other systems as the patient presents.

LABORATORY METHODS

Sputum microscopy and culture

All sputum specimens underwent microscopy for AAFB and culture on Lowenstein Jensen slopes. Cultures from which mycobacterium were grown were counted as positive. Morning sputum was collected on 3 consecutive days. Patients had to come back for their results after one week, and were be told the results and put on appropriate treatment.

Chest radiographs

All patients had routine chest radiographs, which were examined with assistance of a consultant radiologist and at least 2 physician consultants without the knowledge of the sputum results. Each chest radiograph was studied for cavities, infiltration, number of zones with infiltration, upper lobe fibrosis, hilar/paratracheal lymphadenopathy and pleural effusion. They were categorized as either (i) normal or showing abnormalities not consistent with TB or (ii) showing abnormalities consistent with TB (i.e. cavities, upper lobe fibrosis, intrathoracic lymphadenopathy, infiltrations affecting all 6 zones and extensive pleural effusion affecting more than half of one thoracic cavity). Although all these features were taken into consideration, it must be emphasized that the ultimate diagnosis is sputum examination.

DATA COLLECTION:

This was recorded on data collection sheets.

Type, frequency and amount of data

Name, age, sex, file number

Residential address

Diagnosis on admission

Duration of cough

Name of antibiotic given

Other associated symptoms, e.g. fever, weight loss, asthma.

Chest x-ray findings

Sputum results

HIV related illness- oral candidiasis, Kaposi's sarcoma, herpes zoster

STUDY STAFF

Supervisor:

Responsible for the supervision and the coordination of the project in general.

Principal investigator

Worked in conjunction with the supervisor and is actually the subject under training for the masters degree. Will collect the data and ensure that the other staff works well.

Nurses:

Worked with the principal investigator and ensure that patients do the chest x-rays and submit sputum in the correct containers and at the right time.

Data entry clerk:

Worked with principal investigator and entered data on the computer on EPI-INFO.

Biostatistician:

Helped to analyze the data.

ETHICAL CONSIDERATIONS:

- (i) This study underwent ethical committee review and approval was given
- (ii) All patients were given informed consent and therefore made informed choices. If they refused to take part in the study, they would not be treated negatively but would be investigated and treated like any other patient.
- (iii) Data was stored carefully while maintaining patient confidentiality and privacy,
- (iv) Patients were provided with the results of the sputum and were told the chest x-ray findings.

CHAPTER 3

RESULTS

Analysis: Data of patients from whom 3 sputum specimens had reached the laboratory and from whom there was a chest radiograph available were analyzed. Data were entered onto Epi-info statistical program. The χ^2 test was used to assess differences in proportions and the student's t test to assess differences in means. Values of P less than or equal to 0.05 were regarded a significant finding.

Patients

Two hundred and nine patients were screened (125 males, 84 females, mean age 34 years) and two hundred and four had 3 sputum specimens examined in the laboratory and a chest radiograph available for inspection. -Thirty-six (17.2%) patients stated that their cough had been present for 2-3 weeks and the rest had their cough present for less than 2 weeks (table 1 and 2).

Table 1: COUGH-14 TO 21 DAYS

Duration of Cough in Days	Freq	Percent	Cum.
15	1	2.8%	2.8%
16	4	11.1%	13.9%
17	6	16.7%	30.6%
18	5	13.9%	44.4%
19	4	11.1%	55.6%
20	1	2.8%	58.3%
21	15	41.7%	100.0%
Total	36	100.0%	

P-0.00000

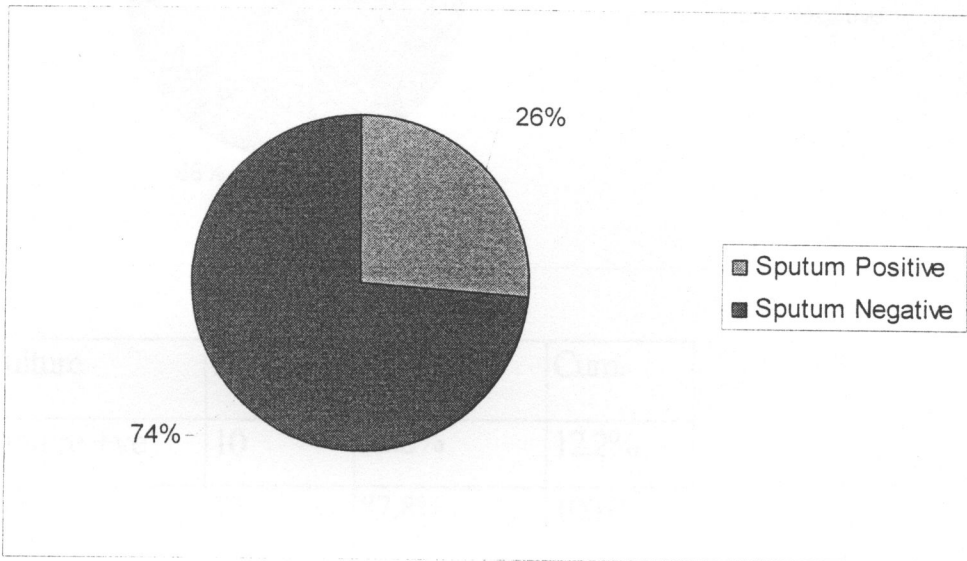
Table 2: Cough duration less than 14 days

Duration of Cough < 14 Days	Freq	Percent	Cum.
3	1	0.6%	0.6%
4	2	1.2%	1.8%
5	1	0.6%	2.4%
7	36	21.7%	24.1%
8	1	0.6%	24.7%
9	2	1.2%	25.9%
10	10	6.0%	31.9%
11	3	1.8%	33.7%
12	4	2.4%	36.1%
13	4	2.4%	38.6%
14	102	61.4%	100.0%
Total	166	100.0%	

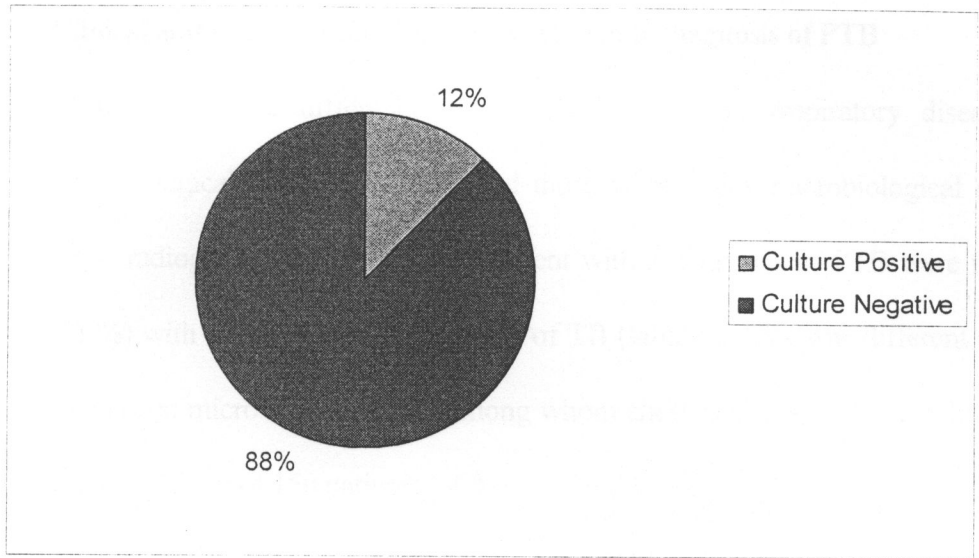
Prevalence of PTB

Fifty-four (26 %) patients out of the two hundred and four who submitted sputum had microbiological evidence of PTB; P -value 0.00000. They had positive sputum smears (table 4)

Table 3: Number of positive smears out of all those that submitted sputum



ZN STAIN	Freq	Percent	Cum.
Sputum +ve	54	26.5%	26.5%
Sputum -ve	150	73.5%	100.0%
Total	204	100.0%	



Culture	Freq	Percent	Cum.
Culture +ve	10	12.2%	12.2%
Culture -ve	72	87.8%	100.0
Total	82	100.0%	

Clinical and radiographic features in relation to diagnosis of PTB

There were some differences in clinical features of respiratory disease between patients with microbiological evidence of PTB and those without any microbiological evidence of PTB (table 6). Chest radiograph abnormalities consistent with a diagnosis of PTB were found in 29 out of 54 patients (53 %) with microbiological evidence of TB (table 5). This was different from findings in patients with no microbiological TB, among whom chest radiograph abnormalities consistent with TB were found in 55 out of 150 patients (36%).

Table 5: SPUTUM RESULTS AND CHEST X-RAY FINDINGS

ZN-STAIN	CHEST X-RAY							Total
	Plenal effusion	Miliary mottling	Hiliar adenopathy	Consolidation	Infiltration < 6 zones	Infiltration > 6 zones	Normal	
Sputum positive	0	17	8	7	13	4	1	53
Sputum negative	26	12	11	7	28	4	61	14

Table 6: CLINICAL FEATURES OF PATIENTS IN SPUTUM SMEAR POSITIVE AND SPUTUM SMEAR NEGATIVE PATIENTS

	SMEAR POSITIVE (MICRO BIOLOGICAL GUIDANCE	SMEAR NEGATIVE
No of Patients	54	150
Fever	48 (88%)	133 (88%)
Hemoptysis	3 (6%)	19 (12%)
Chest pain	36 (67%)	109 (72%)
Dyspnoea	40 (74%)	111 (74%)
Weight loss	48 (88%)	110 (26%)

CHAPTER 4

DISCUSSION

This study showed that 26 % of adult patients with a cough less than 3 weeks who were seen in the outpatient department of 3 Lusaka urban clinics had pulmonary TB. This is in sharp contrast to the myth that one should suspect tuberculosis in patients with coughs longer than 3 weeks. It has implications in that many of the TB patients, at least a quarter are not diagnosed early enough and this may explain some of the poor outcomes seen in this category of patients.

The age range of the patients was from 18 years to 72 years with a mean age of 34 years. This coincides with peak age of HIV infection indicating that probably most of these patients had HIV related coughs or tuberculosis. Zambia is in the midst of a very serious epidemic of both tuberculosis and HIV infection. Tuberculosis today is a major cause of morbidity and mortality and is the persistent threat to the health of the population of Zambia. The tuberculosis epidemic appears to be one of the most severe and this calls for increased efforts at case detection, follow up and improvement in the general management of patients. The annual incidence of tuberculosis has increased four fold between 1982 and 1996. Although it is difficult to measure much of the recorded increase reflects real changes in the incidence of tuberculosis. The increase being both due to HIV epidemic and the traditional factors influencing tuberculosis trends such as poverty, malnutrition and failures in the treatment systems.

In this study, the diagnosis of TB was based on sputum smear examination. Only 82 (table 7) sputum cultures were done (34 %) due to logistical problems. Of these 10 were positive (12 %) and 72 were negative (87 %). There was a problem in the coordination of transportation of sputum

specimens between the various urban clinics and center for sputum cultures in Chelstone. Most of the samples apparently never got there. Among those that did get there cultures were only done on every fifth sample. This is said to be a cost effective measure. Certainly, if all the cultures were all done, the microbiological diagnosis would have shown a higher percentage. The University Hospital at the moment has no reagents to carry out sputum cultures for tuberculosis on a routine basis. The smear results in this study are still significant as all public health measures are based on microscopy and not culture.

In TB suspects with a chronic cough, radiographic diagnosis of PTB is difficult and prone to intra- and inter-observer error. In patients with short duration of cough, who may have pneumonic consolidation, the diagnosis of TB based on radiographic criteria alone is even more liable to error. Although 55 patients with negative sputum smear results had chest x-rays with features suggestive of TB, I am not willing to make a definite diagnosis of TB on these grounds alone. Nearly half of patients with microbiological evidence of TB had chest radiographs not consistent with TB, which emphasizes the inadequacy of the chest radiograph as a TB diagnostic tool in patients with short duration of cough. Many previous studies have demonstrated the difficulties on interpreting chest x rays in HIV infected individuals as the picture tends to be confusing as many opportunistic infections such as PCP, Kaposi Sarcoma, bacterial pneumonias may simulate tuberculosis. It is therefore important that microscopic studies be performed in all patients presenting with coughs in HIV endemic areas. Comparing the clinical features of patients with microbiological evidence of TB and those with no evidence is seen that fever is more or less the same in both groups but weight loss is significant in the sputum positive than those with sputum negative results. This suggests that a combination of



weight loss and fever is more suggestive of tuberculosis rather than fever alone. Acute symptoms like chest pain and dyspnoea were more in the sputum negative group than the positive suggesting more acute afflictions such as pneumonia. There was less hemoptysis seen in patients with sputum Smear positive results than those with negative results. This may be because of the presence of consolidations and rusty sputum of pneumonia. Although all the patients had a cough, this study cohort has shown that cough on its own is not a strong clinical feature for tuberculosis. Presence of fever and more importantly weight loss is significant. If all the patients with short duration coughs were examined for tuberculosis, the number of notified cases will definitely increase and it is possible that this may lead to the reduction in the morbidity and mortality associated with tuberculosis in Zambia.

CONCLUDING REMARKS AND RECOMMENDATIONS:

There is a high number of patients with tuberculosis among patients presenting with short duration of coughs less than three weeks. Of two hundred and four patients who were investigated for the prevalence of PTB in cough of less than 3 weeks duration, a significant number had pulmonary tuberculosis; 54 out of 204 (26 %) had microbiological evidence of tuberculosis.

Weight loss and fever in a patient with a cough less than three weeks should alert one to the possibility of tuberculosis.

Sputum examination for tuberculosis must be part of the routine investigations in all patients presenting to health centers with coughs regardless of the duration. There is strong need to regularly reevaluate diagnostic algorithms for tuberculosis and other diseases in view of an escalating HIV epidemic there is urgent need to reproduce the findings of this study on a large scale.

SOURCES OF BIAS:

The inability of patients to give accurate information concerning the duration of their cough is a source of bias. The interpretation of chest x-rays may differ among different individuals and could also be a source of bias.

STUDY LIMITATIONS:

- I. Inability to conduct adequate sputum cultures for TB. This no doubt has affected the final outcome of the study.
- II. Lack of money to carry out supportive and other diagnostic investigations such as full blood count and erythrocyte sedimentation rate (ESR), blood TB antigen tests, cultures of sputum using the MGIT kit.

REFERENCES

1. Martin G, Lazarus A. Epidemiology and diagnosis of tuberculosis: recognition of at risk patients is key to prompt diagnosis.
2. Dubos R J. The White plague: tuberculosis, man and society. Boston: little Brown, 1952.
3. Global tuberculosis programme. In Global tuberculosis control. WHO report in 1988. Geneva: World Health Organisation, 1988: 237
4. Ravigilion M.C, Snider D.C Jr, Kochi A. Global epidemiology of tuberculosis: morbidity and mortality of a worldwide epidemic. JAMA 1995; 273 (3): 220-6
5. Zambia has 40,000 TB cases each year; Tuesday, January 18, 2000; Africa news.
6. Bates J H, Stead W W. The history of tuberculosis as a global epidemic. Med Clin. North AM 1993; 77 (6): 1205-17
7. Needham D.M, Godfrey Fausset P, Foster S. Barriers to tuberculosis case finding in Zambia; the economic impact and burden on patients prior to diagnosis. Intl. J. Tubercle Lung disease; 1998; 2: 811-817.
8. Woodring J H. Vandiviere H.M, Fred A.M, et al. Update: the radiographic features of pulmonary tuberculosis. AM J Roentgenol, 1986; 146 (3): 497-506.
9. Leung A N. Pulmonary tuberculosis: the essentials. Radiology 1999; 210 (2): 307-22
10. Im GH, Itoh H, Shim Y.S et al. Pulmonary tuberculosis: CT findings - early active disease and sequential change with antituberculous therapy. Radiology 1993; 186 (3): 653-60.

11. Notte F.S, Metchock B. Mycobacterium. In: manual of clinical microbiology. 6th ed. Washington DC: American society for microbiology, 1995: 414
12. Nucleic acid amplification tests for tuberculosis. MMWR Morb Mort wkly Rep 1996; (43): 950-1

Diagnosis of tuberculosis by nucleic acid amplification methods applied to clinical specimens. MMWR Morb Mort wkly rep 1993; 42 (35): 686.
14. Ahmed Y, Mwaba P, Chintu C, Grange J.M, Zumla A. Maternal mortality at University teaching hospital, Lusaka, Zambia: the emergence of tuberculosis as a major non-obstetric cause

of maternal deaths Int. J. Tuberc. Lung disease 1999 Aug; 3 (8): 675-80.
15. Waddell R.D, Von Reyn C.F, Baboo K.S, Mwinga A, Chintu C, Zumla A. The effects of BCG immunization and human immunodeficiency virus infection on dual skin test reactions to purified protein derivative and mycobacterium avium sensitin among adults in Zambia. Int J Tuberc lung disease 1999 Mar; 3 (33): 255-60.
16. Habeenzu C, Lubasi D, Fleming A.F. Improved sensitivity of direct microscopy for detection of acid-fast bacilli in sputum in developing countries. Trans R Soc Trop Med Hygiene 1998 Jul-Aug; 92 (4): 415-6
17. Tshibwabwa-Tumba E, Mwinga A, Pobee J O, Zumla A. Radiographic features of pulmonary tuberculosis in 963 HIV infected adults at three central African hospital. Clin. Radiol. 1997 Nov; 52 (11): 837-41
18. Mwinga A. Drug Resistance in Africa. Ann NY Acad sci 2001 Dec; 953: 106-112.

19. Mwinga A, Mwaba P, Pobee J, Godfrey Fausset P et al. Twice weekly tuberculosis
20. Lazarus A, Epstein A, Slater PE, Waler-Ravel D. Epidemiological analysis of tuberculosis treatment outcomes a tool of changing TB control policy in Israel. *Isr Med Assoc. J.* 2001.M; 3 (7): 533-4
21. Lazarus A, Sanders J. Management of tuberculosis: choosing an effective regime and ensuring compliance. *Postgraduate medicine* 2000; 1089 (2): 71-84
23. American Thoracic Society. Treatment of tuberculosis infection in children. *AMJ respire. Crit care med* 1994; 149: 1359 – 74.
- 24 Bradford W.Z Paley C.L Multidrug resistant tuberculosis. *Infec. Dis Chin North Am* 1998; 12(1) 157-72
- 25 Moore M, Onerato I.M, McCray E et al. Trends in drug resistant tuberculosis in the United States, 1993-1996. *JAMA* 1997; 278 (10): 83326
- 26 Chaulk C.P Kazandjian V.A Directly observed therapy for treatment completion of pulmonary tuberculosis: Consensus statement of the public health tuberculosis guidelines panel: *JAMA* 1998;
- 27 Dooley D.P, Carpenter J.L Tuberculosis: a critical reappraisal of the literature J.L Rademachers adjunctive corticosteroid therapy for *Clin infect dis* 1997; 25 (4): 872-87
- 28 Smith H. Paradoxical responses during the chemotherapy of tuberculosis. (Editorial) *J infect* 1987; 15:13
- 29 H.T Banda, A.D.Harries, S. Welby et al. Prevalence of tuberculosis in patients with a short history of cough. *Transactions of the royal society of tropical medicine and hygiene.* (1998) 92, 161 165.

- 30 Waddell R.D, Chintu C, Lain A.D, Zumla A et al. Society and Immunogenicity of a five dose series of vaccination for the prevention of HIV-associated tuberculosis. Infectious disease section, department of medicine Dartmouth-Hithcock medical center, Lebanon, 03750, USA.
- 31 World Health Organisation. Global Tuberculosis Control : surveillance, planning , financing. WHO Report 2002. Geneva, Switzerland, WHO/CDC/TB/2002.295.
- 32 Mwaba P, Chintu C, Zumla A et al. The relentless spread of tuberculosis in Zambia- trends over the past 37 years (1964-2000) S. Afr.Med.J.2003 Feb; 93 (2): 149-52
33. Moreno S, Mirales P, Diaz M.D et al. Isoniazid preventive therapy in human immunodeficiency virus-infected persons: long term effect on development of tuberculosis and survival. Arch intern Med 1997; 157 (15): 1729-34.
- 34 Chaisson RE, Scheter GF et al. Tuberculosis in patients with acquired immunodeficiency syndrome: clinical features, response to and survival. Am Rev Respir dis 1987; 136 (3) 570 – 4
- 35 Shafer W, Goldberg R et al. Frequency of Mycobacterium tuberculosis bacteremia in patients with tuberculosis in area endemic of AIDS. Am Rev Respir Dis 1989; 140 (6): 1611-3

APPENDIX 1**CONSENT FORM**

I am doing a research study on how much tuberculosis there is in patients who have been coughing for 3 weeks or less.

Confidentiality

All the information collected during your participation in the study will be kept confidential.. All laboratory results will be coded and will be known by the researcher.

Risks and benefits

Study procedures only will consist of collection of sputum from you and radiograph or chest x-ray. This will be painless and has no risk. There is no direct monetary gain but you will benefit from the results of the study. In case your results prove to be positive for tuberculosis, you will be told the results and provided with standard health care as it will provided to any other patient at this clinic.

Participation in the study.

Your participation in this research is voluntary. You are free to ask any questions or seek any clarifications during your participation. You can withdraw from this study any time if you wish to do so. Your withdrawal will not affect the standard care and treatment that you will receive from the clinic.

Consent

By now you have understood the purpose and implications of this study. If you wish to participate, please put your signature or thumbprint with your initials where indicated. Giving consent does not violate your right to withdraw. Please call the following in case of any query:

Dr Caroline Malibata,
University teaching Hospital,
Department of Internal Medicine,
P.O. Box 5001,
Lusaka.

Professor Karashani,
University of Zambia,
School of Medicine,
Ridgeway campus,
Lusaka.
Phone:

Signature

Thumbprint

Witness