FOLLOW UP OF PATIENTS STARTED ON ANTI-TUBERCULOSIS TREATMENT (ATT) USING CLINICAL AND RADIOLOGICAL CRITERIA

BY

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DECLARATION

I here declare that the work presented in this study for the Master of Medicine has been presented either wholly or in past for any other degree and is not being currently submitted for any other degree.

SIGNED: ..... STUDENT

SIGNED: ..... SUPERVISOR

SIGNED: ..... EXTERNAL EXAMINER

SIGNED: ..... BOARD

DATE OF APPROVAL: 8/5/2003

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SUMMARY:

During the last decade there has been an increase, notifications of rates of tuberculosis world over and rate has been higher in developing countries. This upswing is attributed to Acquired Immune Deficiency Syndrome (AIDS) as the predisposing factor to pulmonary tuberculosis. However, it should be remembered that pulmonary disease secondary to AIDS is not always pulmonary tuberculosis.

To address this issue open cross sectional descriptive study was conducted at UTH. Chest Clinic had 711 adult patients put on ATT was followed for a period of two months. The result of the follow up are presented in this dissertation.

Considering the impact tuberculosis has on meagre resources and medical facilities, it is imperative that problems identified in this study be ratified. It may help reduce costs and improve care for patients with tuberculosis.

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INTRODUCTION

Zambia is a land-locked country Sub-Saharan African country lying between latitudes 22 and 34 east and longitude to 8 to 18 South with own attitude between 900 to 1500 metres above sea level.

It has an area of 7,526 square kilometres. Zambia shares boarders with Democratic Republic of Congo in the North, Tanzania NorthEast, Malawi and Mozambique in the East, Zimbabwe and Botswana in the South, Namibia in the South West and Angola on the West. The population projection for 1998 is approximately 10million. Zambia is a low-income country with 51% population living in urban areas. Life expecting is 45 years and per capital expenditure on health was US$14 in 1991 (World Bank 1993).

Lusaka is the capital city of Zambia with 360 square kilometres and projected population of 1.8 million in 1998. In the last 20 years, these has been a proliferation of shanty compounds without a march in provision of essential social amenities, resulting in them being breeding grounds for infectious diseases tuberculosis included. Health facilities include UTH which suppose to a tertiary centre a mine and military hospitals, 21 urban health clinics and many private clinic whose number is increasing rapidly.

Tuberculosis

Tuberculosis is chronic illness affecting the lungs and other organs of the body caused by acid-fast mycobacterium bacilli. We can attribute the recent increase in TB cases to at least three factors: the HIV epidemic, the spread of TB in certain settings, and inadequate funding for TB control and other public health efforts.

Some groups of people are at higher risk for TB disease because they are more likely to be exposed to or infected with Mycobacterium tuberculosis. This category includes close contacts of people with infectious TB disease, people born in areas of the world where TB is common, elderly people, low-income groups with poor access to health care, and people who inject illicit drugs. It also includes people who live or work in certain settings (for example, nursing homes, correctional facilities, homeless shelters, and drug treatment centers) and other people who may be exposed to TB on the job, such as health care workers.

Other groups of people are at higher risk for TB disease because they are more likely to develop the disease once infected - for example, people with certain medical conditions, especially HIV infection. For people infected with Mycobacterium tuberculosis and HIV, the risk of developing TB disease is about 7% - 10% each year. In contrast, for people infected only with

Mycobacterium tuberculosis, the risk of developing TB disease is 10% over a lifetime.

Studies show that there is a connection between the HIV epidemic and the increasing rates of TB. First, the areas that have been the most affected by the HIV epidemic have also reported the largest increases in TB cases. Second, the largest increase in TB cases has occurred among people aged 25 to 44, the age group most affected by AIDS. Third, TB is common among AIDS patients. Fourth, HIV infection is common among TB patients.

More than 70% of TB cases reported in the United States in 1993 were in racial and ethnic minorities. This is probably because a greater proportion of people in these groups has other risk factors for TB.

From 1985 to 1993, the number of TB cases in children increased by 36%. The occurrence of TB disease and infection in children provides important information about the spread of TB in homes and communities. For example, when a child has TB disease or infection, we learn that TB was transmitted relatively recently. This means that the person who transmitted TB to the child may still be infectious. This also means that other adults and children in the household or community have probably been exposed to TB. If they are infected, they may develop TB disease in the future.

Diagnosis of Pulmonary Tuberculosis:

Pulmonary tuberculosis is acquired by inhaling contained air, bacilli in the air is shade by individuals who have pulmonary tuberculosis.

There are four steps in diagnosing TB disease: medical history, tuberculin skin test, chest x-ray, and bacteriologic examination.

A **medical history** includes asking the patient whether they have been exposed to a person with TB, symptoms of TB disease, if they have had TB infection or TB disease before, or risk factors for developing TB disease. The symptoms of pulmonary TB disease include:

- **coughing**
- **pain in the chest when breathing or coughing**
- **coughing up sputum or blood.**
  The general symptoms of TB disease (pulmonary or extra-pulmonary) include:
- **weight loss**
- **fatigue**
- **malaise**
- **fever**
- **night sweats**

The symptoms of extra-pulmonary TB disease depend on the part of the body that is affected by the disease.

Patients with symptoms of TB disease may be given a **tuberculin skin test.** They should be evaluated for TB disease, regardless of their skin tests results.

The **chest x-ray** is used to help rule out the possibility of pulmonary TB disease in a person who has a positive reaction to the tuberculin skin test. And check for lung abnormalities in people who have symptoms of TB disease. The results can not confirm that a person has TB disease. Post-primary tuberculous lesions in the lungs are characteristically located in the posterior segment of the right upper lobe, apico-posterior segment of the left upper lobe and apical segments of the lower lobes. However, the radiographic findings have been described as atypical in the presence of diabetes mellitus (level III evidence) and HIV infection (level I evidence).

A common presentation of primary TB is an acinar lesion (pneumonia) with enlargement of the ipsilateral lymph nodes. In children such a presentation is especially common and is often accompanied by atelectasis. Occasionally the only finding is a pleural effusion. In reactivated pulmonary TB the lesions are more commonly seen in the upper lobes; however, they may appear in any lobe. Radiographic examination is unreliable in determining the activity of the lesion. Such a determination requires serial radiographs and examination of sputum for the presence of bacilli. A normal chest radiograph does not exclude a diagnosis of TB. Chest radiographs in patients with bacteriologically

proven pulmonary TB appear normal in a minority of patients; however, this occurs more often in the presence of HIV infection. Therefore, sputum should be collected for mycobacteriologic tests from patients at high risk who have appropriate symptoms

The fourth step is a **bacteriologic examination**. A sputum specimen is obtained from patients suspected of having pulmonary TB disease; other specimens are obtained from patients suspected of having extrapulmonary TB disease. The specimen is examined under a microscope for the presence of acid-fast bacilli. When AFB are seen, they are counted. Patients with positive smears are considered infectious. The specimen is then cultured, or grown, to determine whether it contains M. tuberculosis. A positive culture for M. tuberculosis confirms the diagnosis of TB disease.

After the specimen has been cultured, it is tested for drug susceptibility. The results of drug susceptibility tests can help clinicians choose the appropriate drugs for use in treatment.

The gold standard for the diagnosis of TB is a positive result of culture for M. tuberculosis. Therefore, the proper collection, handling and identification of each specimen are extremely important.

Three specimens of sputum (respiratory mucus rather than saliva) should be collected on successive days. However, physicians should not discard saliva, especially if the patient is unable to produce mucus, since it may yield a positive result when cultured. Gastric washings are a useful method of obtaining specimens in children or in adults who cannot produce sputum. Three washings should be collected on successive mornings before feeding in the case of an infant or after an overnight fast. If these procedures fail to produce a positive result and suspicion remains, sputum induction or bronchoscopy may be required, and appropriate referral is indicated. If genitourinary or disseminated TB is suspected three early-morning mid-stream urine samples should be collected on successive days.

In some cases tissue samples are required for biopsy. Cervical lymphadenopathy caused by tuberculous infection is a noteworthy example. Such lymphadenopathy in Canadian-born children except for aboriginal children is usually caused by mycobacterial species other than M. tuberculosis. [20,34] In contrast, cervical lymphadenopathy in aboriginal Canadians and immigrants from countries with a high incidence of TB is almost invariably tuberculous. It is extremely important that some tissue collected is reserved for bacteriologic tests and sent to the laboratory in normal saline and that a portion of the sample is not immersed in formalin. Close liaison with the surgeon or radiologist is required to obtain the needed tissue for bacteriologic

testing, since the sample is essential to identification of the organism and its susceptibility to drugs, and hence to diagnosis and proper treatment. The distinction between lymphadenopathy caused by M. tuberculosis and lymphadenopathy caused by other mycobacteria is important because therapy for each differs.

Newer Technologies:

Several research tools, which are not yet used routinely in clinical settings, may prove useful in diagnosing TB. The polymerase chain reaction is the most promising of this group of tools. With the use of synthesized primers (templates) of M. tuberculosis DNA this technique can identify organisms in samples with a low bacteria count (less than 10 bacilli) within a short period (24 to 48 hours) after collection of the sample. Its main disadvantages are its high sensitivity and the risk of contamination of the sample. The practical problems associated with polymerase-chain-reaction testing of various body secretions and tissues are rapidly being overcome. The technique is also useful in distinguishing between M. tuberculosis and other mycobacteria when smears are positive for acid-fast bacilli. [35] Rapid species identification is particularly valuable in patients with HIV infection, because most of the mycobacterial isolates in such patients are not M. tuberculosis.

Serologic techniques using purified antigens or monoclonal antibodies or both have shown encouraging results in identifying extrapulmonary and pediatric pulmonary TB. The sensitivity of some of these techniques is similar to that of smears in identifying pulmonary TB. The main advantage of serologic examination is that blood is easily obtained when sputum is not available. The main disadvantage is the degree of overlap between normal and abnormal test results in the very situations in which such testing would be useful, such as extrapulmonary TB, in which secretions may not be available for culture.

Infectiousness of TB and Infection Control:

The infectiousness of a TB patient is directly related to the number of tubercle bacilli that he or she expels into the air. Patients who expel many tubercle bacilli are more infectious than patients who expel few or no bacilli. Patients are more likely to be infectious if they:

- **Have TB of the lungs or larynx**
- **Have a cavity in the lung**
- **Are coughing or undergoing cough-inducing procedures**
- **Are not covering their mouth when coughing**
- **Have acid-fast bacilli on the sputum smear**
- **Are not receiving adequate treatment**

Infectiou

started,

who have been receiving adequate treatment for 2 to 3 weeks, whose symptoms have improved and who have 3 consecutive negative sputum

smears from sputum collected on different days can be considered noninfectious.

TB can be spread in many places, such as homes or work sites. TB can also be transmitted in health care facilities. TB is most likely to be transmitted when health care workers and patients come in contact with patients who have unsuspected TB disease, who are not receiving adequate treatment, and who have not been isolated from others. All health care facilities should take measures to prevent the spread of TB.

The main goal of an infection control program is to detect TB disease early and to promptly isolate and treat people who have TB disease. The infection control program should involve three types of controls - administrative controls, engineering controls, and personal respiratory protection - as well as training and education and TB screening for health care workers.

Patients who have signs or symptoms of TB disease should be placed in an area away from other patients and promptly given a diagnostic evaluation. Patients who are likely to have TB should start appropriate treatment at once. In hospitals and other inpatient settings, patients known to have TB disease or suspected of having TB disease should be placed in a special isolation room

right away. This isolation room should be at negative pressure relative to other parts of the facility.

Three types of engineering controls are used to prevent the transmission of TB in health care facilities: ventilation, high-efficiency particulate air (HEPA) filtration, and ultraviolet germicidal irradiation (UVGI). HEPA filters and UVGI should be used in conjunction with other infection control measures.

In places where administrative and engineering controls may not fully protect health care workers from infectious droplet nuclei, health care workers should use personal respirators to filter out droplet nuclei.

The health department should work closely with health care facilities to:

- **Help them report confirmed or suspected TB cases as quickly as possible**
- **Do contact investigations**
- **Make sure there is a plan for TB patients to receive follow-up care after they are discharged**
- **Help the facilities with screening, surveillance, outbreak investigations, and other aspects of a TB infection control program**

People with TB disease are most likely to transmit TB before the disease has been diagnosed and treatment has started. TB patients who are receiving treatment are less likely to be infectious. TB patients who may be infectious should be instructed to cover their mouth and nose with a tissue when coughing or sneezing.

Health care workers who visit TB patients at home should take precautions to protect themselves from the spread of TB. They should instruct patients to cover their mouth and nose with a tissue when coughing or sneezing, wear a personal respirator when visiting the home of an infectious TB patient or when transporting an infectious TB patient in a vehicle, collect sputum specimens in a well-ventilated area (if possible outdoors), and participate in a TB screening and prevention program.

Treatment of Tuberculosis infection:

Preventive therapy is medication that is given to people who have TB infection to prevent them from developing TB disease. High-risk people should be evaluated for preventive therapy if they have a positive skin test reaction, regardless of their age. Others should be evaluated for preventive therapy if they have a positive skin test reaction and they are younger than 35 years old. Sometimes preventive therapy is given to people who have a negative skin

test reaction, such as high-risk contacts and children younger than 6 months old who have been exposed to TB.

All patients being considered for preventive therapy should receive a medical evaluation to:

- **exclude the possibility of TB disease**
- **determine whether they have ever been treated for TB infection or disease**
- **identify any medical problems that may complicate therapy or require more careful monitoring**

People who are suspected of having TB disease or who have been adequately treated for TB infection or disease should not be given preventive therapy.

The usual regimen for preventive therapy is isoniazid given daily for 6 months. Children should receive 9 months of preventive therapy; HIV-infected persons should receive 12 months. Patients should be evaluated every month for signs of hepatitis and other adverse reactions to isoniazid. They should also be educated about the symptoms caused by adverse reactions to isoniazid and instructed to seek medical attention immediately if these symptoms occur. In addition, people at greatest risk for hepatitis should have liver function tests before starting isoniazid preventive therapy and every month during therapy.

TB disease must be treated for at least 6 months; in some cases, treatment lasts even longer. In most areas of the country, the initial regimen for treating TB disease should include four drugs: isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin. When the drug susceptibility results are available, clinicians may change the regimen accordingly. TB disease must be treated with at least two drugs to which the bacilli are susceptible. Using only one drug to treat TB disease can create a population of tubercle bacilli that is resistant to that drug. Drug resistance can also develop when patients do not take treatment as prescribed. Thus, to prevent relapse and drug resistance, clinicians must prescribe an adequate regimen and make sure that patients adhere to treatment. The best way to ensure that patients adhere to treatment is to use directly observed therapy.

There are several options for daily and intermittent treatment. For children with certain types of extrapulmonary TB, pregnant women and people with drug-resistant TB, treatment may last longer or involve different regimens. Treatment of drug-resistant TB should be done under the supervision of a medical expert who is familiar with the treatment of drug-resistant TB.

All patients being treated for TB disease should be educated about the symptoms caused by adverse reactions to the drugs they are taking and instructed to seek medical attention immediately if they have symptoms of a

serious side effect. Patients should be seen by a clinician at least monthly during treatment and evaluated for possible adverse reactions. In addition, before starting treatment, patients should have baseline tests to help clinicians detect any abnormalities that may complicate treatment.

Patients who are not receiving directly observed therapy should be carefully monitored for adherence to treatment. The only way to ensure adherence to treatment is to use directly observed therapy.

To determine whether a patient is responding to treatment, clinicians should do clinical evaluations and bacteriologic evaluations during treatment. Patients should be carefully reevaluated if their:

- **Symptoms do not improve during the first 2 months of treatment**
- **Symptoms worsen after improving initially**
- **Culture results have not become negative after 2 months of treatment**

In certain situations, clinicians may also use x-rays to monitor a patient's response to treatment. The treatment of TB can be complicated, especially in patients who fail to respond to treatment, who relapse, or who have drug-resistant TB or adverse reactions to medications. Clinicians who do not have experience with these situations should consult a medical expert.

Problems in Diagnosis:

Many diseases can present with the above symptoms; therefore diagnosis of pulmonary tuberculosis on symptoms alone is difficult. Physical signs are also not specific and indeed there may be none at all.

To help clinician to reach diagnosis, there are laboratory tests that are used, but there are not without inherited problems.

Sputum smear after concentration for AAFB is the gold standard in the diagnosis of pulmonary tuberculosis. This method show sensitivity of 50-70% and specificity is 94-99%. This method may delay starting patient on medication especially those who are seriously ill and a third of patients with early pulmonary tuberculosis may be sputum smear negative. Culture of sputum in our hospital is indicated in patients whose sputum is negative and x-ray is suggestive of pulmonary tuberculosis and those who are positive but not responding to standard anti-tuberculosis drugs. It is done on Lowenstein Jensen medium. This test medium takes about 6 weeks, which is even worse for a patient who is desperately ill. All these methods need a lot of trained manpower and expanded laboratory facilities and especially with ever increasing number of tuberculosis patients.

Chest x-ray is mostly widely diagnostic for pulmonary tuberculosis despite its non-specificity changes for tuberculosis and its relative expense. Its advantage is that it can be ordered and done in very short time. Doctors themselves can interpret x-rays and institute treatment.

Already mentioned above, the problem with chest x-ray, there are so many diseases which mimic tuberculosis radiologically and therefore tuberculosis is over diagnosed in our environment.

The aim of; this study is to look at these diagnostic problems analyse them in Zambian context and make suggestions how to overcome them.

OBJECTIVES

To determine proportion of patients who respond to trial of ATT.

SPECIFIC OBJECTIVES

1. To determine proportion of patient who respond to ATT

2. To determine proportion of patients who are smear negative and became positive on culture.

3. To determine compliance in TB patients attending Chest Clinic, UTH.

4. To determine demographic characteristics of patients attending Chest Clinic – UTH.

PATIENTS AND METHODS

1. Recruitment Procedure:

Patients were referred to UTH from Peripheral clinics; they were referred to UTH for further evaluation because they were suspected to have PTB.

At the time I saw them they had 3 smear for Acid fasting built done which were negative and had Chest x-ray done and sputum for culture and started on ATT by Chest Clinic doctors.

2. Treatment Regime:

Isoniazid (300mg.), Rifampicin(450mg.), Ethambutol(800mg.), Pyrazanamide(1.2g.), x 2/12.

3. A detailed history taken and physical examination was done, explained what I intended to do with them and benefits they might get from the study and had consent signed. None of the recruit members decline to sign the consent. All patients were asked to come for review after two months, this normal review time for patient last on ATT for the first time.

STATEMENT OF PROBLEM/RATIONALE OF THIS STUDY

Many patients with negative sputum results are commenced on anti-tuberculosis drugs on the grounds of clinical suspicion and x-ray showing shadow which could be done to tuberculosis or some other lung diseases. X-ray may be valuable to an individual's problems. However, correct reading of x-ray needs a lot of experience. Patients are treated for tuberculosis when they do not have it.

It is a major error in practice to treat patients in the basis of x-ray and clinical findings and fail to examine sputum. The reasons for not getting sputum smear include non-availability of sputum containers or reagents and in ordinate delay in getting the results. Sometimes, patients cannot produce sputum or too sick to wait until sputum smear results are available to a Doctor.

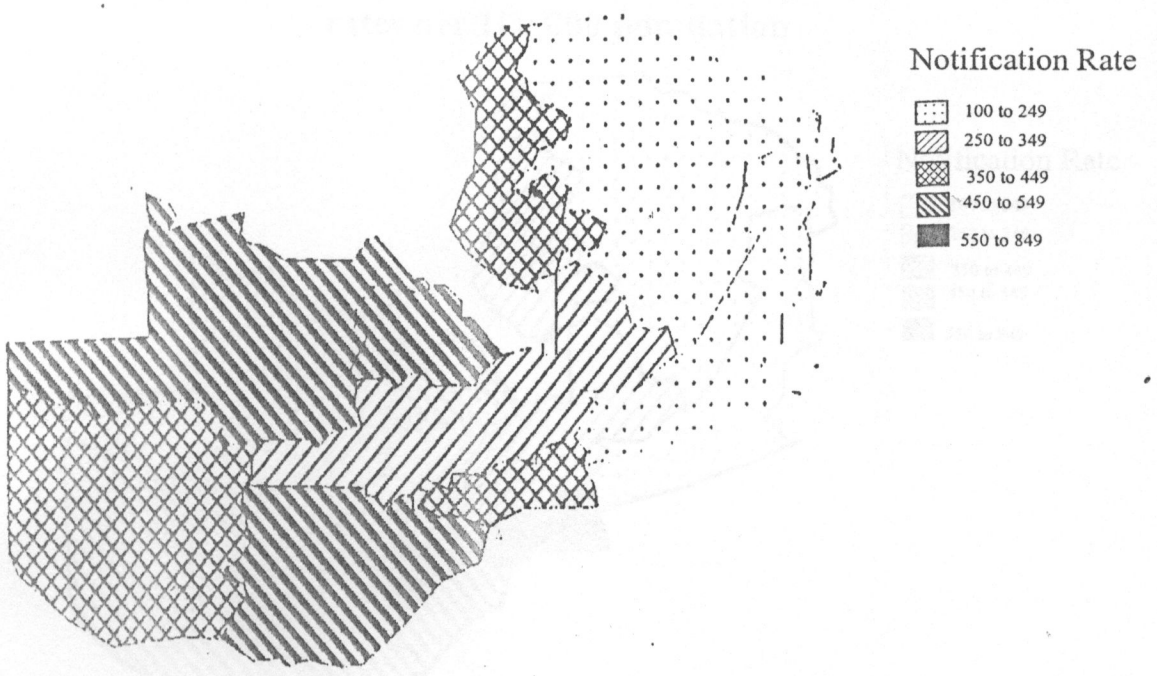
LITERATURE REVIEW

Mankind has known tuberculosis since antiquity and evidence of a disease similar to tuberculosis has been identified in Mummies of Ancient of Egypt. While the epidemic of tuberculosis in the United States and Western Europe reached its peak at the end of eighteenth and the beginning of the nineteenth century is thought that the population in Sub-Saharan Africa was affected only from the beginning of this century (Grzybowski 1991).

Mortality rates in England and Wales declined between 1850 and 1940 even before the introduction of Tuberculosis Services and this natural decline can be attributed to general socio-economic development with improved housing and nutrition. The natural decline has not been observed in many Sub-Saharan African countries even despite the use of chemotherapy and other control measures. This can be attributed to a slower socio-economic growth and weak infrastructure in many of these countries. In the 1990s there has been upswing of the number of reported cases of tuberculosis in both developing and developed countries, this coincided with pandemic of Acquired Immune Deficiency Syndrome (AIDS) which surfaced in 1981. One third of world population has tuberculosis (3).

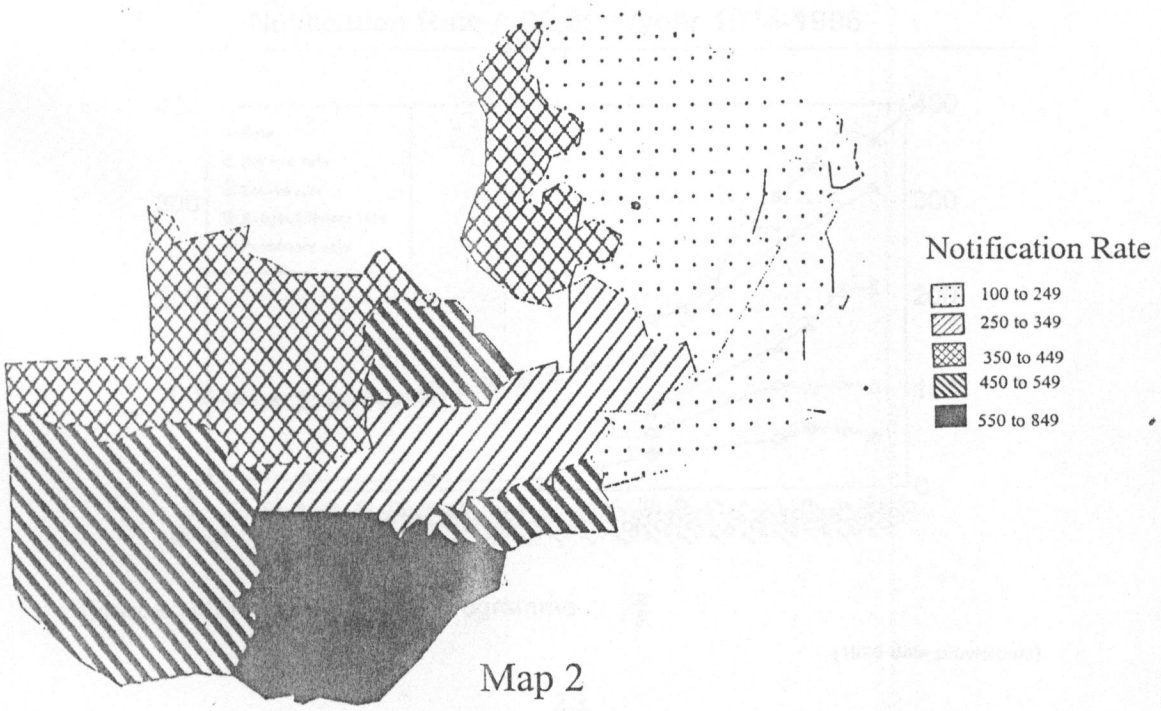
The Zambian scenario is illustrated by maps 1-3, graph number 1, tables 1-6.

INCIDENCE OF TUBERCULOSIS, ZAMBIA 1994
rates per 100,000 population



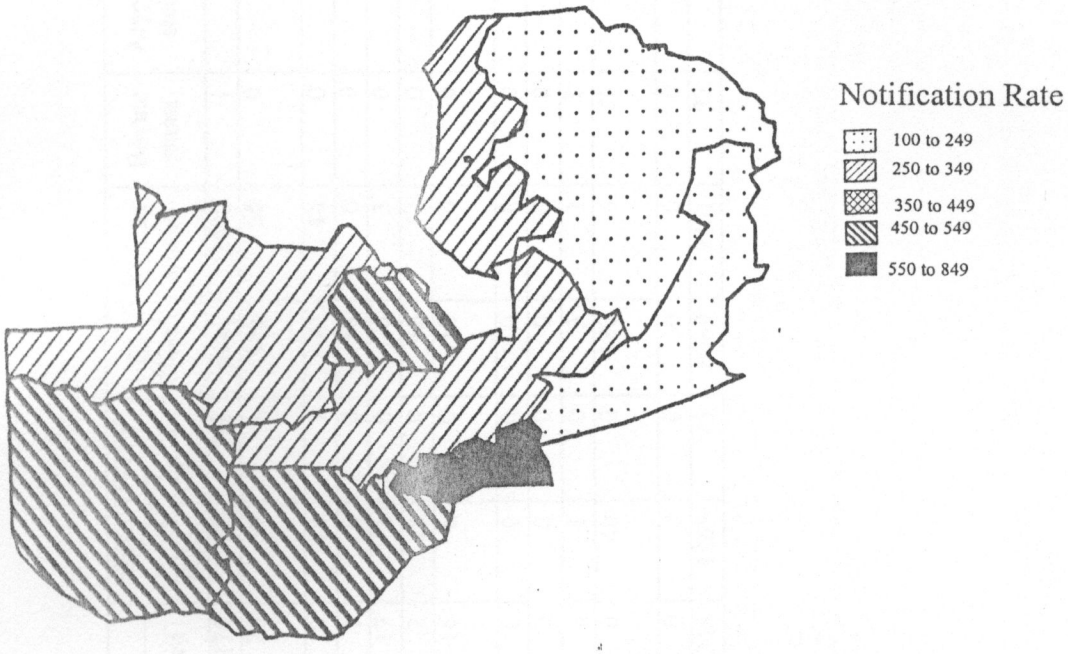
Map 1

INCIDENCE OF TUBERCULOSIS, ZAMBIA 1995
rates per 100,000 population



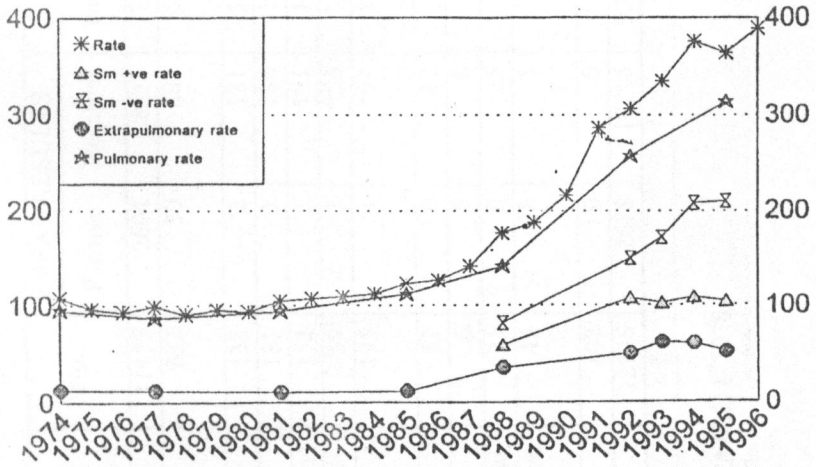
Map 2

INCIDENCE OF TUBERCULOSIS, ZAMBIA 1996
rates per 100,000 population



Map 3

New Cases of Tuberculosis in Zambia
Notification Rate /100,000 /year 1974-1996



Source : MoH AIDS/STD/TB Programme ; 1

(1996 data provisional)

SPECIMEN	No.	SMEAR RESULTS		CURATIVE RESULTS				SENSITIVITY TEST		ID Test	Human strains	Bovine stains	Atypical stains	Antibiotic assay
		Positive	Negative	No.	Tubercle Bacilli		Contaminated	Prim.	Sec.					
					Isolated	Not isolated								
Sputum	11455	2604	8851	7728	2166	5386	176	1727	238	6498	2165	1	1	0
Gastric Lavage	633	30	603	633	56	551	26	56	6	168	56	0	0	0
Body fluids	133	2	131	133	14	109	10	14	1	42	14	0	0	0
C.S.F.	181	1	180	181	6	174	1	6	0	18	6	0	0	0
Urine (24 Hrs)	152	1	151	152	3	132	17	3	0	6	3	0	2	0
Pus	59	1	58	59	12	45	2	12	0	36	12	0	0	0
Uterine curetting	195	1	194	195	6	173	16	6	0	18	6	0	15	0
Tissue	12	0	12	12	0	12	0	0	0	0	0	0	0	0
Faeces	6	0	6	6	0	6	0	0	0	0	0	0	0	0
Bone Marrow	25	0	25	25	1	24	0	1	0	3	1	0	0	0
Cattle/Lechwe /Goat	45	38	5	89	40	49	0	40	0	180	4	36	2	0
Urine	102	0	0	0	0	0	0	0	0	0	0	0	0	102
TOTAL	12996	2678	10216	9213	2304	6661	248	1865	245	6969	2261	37	20	102

TABLE 1 1978

SPECIMEN	No.	SMEAR RESULTS		CURATIVE RESULTS				SENSITIVITY TEST		Research	ID Test	Human strains	Bovine strains	Atypical strains	Antibiotic assay
		Positive	Negative	No.	Tubercle Bacilli		Contaminated	Prim.	Sec.						
					Isolated	Not isolated									
Sputum	12378	2993	9385	12066	3498	8414	154	2901	257	281	10598	3494	4	14	0
Gastric Lavage	657	34	623	657	103	543	11	103	1	0	312	103	0	0	0
Body fluids	285	4	281	285	16	265	4	16	0	0	48	16	0	0	0
C.S.F.	65	0	65	65	1	63	1	1	0	0	3	1	0	0	0
Urine (24 Hrs)	123	5	18	123	10	100	13	10	0	0	30	10	0	1	0
Pus	26	1	25	26	8	18	0	8	0	0	24	8	0	0	0
Uterine curetting	184	1	183	184	3	181	0	3	0	0	9	3	0	0	0
Tissue	29	2	27	29	6	23	0	6	0	0	18	6	0	0	0
Faeces	1	0	1	1	0	1	0	0	0	0	0	0	0	0	0
Bone Marrow	17	0	17	17	0	17	0	0	0	0	0	0	0	0	0
Cattle/Lechwe /Goat	12	9	3	12	10	2	0	10	10	0	50	0	10	0	0
Urine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL	13777	3049	10728	13465	3655	9627	183	3058	268	281	11092	3641	14	15	0

TABLE 2 1979

SPECIMEN	No.	SMEAR RESULTS		CURATIVE RESULTS				SENSITIVITY TEST		Research	ID Test	Human strains	Bovine stains	Atypical stains	Antibiotic assay
		Positive	Negative	No.	Tubercle Bacilli		Contaminated	Prim.	Sec.						
					Isolated	Not isolated									
Sputum	17923	2679	15244	1723	3912	13788	223	3807	385	132	13798	3801	6	5	0
Gastric Lavage	1150	27	1123	1150	106	1022	22	106	16	0	366	106	0	0	0
Body fluids	331	3	328	331	23	300	8	23	2	0	69	23	0	1	0
C.S.F.	206	0	206	206	8	196	2	8	0	0	24	8	0	0	0
Urine (24 Hrs)	122	4	118	122	12	107	3	12	2	0	42	12	0	0	0
Pus	43	2	41	43	13	28	2	13	4	0	51	13	0	0	0
Uterine curetting	205	1	204	205	9	195	1	9	1	0	30	9	0	0	0
Tissue	13	1	12	13	1	12	0	1	0	0	3	1	0	0	0
Faeces	28	0	28	28	2	25	1	2	0	0	6	2	0	0	0
Bone Marrow	19	0	19	19	0	0	0	0	0	0	0	0	0	0	0
Urine	341	0	0	0	0	0	0	0	0	0	0	0	0	0	341
TOTAL	20381	2717	17323	20040	4086	15673	262	3981	410	132	14349	3975	6	6	341

TABLE 3 1981

SPECIMEN	No.	SMEAR RESULTS		CURATIVE RESULTS				SENSITIVITY TEST		Research	ID Test	Human strains	Bovine strains	Atypical strains	Antibiotic assay
		Positive	Negative	No.	Tubercle Bacilli		Contaminated	Prim.	Sec.						
					Isolated	Not isolated									
Sputum	18815	3894	14921	18815	5410	13081	324	3710	360	239	18065	5407	3	13	0
Gastric Lavage	1309	21	1288	1309	113	1150	46	103	12	0	448	113	0	1	0
Body fluids	289	3	286	289	18	267	4	18	4	0	88	18	0	0	0
C.S.F.	154	1	153	154	10	143	1	10	2	0	48	10	0	0	0
Urine (24 Hrs)	71	0	71	71	5	59	7	5	3	0	32	5	0	1	0
Pus	40	2	38	40	9	30	1	9	2	0	44	8	1	0	0
Uterine curetting	106	1	105	106	7	96	3	7	1	0	32	7	0	0	0
Tissue	15	1	14	15	2	12	1	2	0	0	8	2	0	0	0
Faeces	2	0	2	2	0	1	1	0	0	0	0	0	0	0	0
Bone Marrow	11	0	11	11	0	11	0	0	0	0	0	0	0	0	0
Urine	264	0	0	0	0	0	0	0	0	0	0	0	0	0	264
TOTAL	21076	3823	16889	20812	5574	14850	388	3864	384	239	18765	5570	4	15	264

TABLE 4: ANALYSIS OF BACTERIOLOGICAL INVESTIGATIONS 1982

SPECIMEN	No.	SMEAR RESULTS		CURATIVE RESULTS				SENSITIVITY TEST	Research	ID Test	Human strains	Bovine stains	Atypical stains	Antibiotic assay
		Positive	Negative	No.	Tubercle Bacilli		Contaminated	Routine						
					Isolated	Not isolated								
Sputum	18484	3174	15310	18484	4086	12792	1606	2939	615	14808	4083	3	7	0
Gastric Lavage	1195	24	1171	1195	80	992	123	80	0	240	80	0	0	0
Body fluids	317	1	317	26	259	32	26	78	26	0	0	0	0	0
C.S.F.	137	0	137	137	11	116	10	11	1	330	11	0	0	0
Urine (24 Hrs)	87	3	84	87	10	63	14	10	0	30	10	0	1	0
Pus	22	1	21	22	7	14	1	7	0	21	7	0	0	0
Uterine curetting	29	0	29	29	2	22	5	2	0	6	2	0	0	0
Tissue	6	0	6	6	1	4	1	1	0	3	1	0	0	0
Faeces	4	0	4	4	0	4	0	0	0	0	0	0	0	0
Bone Marrow	8	0	8	8	0	7	1	0	0	0	0	0	0	0
Urine	908	0	0	0	0	0	0	0	0	0	0	0	0	908
TOTAL	21197	3203	17086	20289	4223	14273	1793	3076	615	15219	4220	3	8	908

TABLE 5: ANALYSIS OF BACTERIOLOGICAL INVESTIGATIONS 1983

SPECIMEN	No.	SMEAR RESULTS		CURATIVE RESULTS				SENSITIVITY TEST	Research	ID Test	Human strains	Bovine strains	Atypical strains	Antibiotic assay
		Positive	Negative	No.	Tubercle Bacilli		Contaminated	Routine						
					Isolated	Not isolated								
Sputum	16162	2560	13062	16162	12289	3697	176	3493	204	11499	3694	3	0	0
Gastric Lavage	268	4	264	268	244	21	3	21	0	63	21	0	0	0
Body fluids	417	4	413	417	382	30	5	30	0	90	30	0	0	0
C.S.F.	168	0	168	168	161	6	1	6	0	18	6	0	0	0
Urine (24 Hrs)	78	1	77	78	67	2	9	2	0	6	2	0	1	0
Pus	43	1	42	43	37	4	2	4	0	12	4	0	0	0
Uterine curetting	39	0	39	39	39	0	0	0	0	0	0	0	0	0
Tissue	2	0	2	2	2	0	0	0	0	0	0	0	0	0
Faeces														
Bone Marrow	7	0	7	7	7	0	0	0	0	0	0	0	0	0
Urine	673	0	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL	18460	2570	14614	17184	13228	3760	196	3556	204	11688	3757	3	5	673

TABLE 6: ANALYSIS OF BACTERIOLOGICAL INVESTIGATIONS 1984

The relationship between tuberculosis and AIDS are

(a) AIDS activates latent tuberculosis

(b) Primary infection results in tuberculosis disease

(c) Tuberculosis accelerates latent HIV infection to AIDS (13).

Tuberculosis is diagnosed by various methods and each of the methods has its own pitfalls. It starts with detailed history and physical examination.

Specific diagnosis of tuberculosis (pulmonary) is achieved by isolating the organism from the specimens being examined in case of pulmonary tuberculosis from the sputum. Direct smear examination for Alcohol Acid Fasting Bacilli (AAFB) is the gold standard in the diagnosis of pulmonary tuberculosis. It has low sensitivity of 50-70% specificity of the test is 94-99%. Culture is more sensitive for isolating AAFB than direct smear.

Chest x-ray is also used as diagnostic tool in clinical management of pulmonary tuberculosis. Others include polymerase chain reaction, myobacterial antigen, adenosine deaminase, pleural and lung biopsy, and Restricted Length Fragment polymorphism (RLF) (13).

As already mentioned each of these diagnostic methods has pitfalls e.g. Direct Smear is not very sensitive only 50-70% case are picked, 30% may be missed (3). For culture, the specimen must be examined within specified time frame or properly stored; otherwise bacilli may die and therefore become negative despite the patient having pulmonary tuberculosis. The negativity of result in both methods may not be true reflection of the patient's condition and HIV; the yield tends to be low in these patients. Changes on x-ray changes are not specific for pulmonary tuberculosis especially on patients with AIDS (11).

In our environment chest x-ray despite being expensive and inaccurate is still commonly used to diagnose pulmonary tuberculosis. There are many conditions which mimic pulmonary tuberculosis radiologically. A cavitation in the lung does not necessarily mean tuberculosis. Staphylococcal and Klebsiela Pneumonia and bronchogenic carcinoma may present with cavities radiologically. Enlarged hilar lymph nodes enlargement may be due to pulmonary vascular shadows and large azygous veins. Multiple small opacities may due to arterio-venous fistulae, cysticercosis, neurofibromatois and pulmonary Kaposi Sarcoma. Pleural effusion could be due to other pulmonary bacterial infection. Metabolic diseases can also present with pleural effusion e.g. right-sided heart failure and nephrotic syndrome.

It is for the above reasons that connect reading of x-rays need a lot of experience. Patients are treated for tuberculosis when; they do not have it. It is major error in practice to treat patients for pulmonary tuberculosis on the basis of x-ray and clinical findings and fail to examine sputum.

Anti tuberculosis Drugs:

Prior to the introduction of chemotherapy, 75% of patients with sputum positive TB would die within 5 years. Modern chemotherapy, is so effective that if proper drug regiments are prescribed and the patient wholly compliant, then cure takes place in 100% of patients.

It is of crucial importance, especially with patients harboring large bacterial populations, to prevent further bacterial multiplication, so that the disease is restrained as soon as possible. This not only saves lives of the patients' and prevents disastrous gross lung destruction, but also limits the spread of the infection in the community. Treatment with three or four drugs in the initial phase will almost always prevent emergence of drug resistant mutants thus securing a cure even for patients with initially drug resistant infection.

With the challenging problem of the AIDS pandemic and the subsequent increase in active TB cases, the treatment of TB has taken on an even greater significance. The World Bank recognizes good anti-TB treatment as one of the most cost-effective health interventions. The WHO's 'strategy and framework

for effective TB control' in response to the global emergency has incorporated the Directly Observed Treatment Short course ('DOTS') regimen with encouraging results in areas where fully implemented. The DOTS course (recently implemented in Zambia) comprises the following four drugs namely: **isoniazid, rifampicin, pyrazinamide** and **ethambutol.** Isoniazid and rifampicin are the most effective bactericidal drugs; rifampicin and pyrazinamide are the main sterilizing drugs as they kill different sub-populations of semi-dormant organisms. Finally rifampicin and isoniazid are the most effective in preventing the emergence of resistance to other drugs. An important point in the use of anti-tuberculous drugs is that they have to be used in combination otherwise mycobacterial resistance develops rapidly!

The individual properties of the first-line anti-tuberculous drugs are discussed below.

ISONIAZID

It is a hydroxide of isonicotinic acid. Most anti-tuberculosis regimens include isoniazid (molecular wt. 137.1). The dry powder is stable at 25°C. It is a weak base, soluble in water, ethanol or methanol. There is contention over the stability of the drug in frozen plasma samples and as a precaution it is probably wise to deproteinise samples within 6 hours of sampling or to extract

the drug as soon as possible. Isoniazid is available as tablets/capsules or as combined formulation with Rifampicin, ethambutol or Pyrazinamide.

Table 7.

Pharmacokinetic properties and MICs of anti-mycobacterial drugs

Drug	Dose (mg)	Fraction absorbed (%)	Peak (mg/L)	Half-life	Protein binding	MIC (mg/L) for M. tuberculosis
Isoniazid	300	Well absorbed *	5 (slow-acetylators) 4 (rapid-acetylators)	3 hours 1.3hours ↑ in cirrhosis, neonates, uremia	0-20	0.2
Rifampicin	600	Well absorbed *	10	3 hours ↑ hepatitis, cirrhosis, uremia.	85	0.2
Ethambutol	1200	70-80	3	4 hours ↑ uremia	20	1.5
Pyrazinamide	2000	Well absorbed *	40	9 hours ↑ cirrhosis	0-40	20

* Absorption is almost 100% but food and other medication can decrease this. In addition hepatic 1st pass-effect can also be a factor though the metabolites produced can still be active.

Parental preparations are also available. Usual dose is 300mg per oral. It is bacteriostatic for resting bacilli but bactericidal for rapidly dividing organisms. Mechanism of action is unknown but thought to act by inhibiting the biosynthesis of mycolic acid of the cell wall.

It is readily absorbed though it can be affected by food resulting in lower than normal peak plasma concentration. Peak plasma concentration of 3 to 5 ug/ml develops 1 to 2 hours after oral ingestion of the usual dose. Isoniazid readily diffuses into all body fluids and cells in significant concentration, penetrating well into caseous material. 75 to 95% of dose is excreted in urine as metabolites (result of acetylation and hydrolysis). Extent individuals acetylate varies considerably and subjects are characterized as either slow or fast acetylators. Half-life is 1-4 hours. Other properties include its high selectivity for Mycobacteria. Rate of acetylation significantly alters concentration of drug in plasma and its half-life in circulation. Half-life is also increased by hepatic insufficiency. Peripheral neuropathy is related to pyridoxine deficiency especially in slow acetylators.

Uncommon side effects include hepatitis, peripheral neuropathy, and cutaneous hypersensitivity. Rare effects are convulsions, mental symptoms, hemolytic anemia, arthralgia, aplastic anemia, and gynecomastia and lipid reactions.

RIFAMPICIN

Is a synthetic derivative of a natural antibiotic, rifamycin B, and is a first line anti-tuberculous drug. Rifampicin is a zwitterion, with a molecular weight of 822.9. It is freely soluble in ethanol, methanol and chloroform. Clinically rifampicin is available as capsules, tablets or syrup and in combined formulations. Usual dose is 600mg if weight is greater than 50kg and 450mg if weight is less than 50kg. It acts by inhibiting DNA dependent RNA polymerase of mycobacteria and is bactericidal both for intracellular and extracellular organisms.

Oral administration leads to peak plasma concentration in 2 to 4hours of about 7ug/ml but is considerably variable. It should be administered before meals rather then after as absorption is sometimes impaired by food. Following absorption it is rapidly eliminated in bile and enterohepatic circulation occurs. It is a potent inducer of hepatic microsomal oxidases thus on repeated dosages would induce its own metabolism, so reducing its elimination half-life. It is progressively deacetylated though the metabolite is fully active. Half-life is progressively shortened by 40% during first 14 days due to induction of hepatic enzymes. 30% is excreted in urine and 60-65% in stool. Distribution is throughout the body and present in effective concentration.

Other properties include its activities against most gram-positive and negative organisms. Aspirin may delay absorption. Half-life wanes from 1.5 to 5 hours.

Uncommon side effects include hepatitis, GIT reactions, coetaneous reactions, thrombocytopenic purpura, and febrile reactions during irregular administration. Rare effects include dyspnoea, shock, hemolytic anemia, and acute renal failure especially during intermittent regimens.

ETHAMBUTOL

It is another first-line anti-tuberculosis agent, which is tuberculostatic and thought to act by incorporation of mycolic acid. It is a strong base with a molecular weight of about 277.2.

Ethambutol is available for oral use as a tablet or powder containing hydrochloride (which is very water-soluble). Usual dose is 15mg/kg. Single dose of 25mg/kg will lead to serum levels of 2 to 5 ug/ml in 2 to 4hours. 70 to 80% is absorbed from the GIT. Within 24 hours 75% is excreted unchanged in urine by renal tubular secretion. Remainder is excreted as inactive dialdehyde and dicarboxilic acid metabolites. Despite this dependence on renal excretion only a modest increase has been reported in-patients with renal impairment. However a recent review has concluded that ethambutol should not be recommended for treatment of patients in renal failure due to the significant

risk of over-dosage, as the drug tends to accumulate in-patients with impaired renal function. It is distributed to most tissues. Half-life is 3-4 hours.

Uncommon side effects include retrobulbar neuritis (dose related), and arthralgia. Hyperuricemia is common, but not clinically significant. Rare effects include hepatitis, cutaneous hypersensitivity, and peripheral neuropathy.

PYRAZINAMIDE

Pyrazinamide is an anti-tuberculous agent only used in combination with other drugs. It has a molecular weight of 123.1 and is a very weak base that readily soluble in water, ethanol and methanol. It is bactericidal for intracellular mycobacteria. Pyrazinamide is only active against M. tuberculosis under acidic conditions. Although its MIC is high and the serum concentration after therapeutic doses only exceeds the MIC by a factor of two, it is considered to have a unique sterilizing activity when included in multi-drug regimens.

Clinically it is available as tablets in combination formulations. Usual dose is 2g for patients over 60kg and 1.5kg for those less than 60kg, given in single or divided doses. Pyrazinamide is well absorbed and widely distributed throughout the body water, readily penetrates the blood-brain barrier. 1g produces a serum level of 45ug at 2 hours and 10ug/ml at 15 hours. Pyrazinamide is extensively metabolized to inactive metabolites, pyrazinoic acid and 5-hudroxypyrazinoic acid. It is excreted primarily by renal glomerular

filtration in a hydroxylated form (5-hydroxypyrazinoic acid). Only 3% are excreted unchanged. Urinary concentrations following a 1.5g dose reaches about 50mg/L. It is not thought to bind to plasma protein, although a report, using HPLC method put the binding at 40%.

Adverse effects are usually mild, and include cutaneous hypersensitivity, anorexia and nausea. More serious side effects are hepatitis (which is dose-related and occurs in <1% of patients), arthralgia (due to active gout), cutaneous hypersensitivity. Sideroblastic anemia and photosensitivity are rare side effects.

RECRUITMENT SITES

Sample Size 711 patients

The study clinic was situated in the Chest Clinic of the University Teaching Hospital in Lusaka. The University Teaching Hospital is a 2,000 bed hospital. It is tertiary centre of general medical clinics, surgical, Paediatrics and Obstetrics and Gynaecology. In addition there are specialist clinics and chest clinic is one of them.

All patients from peripheral clinics who have symptoms and signs suggestive of pulmonary tuberculosis and smear negative are sent to UTH, Chest Clinic for further evaluation by chest clinic doctors and have chest x-ray done and sputum taken for smear.

Methods of Patient Selection

All patients who attended Chest Clinic on Tuesday and Friday who met inclusion criteria see from below included in the study.

Follow up Visit

Follow up Visit

All patients who were recruited were reviewed after two (2) months. During this visit, history taken and physical examination performed again. A second chest x-ray was taken.

Exclusion Criteria

1. Positive sputum smear for AAFB
2. No chest x-ray done
3. Those with Kaposi Sarcoma.... Cutaneous or oral
4. Those with Neurofibromatosis
5. Those who did not consent to participate in the study

Inclusion

1. Males and females above 16 years of age
2. Those treated with ATT after chest x-ray and sputum smear microscopy
3. Those who have consented to participate in the study

Ethical Approval

Ethical approval to conduct the study was obtained from Research and Ethics Committee of the University of Zambia.

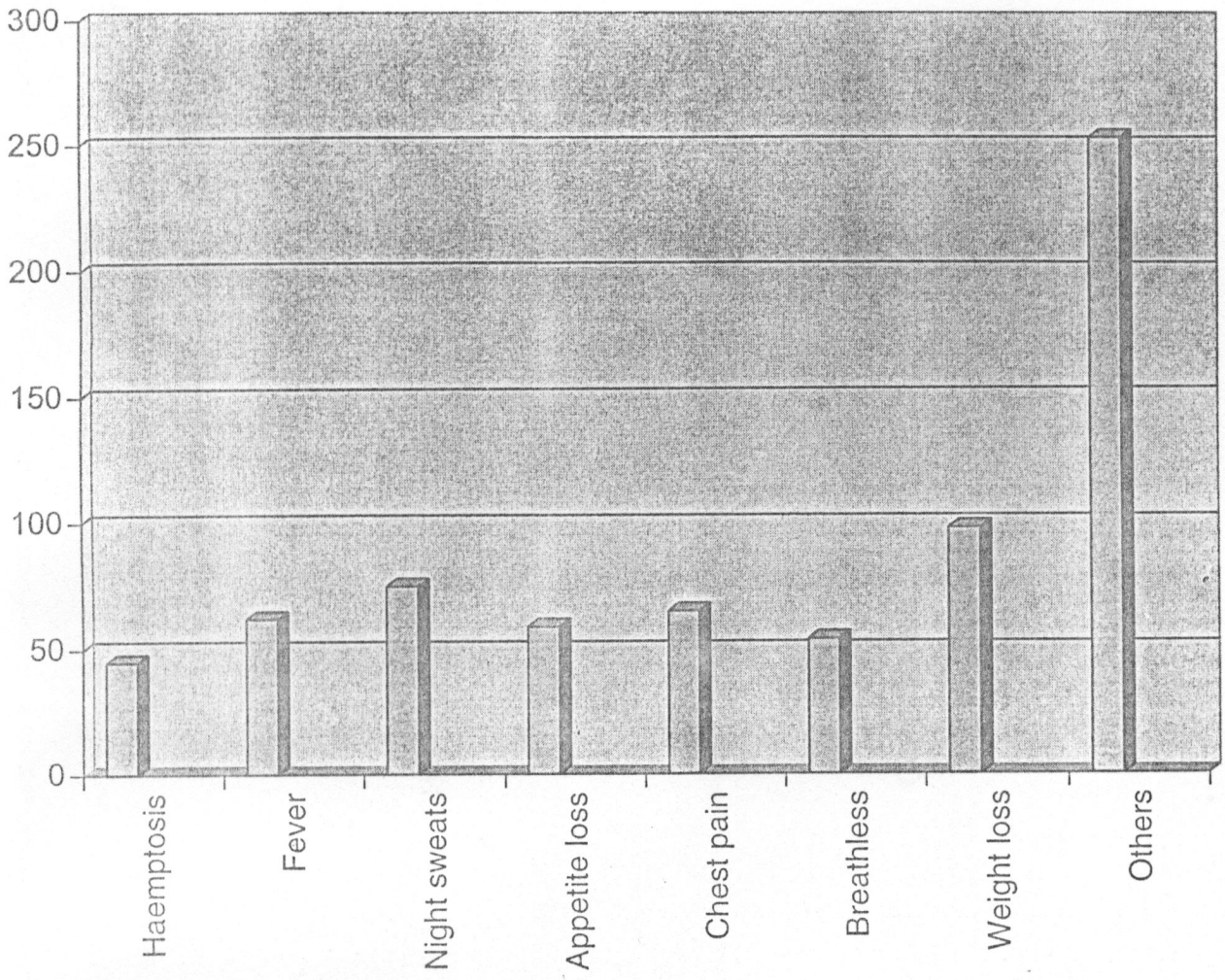
RESULTS

Time frame for study : 12 months.

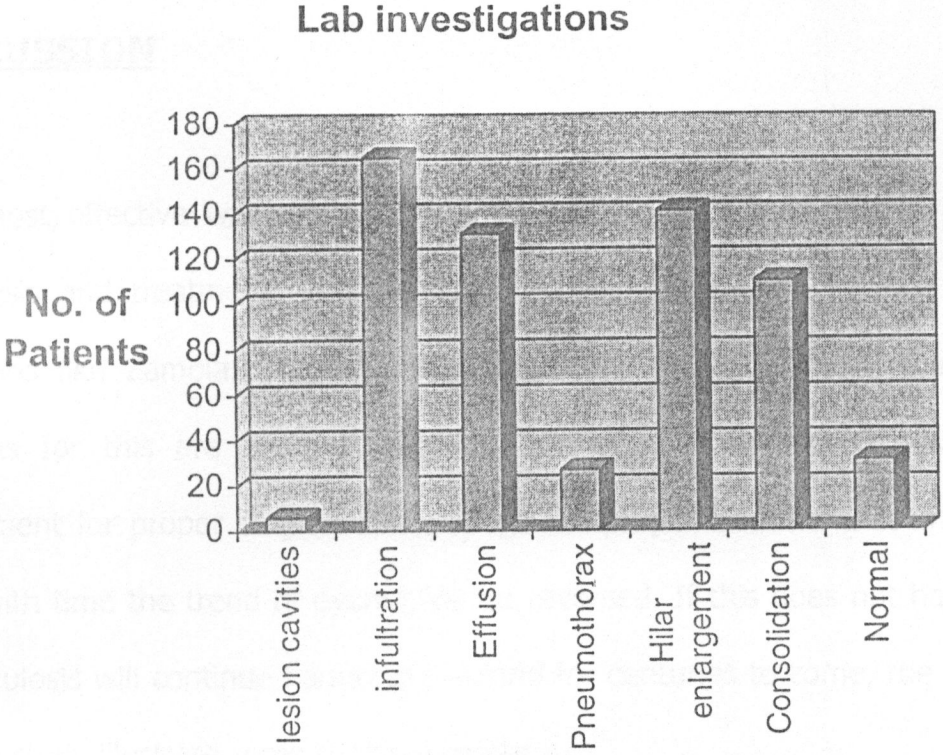
Total number of patients	-	711
Defaulters	-	47
Deaths	-	20
Reviewed	-	644
Females	-	378 (53.16%)
Males	-	333 (46.84%)
Age range	-	16 – 77 years
High density	-	600 (90.01%)
Low density	-	71 (9.99%)
Employed	-	400 (56.25%)
Not employed	-	311 (43.75%)

History of positive TB Contact : 279 (39.24%).

No contact with tuberculosis 432 (60.76%).



Bar Chart 1, showing symptoms and number of patients



Bar chart 2, showing type of lesions and distribution. Infiltration was the largest number followed by hilar enlargement and least was cavities.

DISCUSSION

The most effective way of controlling the spread of tuberculosis is proper diagnosis and treatment. But this has not been happening in third world countries like Zambia. Diagnosis and treatment is very difficult, the main reasons for this are meagre resource, untrained manpower and lack of equipment for proper diagnosis and drugs for proper treatment. It is hoped that with time the trend of events will be reversed. If this does not happen , tuberculosis will continue haunting mankind for centuries to come, the results of this study illustrate some of these points.

The sex distribution of patients was not equal with 53.1% females and 46.8% males. It a well-established fact that tuberculosis tends to inflict women than men everything being equal, reasons for this is not known(6). It is not surprising that majority of the patients came from high density areas where most people are poor. Poverty and overcrowding play major role in the spreading of pulmonary tuberculosis, the other reason why most patients who attend chest clinic are of poor social background is that pulmonary tuberculosis is associated with AIDS and therefore those who can afford opt to go to private clinics if they have chest problems, they do not want to associate with AIDS. If you compare employed and unemployed those in employment are 400 (56.23%) because they can afford transport money to hospital and to

pay for laboratory tests when asked to. Unemployed 311 (43.74%) whose circumstances are reverse of the above. There is no symptom that is predominant.

Chest x-ray

Infiltration was the commonest radiological diagnosis. Infiltration is a vague radiological term, it is not surprising that it is the commonest diagnosis. Cavitation was 6 (0.84%) was the least cavitating tuberculosis has high smear yield. Therefore, bacilli could have been picked by smear anyway. Thirty one x-rays (4.36%) were passed as normal by the radiologist.

Clinical Response

- Weight gain 363 (56.37%)
- No improvement 281 (43.63%)

Radiological Changes

- Improved 430 (66.77%)
- No improvement 214 (33.22%)

We may be deceived by above results that we were treating PTB, this is not 100% true, Some radiological changes that could have been due to bacterial

pneumonia or other respiratory diseases. As you known ATT is a combination of broad spectrum and powerful antibiotics. For those who did not respond some of them may have PTB with resistant strains to ATT currently in use, or may not have taking drugs despite drugs being made available to them, and may have other diseases which do respond to ATT.

As we all know the only confirmatory diagnosis of tuberculosis is the isolated of the bacilli from the specimen in question. In this study, second test, which is culture, is more sensitive than smear traditionally. Seven hundred and eleven (711) specimens of which only 15 were positive, 14 of them were 3+ and one was 2+ of bacilli, which is 2.10 in terms of percentages. Some of the reasons for low diagnostic yield for culture could be:

1. Specimens are not concentrated with sodium hypochloride (NaOCl) before examination.
2. Methods of specimen collection by patients could be faulty.
3. Time lag between specimen collection and examination may be too long.
4. Specimen storage facilities may be faulty.
5. Workload on the technicians may be too high per head.

Compliance

47 did not come back for review if they have tuberculosis they might have continued spreading the disease to others.

Deaths

Twenty died before second review, diagnosis could have been missed and started on ATT in appropriately.

CONCLUSION

Chest x-ray is very unreliable way of diagnosing chest diseases including pulmonary tuberculosis; this evidenced by a large number of culture negative sputum obtained from patient started on ATT on clinical and radiological criteria. Clinical response cannot be used as concrete evidence of having pulmonary tuberculosis as drugs used for treating pulmonary tuberculosis have broad spectrum of anti-bacterial activity hence can treat other bacterial pneumonia and give clinical and radiological response as shown in this study. Concomitant HIV infection could have contributed to both smear, and culture negativity also affects radiological changes.

RECOMMENDATIONS

1. Chest x-ray should not be used as sole diagnostic investigation for pulmonary tuberculosis especially by people who are not properly trained in interpreting
   X-rays.

2. Sputum be examined on spot after submission

3. To have more laboratories for culture situated at UTH and local clinics, which cater for patients with chest infections.

4. With this bad yield for culture, culture is reserved for only those patients whose smear positive not responding to treat for culture and sensitivity.

5. To provide more diagnostic facilities in chest clinic so that specific diagnosis are made instead of syndromic management of chest diseases which is prevailing currently in our chest clinic e.g. bronchoscopies, facilities for doing pleural and lung biopsies. With provision of more diagnostic facilities, chest clinic will reflect its meaning, as it is now just tuberculosis clinic.

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Appendix 1

DATA COLLECTION FORM

Identity:

- Study Number
- File Number
- Age
- Sex
- Duration of symptoms
- Residential area
- H/O contact with TB patient YES/NO
- Ocupation Previous.....

  Current.....

Clinical features: Tick

(a) Cough Duration.....

(b) Haemoptysis YES/NO

(c) Fever YES/NO

(d) Night sweats YES/NO

(e) Loss of apetite YES/NO

(f) Chest pains YES/NO

(g) Breathlessness YES/NO

Investigations Done:

Sputum smear examination

1 2 3

Chest X-Ray Findings

a) Cavitation

b) Infiltration

c) Consolidation

d) Pleural effusion

e) Pneumothorax

f) Enlarged hilar lymphnodes

g) Other

Sputum Culture

Response: (tick)

a) To ATT

b) No response to ATT

Postmortem:

a) Full convention autopsy

b) Percutaneous needle autopsy of the lung

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Appendix 2

CONSENT FORM

I.....under signed, Give censent to be included in the study. Everything has been explained and I fully understand
Date.....

INCLUSION CRITERIA:

- Males and Females above age of 16 years of age
- Those treated with ATT after CXR and sputum smear microscopy
- Those who have consented to participate in study

EXCLUSION CRITERIA:

- Positive sputum smear for AAFB
- No CXR done
- Those with Kaposis sarcoma lesions
- Those with Neurofibromatosis
- Those who have not given consent participate in the study

TIME FRAME OF STUDY:

June 1998 to June 1999

SPONSORSHIP

Ministry of Health, GRZ
International Organisation for Migration