

Safety in Mines Research Advisory Committee

Final Report

**Clinico-Pathological Study to reduce the rate of missed
and misdiagnosis of Pulmonary Tuberculosis in the South
African Mining Industry**

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EXECUTIVE SUMMARY

“What the patient died of and what he is said to have died of
are not always one and the same thing”

Philip R, 1918. Inaugural address delivered on the institution of the chair of tuberculosis in the University of Edinburgh.

Tuberculosis, declared a global emergency by the World Health Organisation in 1991, is a major infectious disease in the South African mining industry and deaths from tuberculosis (TB) exceed those due to mine accidents (Dr M A la Grange, Chamber of Mines). TB is a potentially curable disease and misdiagnosis has important implications for the individual, spread of TB in the community and compensation in terms of the Occupational Diseases in Mines and Works Act (ODMWA). Improved management can only occur if the diagnosis is correctly established, targeting areas for intervention.

The National Centre for Occupational Health (NCOH) examines the lungs of deceased mineworkers in terms of ODMWA and is thus in a unique position to assist with strategies for improving the accurate and timely diagnosis of pulmonary TB (PTB). The objectives of the study were to correlate the ante- and postmortem diagnoses of PTB, review medical data from a representative group of mine medical services to assess current clinical practice, and identify possible reasons for discordant diagnoses and strategies for improving clinical practice.

There were 1858 autopsies performed during 1999 (excluding cases from Anglo Gold which did not participate in the study) of which 350 were study cases with a clinical diagnosis of PTB as a major factor in the cause of death and/or an autopsy diagnosis of PTB. Clinicians correctly ascribed PTB as the cause of death in 27% of cases, failed to diagnose PTB in 44% and incorrectly ascribed PTB as the cause of death in 29%. Poor clinico-pathological correlation is not unique to the mine medical services but also occurs in medical centres in America, Britain etc.

Clinical practice was assessed by reviewing medical records from 8 different medical centres representing gold, coal and platinum mining commodities. Of the 187 patients whose records were reviewed, 76% were known to be HIV infected and of those who had had CD4+ cell count measurements, 90% had advanced AIDS. Autopsies showed lungs with extensive TB even though surveillance chest radiographs taken only months prior to death were normal.

In patients in whom the clinical diagnosis of PTB was not made, important factors influencing the missed diagnosis of TB were the presence of miliary TB, the simultaneous presence of a second lung disease such as bacterial pneumonia and omission of accurate laboratory diagnostic tests such as sputum smears and culture for TB bacilli.

About half of the cases, in whom the clinicians had correctly diagnosed TB, presented with advanced disease and had had a rapidly terminal course. In this group and in the undiagnosed group, there were missed ‘windows of opportunity’ for the clinicians to have made an earlier diagnosis as many patients had attended the mine clinics and/or hospitals in the preceding three months. Cases were identified with extensive TB at autopsy who had been on prolonged treatment for TB. These patients (and especially those who also had previous TB) are at risk

of being drug resistant; drug susceptibility testing had not been performed for the majority of them.

Of the patients for whom clinicians incorrectly ascribed PTB as a cause of death, 72% had been treated for TB for over 30 days. They appear to have responded to TB treatment and sequential development of other diseases, many of which would have been amenable to treatment if diagnosed, accounted for the discrepancies in ante- and postmortem diagnoses.

About 250 health care workers attended the clinico-pathological conferences held to disseminate the study findings, present illustrative cases and discuss best practice clinical strategies, as the study progressed. A wide range of health care workers attended and the doctors appear to have subsequently incorporated at least some of the suggestions made into their practices as indicated in their responses to the evaluation questionnaire distributed to them .

The considerable effort made to reduce fatalities due to mine accidents must be duplicated to reduce deaths due to a disease which, in theory at least, could be eradicated with the application of present knowledge.

IMPORTANT RECOMMENDATIONS INCLUDE:

- **More frequent medical surveillance for groups of employees at high risk for TB**
- **Improving the skills of nurses both with regard to case finding and monitoring of patients while on treatment for TB**
- **Actively excluding TB in all patients admitted to hospital with respiratory signs and symptoms, including use of sputum culture for TB, even if patients show some response to treatment for bacterial pneumonia**
- **A training course on the interpretation of chest radiographs**
- **Empirical treatment for suspected miliary TB while awaiting culture results**
- **All employees found unfit for continued employment to be actively investigated for TB before leaving the mines. Special attention to be paid to men with advanced AIDS**
- **Deterioration in a patient's condition should not be ascribed to progressive HIV infection without considering the possibility of TB**
- **Testing for drug susceptibility in all previously treated patients and those who fail to respond to treatment**
- **The NCOH should continue to provide autopsy reports if requested by the clinician, to enable them to undertake reviews of their performance**

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- Dr Lettie La Grange presented industry perspectives at the seminar hosted by Gold Fields Ltd.
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GLOSSARY

A

Acquired Immuno-deficiency Syndrome (AIDS)

A variety of secondary diseases caused by primary infection with the HIV

Aspergillus

A genus of fungi, several species of which cause disease in immune compromised patients

B

Bronchiectasis

Chronic dilatation of the bronchi marked by fetid breath and coughing

C

Case Fatality Rate

The proportion of cases of a specified condition which are fatal as a result of that condition within a specified time period.

Culture

Propagation of micro-organisms or living cells in special media conducive to their growth, e.g. Bactec Middlebrook used to culture *Mycobacterium tuberculosis*

CSF

Cerebrospinal fluid

Cytomegalovirus

One of a group of highly host-specific herpes viruses that infect man

D

Discordant

Disagreement

E

Embolus

A clot which obstructs the circulation

Encephalitis

Inflammation of the brain

Emphysema

A pathological accumulation of air in tissues or organs applied especially to a condition of the lungs

Empirical

Based on experience

H

Haemoptysis

The spitting of blood

Human Immuno-deficiency virus (HIV)

The retrovirus responsible for AIDS

K

Kaposi's sarcoma

Tumour made up of embryonic connective tissue often highly malignant

L

Lymphocytic interstitial pneumonitis

Pertaining to lymphocytes infiltrating the lungs

Lymphoma

Neoplastic disorder of lymphoid tissue including Hodgkins' disease

M

Medical station

Clinic situated on a mine

Meningitis

Inflammation of the meninges surrounding the brain

Metastatic carcinoma

Malignant tumour which has spread from one organ to another which is distant from it

N

NCOH

National Centre for Occupational Health

Nocardia

A fungus of the genus of actinomycetes. *Nocardia asteroides* produces pulmonary infections in man resembling tuberculosis

Non-tuberculous mycobacteria (NTM)

Organisms belonging to the genus *Mycobacterium* that do not cause TB

Nosocomial

Disease acquired in health care facilities or from medical treatment

O

ODMWA

Occupational Diseases in Mines and Works Act (Act 78 of 1973)

Opportunistic infection

Micro-organism which does not ordinarily cause disease but which under certain circumstances (e.g. impaired immune responses) becomes pathogenic

P

PATHAUT

Pathology Automation System. Computerized database at the Pathology division of the NCOH

Pericarditis

Inflammation of the pericardium surrounding the heart

Pleural effusion

Collection of fluid in the pleural space surrounding the lungs

Pneumocystis

A genus of fungi causing *Pneumocystis carinii* pneumonia

Pneumonia

Inflammation of the lungs with solidification of the air spaces

Pulmonary oedema

Fluid in the lungs

Pyuria

Presence of pus in the urine indicative of urinary tract infection

S

Sensitivity

The ability of a test to correctly identify those who have the disease under study

Specificity

The ability of a test to correctly identify those who do not have the disease under study

Septicaemia

Systemic disease associated with the presence of pathogenic organisms in the blood

Silicosis

Pneumoconiosis due to the inhalation of dust containing silica

Stain

Substance used in colouring tissues or micro-organisms for microscopical study, e.g. Ziehl-Neelsen, Haematoxylin and Eosin

Surveillance

Ongoing monitoring usually aimed at early detection of disease

T

Tuberculosis (TB)

Specific disease caused by the presence of *Mycobacterium tuberculosis* organisms

Miliary TB

TB Characterized by the formation of widespread lesions resembling millet seeds. The disease spreads widely to involve extra-pulmonary organs such as the liver, kidney etc.

Multidrug resistant TB (MDR)

Organisms resistant to rifampicin and isoniazid

Single Drug resistant TB (SDR)

Organisms resistant to any one drug on the standard treatment regimen

1. INTRODUCTION

1.1 Background to the study

Pulmonary tuberculosis (PTB), declared a global emergency by the World Health Organisation in 1991, is a major infectious disease in the South African mining industry (Leon, 1995). Patients who are timeously diagnosed have an excellent response to treatment and yet, despite comprehensive TB control programs in the mining industry, deaths from TB exceed those due to mine accidents (La Grange, 2000).

TB is a potentially curable disease and failure to diagnose it accurately and timeously has important implications for the individual, spread of PTB in the community and compensation in terms of the Occupational Diseases in Mines and Works Act (ODMW Act). However, improved management can only occur if the diagnosis is correctly established to target areas for intervention.

Unsuspected TB as a cause of death has been described in the American, European and African medical literature in both general and HIV infected populations. These studies have emphasised the importance of autopsies for recognising TB that has not been clinically suspected and diagnostic discrepancies have been observed in over half the cases (d'Arminio Monforte, 1996; Wilkes, 1988). Data from SIMRAC project GEN 509 (Surveillance of respiratory diseases across the mining industry using the autopsy database) showed that during 1997 there were 379 cases of PTB diagnosed at autopsy, most of which were very extensive. However, the clinicians had correctly ascribed TB as the cause of death in only 31% of these cases.

The National Centre for Occupational Health (NCOH) examines the lungs of deceased mineworkers, with an autopsy rate of around 80% for men dying while in employment. The NCOH is thus in a unique position to assist with strategies for improving the accurate diagnosis of PTB.

1.2 Objectives

1. Correlation of the ante- and postmortem diagnoses of PTB on a representative sample of miners in South Africa
2. Review of medical data to assess current clinical practice and identify possible reasons for discordant diagnoses
3. Identify strategies for improving clinical practice

2. METHODS

2.1 Study setting

The study was undertaken on South African gold, coal and platinum mines.

2.2 Study population and Selection of study cases

The study population comprised all men who died and had an autopsy examination of their lungs between January and December 1999, in terms of the ODMW Act. The study subjects comprised men with a clinical diagnosis of PTB (i.e. PTB was mentioned on death certificate as a factor in the cause of death) and / or an autopsy diagnosis of PTB. They were selected from the autopsy database using the programs written for a previous SIMRAC project (GEN509: Surveillance of respiratory diseases across the mining industry using the autopsy database).

2.3 Autopsy Methods

Briefly, the autopsy methods are as follows: lungs are removed locally at the mines, placed in formalin and sent to the NCOH in Johannesburg for pathological examination. Tissue sections are routinely stained with hematoxylin, eosin and alcian-blue (for *Pneumocystis carinii*). All the study subjects also had a Ziehl-Neelsen (for acid fast bacilli) and Grocott stain (for Cryptococcus, other fungi and nocardia). Autopsy reports and microscopic slides of tissue sections from the lungs of all the study subjects were reviewed to confirm the pathological findings, prior to clinical record review.

Bacterial pneumonia was defined as the presence of consolidation with polymorphonuclear leukocytes in the bronchioles and alveoli.

The diagnosis of TB was made in the presence of granulomatous inflammation with or without acid fast bacilli, other causes of granulomatous inflammation having been excluded on special stains for fungi. TB was also diagnosed if no granulomata were identified but there was extensive necrosis with nuclear debris and large numbers of acid fast bacilli on Ziehl-Neelsen stains (the pattern of non-reactive TB)

2.4 Review of clinical records

Current clinical practice was assessed by a review of the patients' medical records. Data pertaining to hospital admissions, diagnostic tests, TB history and primary clinic visits were collected by the study members at regular visits to the mine hospitals. A single data capture sheet for autopsy and clinical data was developed (Appendix 1)

2.5 Analysis of data

Autopsies from Anglo Gold were excluded from all the analyses. Study subjects were divided into three groups: 1) patients with a diagnosis of PTB at autopsy only; 2) patients with both a clinical and autopsy diagnosis of PTB; 3) patients with a clinical diagnosis of PTB which was not confirmed at autopsy. The clinical and autopsy data were analysed to identify possible reasons for discordant diagnoses.

2.6 Ethics approval

Ethics approval was obtained from the University of the Witwatersrand Committee for Research on Human Subjects. Ethics approval was not obtained from Anglo Gold Health Service (Pty) Ltd Medical Research Ethics Committee. The issues which they raised were discussed at a meeting with Prof. Cleaton-Jones (chairperson of the WITS ethics committee)

and Dr Ross (Simpross) and subsequently by the WITS Committee for Research on Human Subjects. Assurance was given by the committee that the study could proceed with the medical centres which had agreed to participate and ethical approval was confirmed.

3. RESULTS

3.1 Study subjects

During 1999, there were 1858 autopsy examinations of the lungs of miners performed at NCOH (excluding Anglo Gold). There were 350 study subjects and Table 1 shows the distribution of the study population and subjects by ethnic group and commodity mined.

TABLE 1 STUDY SUBJECTS AS A PROPORTION OF AUTOPSIES DONE AT NCOH BY ETHNIC GROUP AND COMMODITY JANUARY – DECEMBER 1999

Ethnic group and commodity	Study subjects / Autopsies at NCOH	
	N	%
Black men		
Gold	243/791	31
Coal	26/83	31
Platinum	47/173	27
Other*	14/68	21
Unknown	1/17	6
Total	331/1132	29
White men		
Gold	6/452	1
Coal	2/58	3
Platinum	0/38	0
Other*	3/106	3
Unknown	1/22	5
Total	12/676	2
Coloured men		
Asbestos	5/25	20
Other*	2/4	50
Total	7/29	24
Unknown	0/21	0
Total	350/1858	19

* Other includes copper, diamond etc.

The 350 study patients were grouped according to clinico-pathological correlation as:

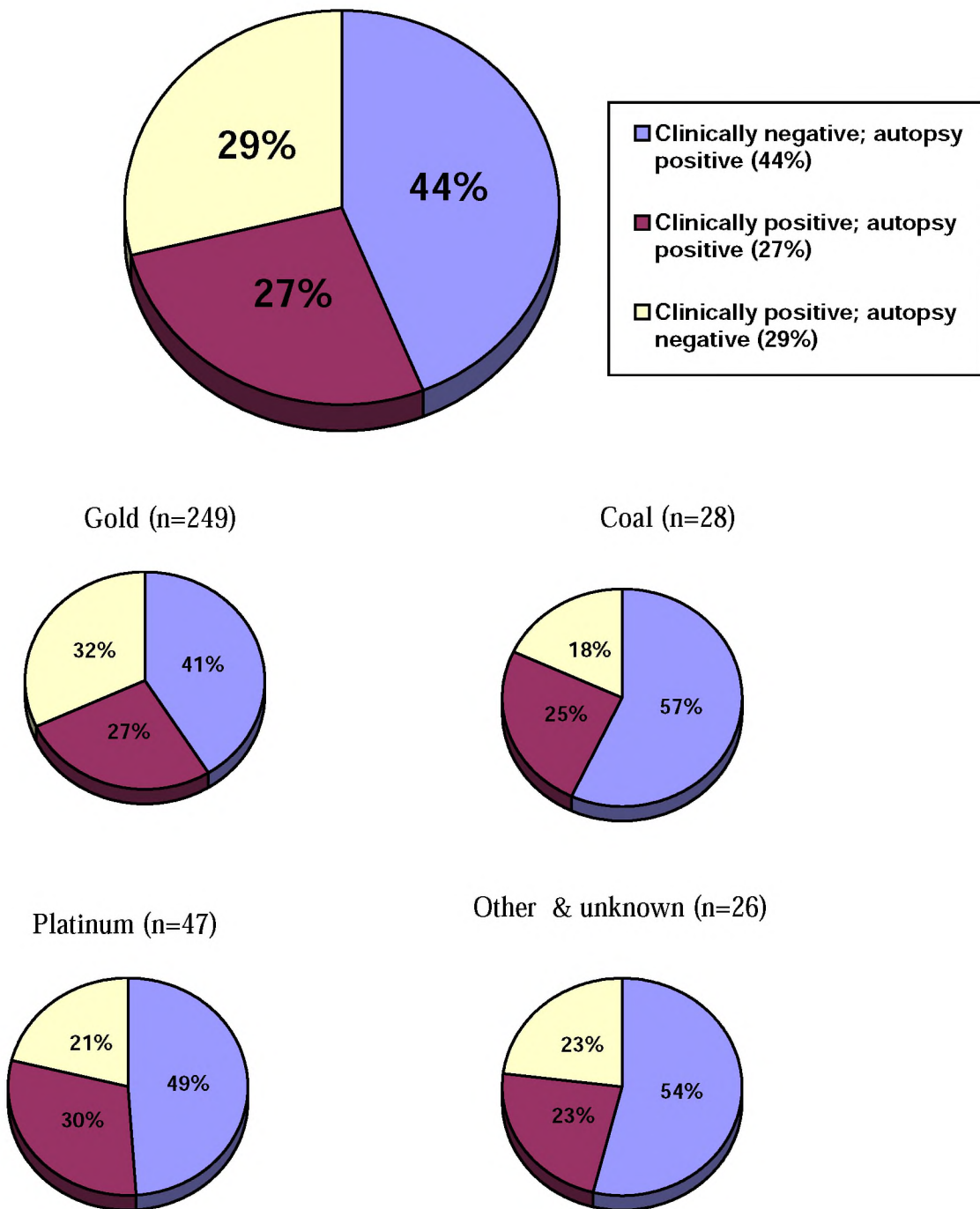
1. PTB clinically negative : autopsy positive 155 cases (44%)
2. PTB clinically positive : autopsy positive 95 cases (27%)
3. PTB clinically positive : autopsy negative 100 cases (29%)

PTB was correctly clinically ascribed according to autopsy findings in 27% of the study subjects. The distribution of the study subjects by clinico-pathological correlation, ethnic group and commodity mined is shown in Table 2 and Fig 1.

TABLE 2 DISTRIBUTION OF 350 STUDY SUBJECTS BY CLINICO-PATHOLOGICAL CORRELATION, ETHNIC GROUP AND COMMODITY

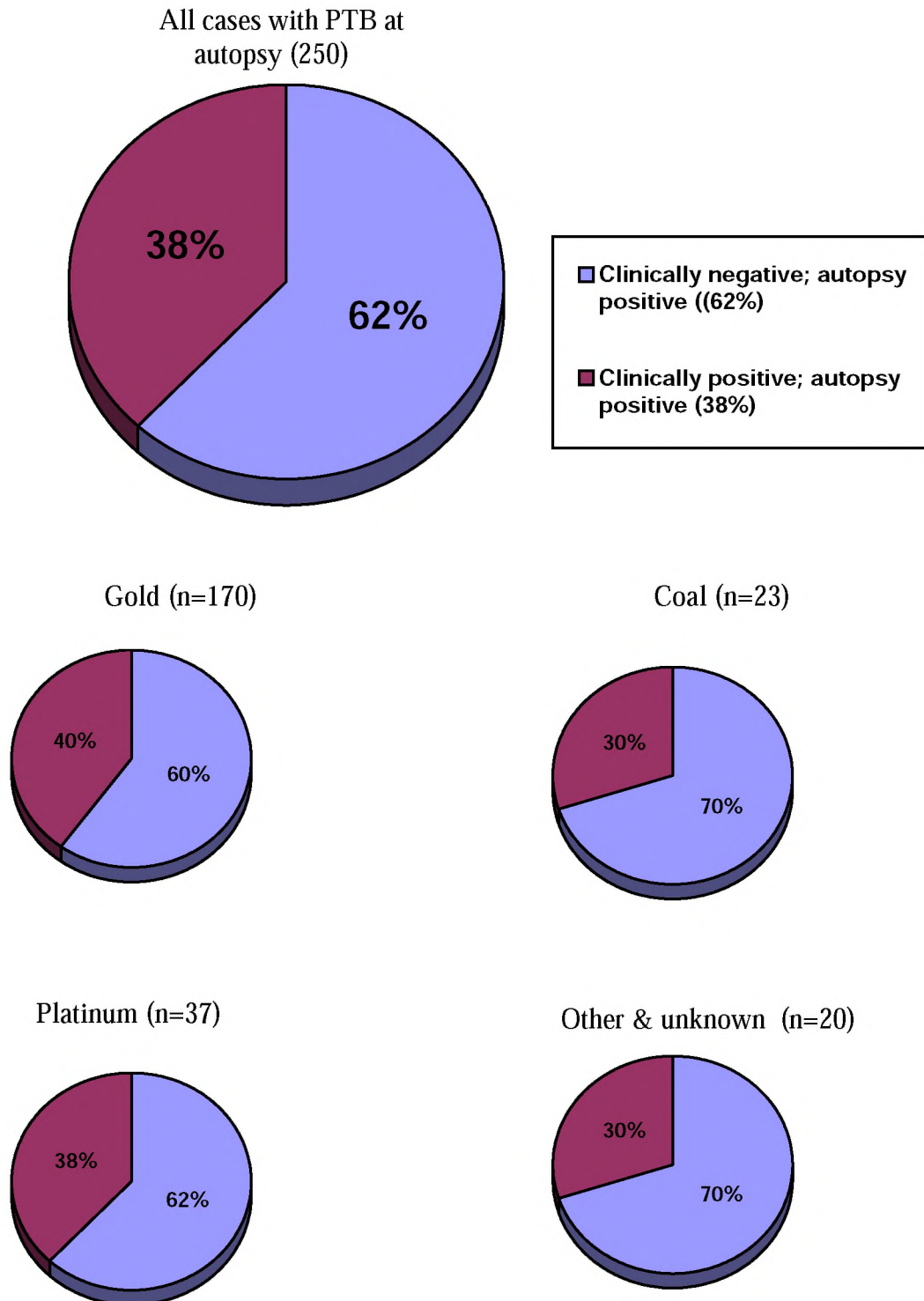
	Clinically negative : autopsy positive		Clinically positive : autopsy positive		Clinically positive : autopsy negative		Total	
	n=155	44%	n=95	27%	n=100	29%	n=350	
	N	%	N	%	N	%	N	%
Ethnic group								
Black	142	92	91	96	98	98	331	95
White	10	6	2	2	0	0	12	3
Coloured	3	2	2	2	2	2	7	2
Total	155	100	95	100	100	100	350	100
Commodity								
Gold	102	66	68	72	79	79	249	71
Coal	16	10	7	7	5	5	28	8
Platinum	23	15	14	15	10	10	47	13
Other	11	7	0	0	0	0	11	3
Unknown	3	2	6	6	6	6	15	4
Total	155	100	95	100	100	100	350	100

FIGURE 1 DISTRIBUTION OF 350 STUDY SUBJECTS BY CLINICO-PATHOLOGICAL CORRELATION AND COMMODITY MINED



Of all the cases where PTB was found at autopsy, PTB was correctly clinically diagnosed in 38% (95/250) of cases. Figure 2 shows the distribution of these 250 cases; the 100 cases where the clinical diagnosis of PTB was not confirmed are excluded.

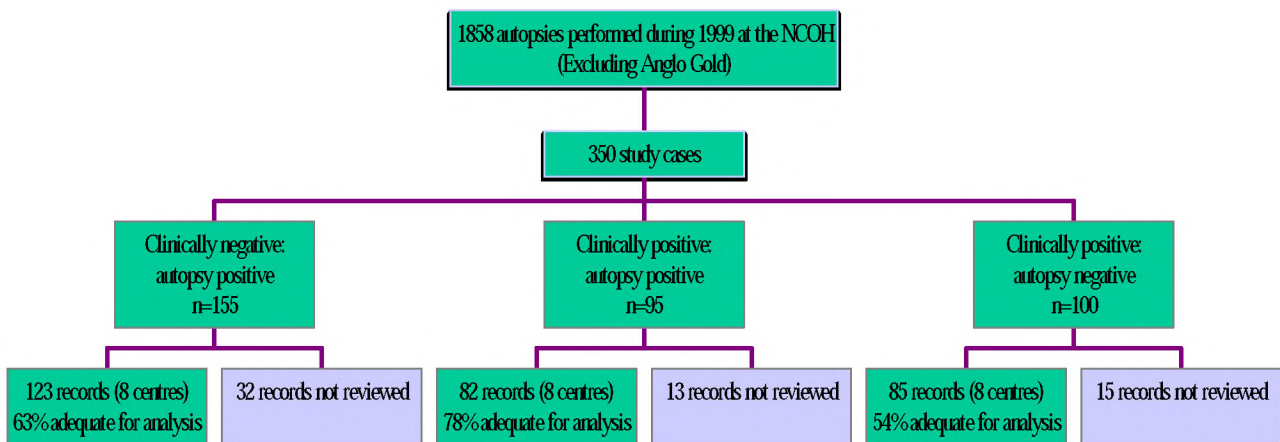
FIGURE 2 DISTRIBUTION OF 250 CASES WITH PTB AT AUTOPSY BY CLINICO-PATHOLOGICAL CORRELATION; 100 CASES WHERE CLINICAL DIAGNOSIS OF PTB WAS NOT CONFIRMED ARE EXCLUDED



3.2 Medical record review

Eight mine medical centres (Leslie Williams, Gold Fields West, Duff Scott, Harmony, St Helena, SASOL-Secunda, ERPM and Amplats), which accounted for (81%) of all the study subjects were selected for medical record review. 65% (187/290) of the medical records of these patients were adequate for statistical analysis. The distribution of adequate medical records (from all 350 study cases) reviewed by clinico-pathological category and commodity is shown in Figure 3.

FIGURE 3 DISTRIBUTION OF AUTOPSIES DONE AT THE NCOH AND REVIEWED FOR THIS STUDY



THE 187 CASES WHERE MEDICAL RECORDS WERE ADEQUATE FOR STATISTICAL ANALYSIS WERE USED FOR THE REST OF THE RESULTS SECTION

3.2.1 Age

The mean age of cases was 41.3 years (SD 7.1), median 41 and range 26-58.

3.2.2 Place of Death

The study subjects included men who died in a mine hospital, as well as those dying elsewhere such as mine hostels, provincial hospitals and at home. The place of death of the study subjects by clinico-pathological category is shown in Table 3.

**TABLE 3 PLACE OF DEATH BY CLINICO-PATHOLOGICAL CATEGORY
(N=186*)**

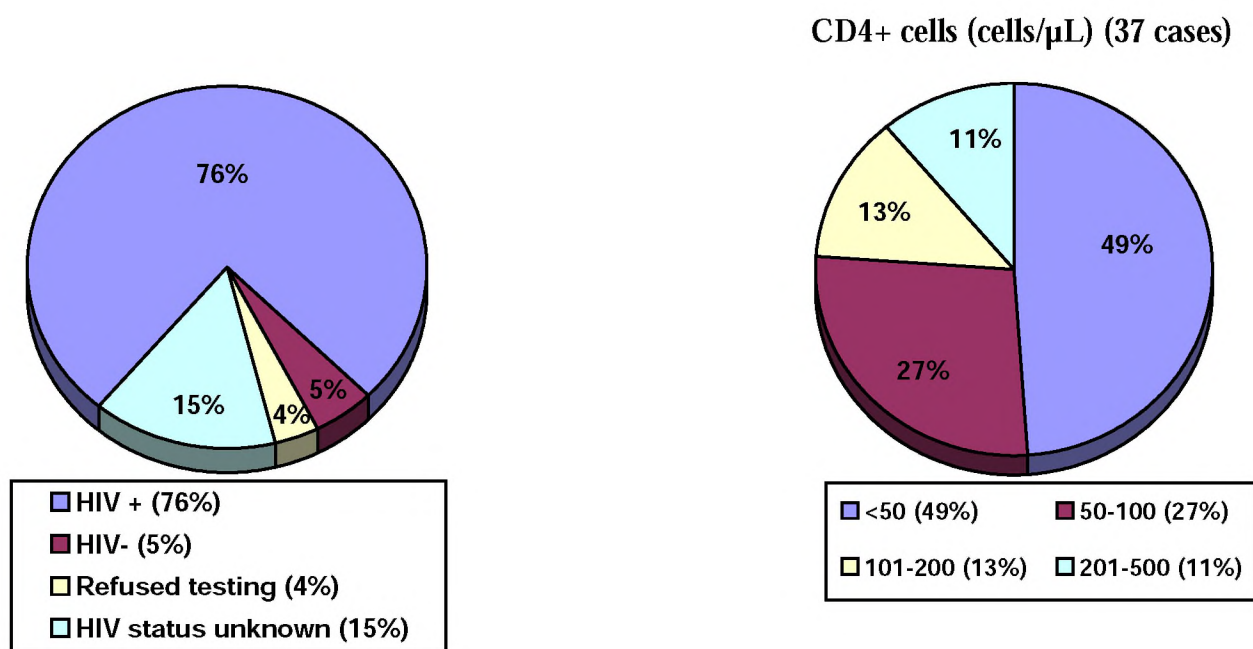
Place of death	Clinically negative: autopsy positive		Clinically positive: autopsy positive		Clinically positive: Autopsy negative	
	N	%	N	%	N	%
Mine hospital	53	70	51	80	35	76
On mine	16	21	8	12	11	24
Off mine	7	9	5	8	0	0
TOTAL	76	100	64	100	46	100

* excluded is 1 case where the place of death could not be ascertained

3.2.3 HIV infection

76% (143/187) of the men were known to be HIV infected. CD4+ counts were known in a minority of the cases who were HIV infected (37/143) (Figure 4). There were no cases with a count greater than 500 cells/ μ L, and 90% had a count of <200 cells/ μ L. No patients were on anti-retroviral therapy nor were any on TB chemoprophylaxis.

FIGURE 4 HIV STATUS IN 187 CASES



3.3 PTB CLINICALLY NEGATIVE:AUTOPSY POSITIVE

There were 77 medical records in this category which were adequate for statistical analysis.

3.3.1 Case finding

3.3.1.1 Surveillance chest radiographs

27 (35.1%) patients were known (we did not specifically access the annual medical surveillance records) to have had a surveillance chest radiograph taken within the year preceding death, and all were assessed as having no active TB.

3.3.1.2 Attendance at mine health facilities in the 3 months preceding death or the terminal hospital admission

64% of patients (48/75) had attended the mine health facilities at least once in the 3 months preceding death, excluding a primary clinic visit that resulted in a hospital admission. Most patients (51; 68%) died in a mine hospital and of these, 61% had attended the medical facilities within the three months preceding their terminal admission (Table 4 and Fig 5). At a majority of the visits to the health facilities (26/48; 54%), the patients had respiratory symptoms and / or signs. Several patients were attending the mine health facilities monthly for chronic conditions such as diabetes and hypertension. Of the patients who died outside a mine hospital, 71% (17/24) had also attended the health facilities in the 3 months prior to death.

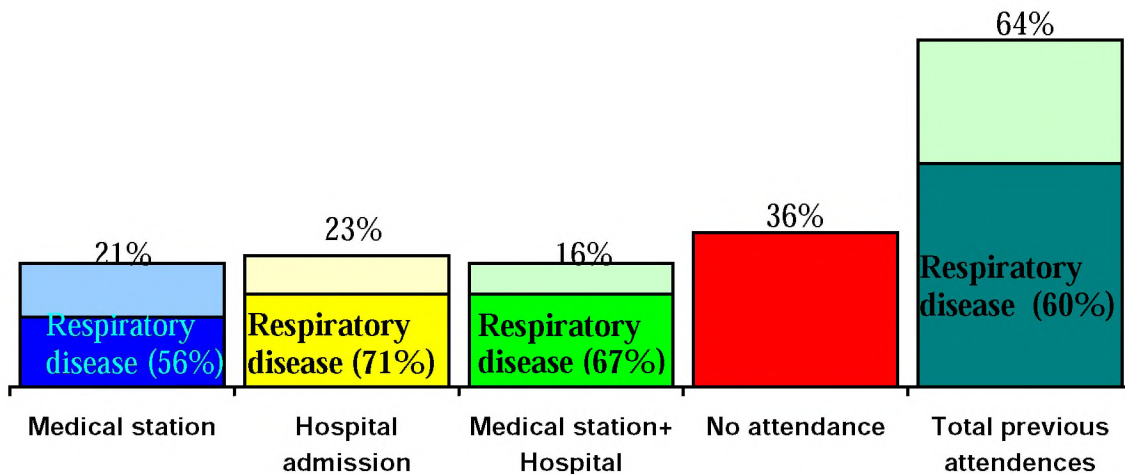
TABLE 4 ATTENDANCE AT MINE HEALTH FACILITIES IN THE 3 MONTHS PRECEDING DEATH
PTB: clinically negative : autopsy positive patients; n=75*

	Died in Mine hospital N=51* (68%)	Died outside Mine hospital N=24** (32%)	Total
Attendance at mine health facility	%	%	%
Medical station (% with respiratory disease)	21 (64)	21 (40)	21 (56)
Hospital (% with respiratory disease)	18 (78)	33 (63)	23 (71)
Med Stat & Hosp (% with respiratory disease)	18 (78)	13 (33)	16 (67)
Surveillance (% with respiratory disease)	4 (0)	4 (0)	4 (0)
Total attendances (% with respiratory disease)	61 (68)	71 (47)	64 (60)

* 2 patients where data was not available are excluded

** 1 patient where place of death could not be ascertained is included

FIGURE 5 ATTENDANCE AT MINE HEALTH FACILITIES IN THE 3 MONTHS PRECEDING DEATH OR THE TERMINAL HOSPITAL ADMISSION
PTB: CLINICALLY NEGATIVE: AUTOPSY POSITIVE
 (Attendance at occupational health centre for surveillance examination is not shown (4%))



Case histories and photographs of lungs illustrating previous attendance at mine health facilities

Case 1 – Previous hospital admission for pneumonia

Case 2 – Previous attendance for chronic disease at medical outpatients

Case 3 – Previous attendance at primary clinic for respiratory symptoms

3.3.2 Management during the terminal hospital admission

3.3.2.1 Investigations for PTB

The 53 patients who died in a mine hospital were grouped according to the presence or absence of clinical signs and symptoms of respiratory disease, and investigations which may have led to the diagnosis of PTB were evaluated. Patients who were clinically assessed as having respiratory signs and symptoms were more likely to have chest radiographs and sputum smears examined for TB (Table 5). Duration of hospital stay was similar in both groups. No cultures for TB were requested.

TABLE 5 INVESTIGATIONS FOR PTB DURING THE TERMINAL HOSPITAL ADMISSION ACCORDING TO SIGNS AND SYMPTOMS OF RESPIRATORY DISEASE

PTB: Clinically negative : Autopsy positive patients; n=53*

Investigations Requested	Respiratory signs & symptoms	
	Present	Absent
	n=33 (62%)	n=20 (38%)
	%	%
Chest radiograph	88	55
Sputum smears for TB	61	5
Sputum culture for TB	0	0
Hospital stay mean days (sd)	16.7(9.4)	17.2(12.4)

* 7 patients with focal TB are included.

3.3.2.2 Chest radiographs

Table 6 shows the number of chest radiographs requested, as well as the interpretation of the radiograph where this was recorded by the clinician in the medical record. The most frequent assessment of the radiographs were normal, pneumonia and possible TB, however, in these latter cases, TB was not mentioned on the death certificate

TABLE 6 CHEST RADIOGRAPHS OF PATIENTS WHO DIED IN HOSPITAL

PTB Clinically negative: autopsy positive patients; n=53

	Respiratory signs & symptoms	
	Present N= 33	Absent n=20
Chest radiograph:		
Requested	29	11
Taken	28	9
Reading recorded	26	7
Reading:		
Clear	6	7
Pneumonia	5	
Inactive TB	3	
Query TB	5	
Other*	7	

*includes comments such as interstitial infiltrate, oedema etc.

3.3.2.3 Sputum examination

61% of the patients admitted to hospital with clinical signs and symptoms of respiratory disease had at least one sputum sent for smear examination for TB (Table 7). In 39% of the patients no sputum was requested, these patients survived at least one day in hospital. Sputum could not be obtained in 2 mentally confused patients.

TABLE 7 SPUTUM SMEAR EXAMINATION OF THE PATIENTS WITH SIGNS AND SYMPTOMS OF RESPIRATORY DISEASE WHO DIED IN HOSPITAL

PTB: Clinically negative : Autopsy positive patients; n=33

Number of specimens sent *					Sputum negative	Result not available	Sputum positive
1	2	3	3+				
2 **	2	12	3		18	1	1 ***

* for one patient data on the number of smears sent were missing

** one patient died the same day, one became confused

*** patient with hepato-renal failure; TB was not mentioned on the death certificate

3.3.2.4 Clinical management

58% of the hospitalized patients with signs and/or symptoms of respiratory disease were clinically assessed and managed as having non-specific pneumonia. 88% of them also had a diagnosis of AIDS.

Of those without respiratory signs and/or symptoms, 90% had 'AIDS', in 40% of whom this was the only clinical assessment. The remaining 60% had a variety of clinical disorders including meningitis, septicemia, diarrhea, pancreatic pseudocyst, Kaposi's sarcoma and renal failure. Of the two patients without AIDS, 1 had encephalitis and 1 renal failure.

3.3.2.5 Previous PTB

A history of previous TB was present in 16%.

3.3.3 Autopsy findings

The autopsy findings are shown in Table 8. Miliary TB was the predominant pathological pattern, being present in 57% of cases. 27% of the patients had PTB together with at least one other additional pathology, of which 76% were infectious with non-specific pneumonias predominating.

**TABLE 8 AUTOPSY FINDINGS IN PTB CLINICALLY NEGATIVE :
AUTOPSY POSITIVE PATIENTS n=77**

Pathology	Number of patients
PTB pattern:	
Focal	7
Miliary	44
Extensive bronchopneumonic and Fibrocaseous	26
PTB and pericardial TB	2
PTB and pleural TB	1
PTB and another lung disease:	21*
Infective:	16
Non-specific Pneumonia	10
<i>Pneumocystis carinii</i>	3
Nocardia	1
Cytomegalovirus	1
<i>Aspergillus</i>	1
Non-infective:	
Kaposi's sarcoma	1
Silicosis	6
Embolus	2
Emphysema	1
Bronchiectasis	1
Pulmonary oedema	1
Pleural exudate	1

* 21 patients, some had more than one additional lung disorder

Case histories and photographs of lungs illustrating autopsy features which made a clinical diagnosis of TB difficult

Case 5 – Fine miliary TB

Case 6 – Multiple respiratory diseases: at autopsy: TB + *Pneumocystis carinii* pneumonia

Case 7 – Multiple respiratory diseases: at autopsy: TB + bronchopneumonia + Kaposi's sarcoma

Case 8 – Multiple respiratory diseases: at autopsy: Miliary TB + nocardia with cavitation

3.3.3.1 Correlation of pathology, radiology and clinical assessment for those who died in hospital

Of those patients who were clinically assessed as having no evidence of respiratory signs or symptoms, 71% (5/7) had miliary PTB at autopsy, 1 had extensive pneumonic type PTB (he died after 38 days in hospital and was being managed as Kaposi's sarcoma of the palate) and one had focal PTB. None of these patients had another respiratory disease at autopsy.

Of the patients with respiratory signs and symptoms, 69% had miliary PTB at autopsy, 15% had focal PTB and the rest extensive fibrocaseous and bronchopneumonic type PTB. Miliary PTB alone was present in 38% and miliary PTB together with another pathology was present in 61%, this was predominantly non-specific pneumonia (44%).

3.4 PTB CLINICALLY POSITIVE : AUTOPSY POSITIVE

There were 64 medical records which were adequate for statistical analysis in this category. In 48%, the diagnosis of PTB was made during their terminal hospital admission. In 52%, the diagnosis had been previously made, they either died during a readmission to the mine hospital or elsewhere while on treatment for PTB.

3.4.1 Case finding

3.4.1.1 Surveillance radiographs

Data pertaining to this were scanty in the hospital bed letters. Four patients were recorded as having had a surveillance radiograph in the year preceding death but in the rest, this data could not be ascertained.

3.4.1.2 Attendance at mine health facilities in the 3 months preceding death

Of the 31 patients in this category who were diagnosed with PTB during their terminal hospital admission, 39% had attended the mine health facilities in the 3 months preceding death (Table 9 and Fig 6). The majority of the previous attendances (75%) were for respiratory conditions.

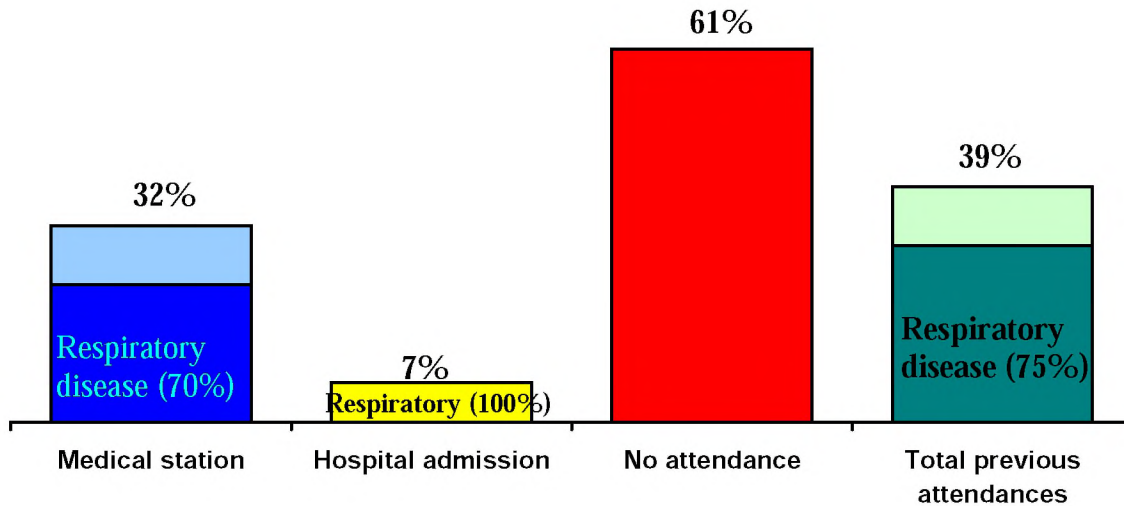
The rest of the patients had been receiving treatment for TB at the medical stations.

TABLE 9 ATTENDANCE AT MINE HEALTH FACILITIES IN THE 3 MONTHS PRECEDING DEATH BY PATIENTS IN WHOM PTB WAS DIAGNOSED DURING THEIR TERMINAL HOSPITAL ADMISSION
PTB: Clinically positive : Autopsy positive (n=31)*

		Died in mine hospital N=31 (84.2%)	
Attendance at mine health facility		%	
Medical station	(% with respiratory disease)	32	(70)
Hospital admission	(% with respiratory disease)	7	(100)
Total attendances	(% with respiratory disease)	39	(75)

* 8 people who died before treatment started are included

FIGURE 6 ATTENDANCE AT MINE HEALTH FACILITIES IN THE 3 MONTHS PRECEDING DEATH BY PATIENTS IN WHOM PTB WAS DIAGNOSED DURING THEIR TERMINAL HOSPITAL ADMISSION
PTB: Clinically positive: autopsy positive



3.4.2 Management

3.4.2.1 Management of newly diagnosed patients during their terminal hospital admission

The diagnosis was made by chest radiograph in 42% (Table 10), positive sputum smear in 39% and by other means in a few (one had a positive culture which was sent on a previous admission, 1 had no x-ray but was diagnosed because of haemoptysis, one following surgery for a TB caecal mass, and in 3 patients we could not establish how the diagnosis was made). 65% died within 10 days of admission, and 26% died before treatment was started.

Diagnostic delay was much lower in the sputum smear positive cases: (One outlier of 46 days is excluded) $21/11 = 1.9$ days versus $92/15 = 6.1$ days for the other cases

TABLE 10 CHARACTERISTICS OF PATIENTS DIAGNOSED DURING THEIR TERMINAL HOSPITAL ADMISSION
PTB: Clinically positive : Autopsy positive n=31

TB treatment duration (days)	Diagnostic delay	Length of hospital stay	Method of diagnosis
0	1	1	x-ray
0	2	2	x-ray
0	2	2	Empiric (haemoptysis)
0	8	8	x-ray
0	3	3	x-ray
0	4	6	Smear+
0	Unknown	5	Couldn't establish
0	Unknown	6	Couldn't establish
1	5	6	x-ray
1	1	2	x-ray
1	3	4	Smear+
1	5	6	x-ray
1	10	11	x-ray
1	2	3	x-ray
1	8	9	x-ray
2	5	7	Smear+
2	1	3	Smear+
3	3	6	x-ray
5	3	8	Previous culture now +
5	3	8	Smear+
6	10	16	Couldn't establish
7	2	9	Smear+
14	46	60	Smear+
18	18	36	Caecal TB (Biopsy)
19	14	33	x-ray
26	3	29	Smear+
29	0	29	Smear+
32	10	42	x-ray
51	0	51	Smear+
57	0	57	Smear+

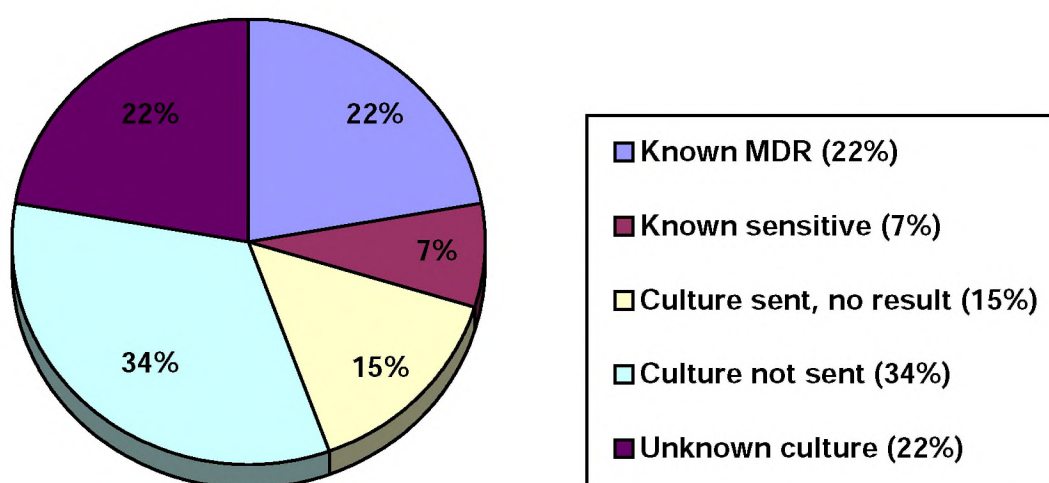
81	0	81	Smear+
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3.4.2.2 Management of patients on TB treatment for longer than 30 days

There were 27 patients who had received treatment for TB for more than 30 days, 85% of whom had extensive TB at autopsy and most of whom had been treated for longer than 100 days (Table 11).

Of those cases treated for more than 30 days, 2 (7%) were known to be fully drug susceptible, 6 (22%) were known multi-drug resistant TB (MDR) and in 34% a sputum had not been sent for culture (Fig 7).

FIGURE 7 DRUG SUSCEPTIBILITY STATUS FOR PATIENTS ON TB TREATMENT FOR LONGER THAN 30 DAYS
PTB: Clinically positive : Autopsy positive n=27



Case histories and photographs of lungs illustrating:

Case 9 – Known MDR TB

Case 10 – Patient at high risk for MDR, drug susceptibility not done

Case 11 – Patient at risk for MDR TB with sputum not assessed at end of previous episode of TB treatment

Case 12 – Patient with multiple recurrent episodes of TB known to still not have drug resistance

TABLE 11 TREATMENT DURATION, DRUG SUSCEPTIBILITY AND HISTORY OF PREVIOUS TB IN PATIENTS ON TB TREATMENT FOR LONGER THAN 30 DAYS

PTB: Clinically positive: autopsy positive; n=27

Treatment days	Culture status	MDR status	Previous TB
32	Done, result n/a	Unknown	Yes
36	Done	Unknown	No
51	No culture	Unknown	Yes
57	No culture	Unknown	Yes
70	Done	MDR	Unknown
72	Done	Sensitive	Yes
81	No culture	Unknown	No
90	Unknown	Unknown	Yes
96	Unknown	Unknown	No
116	Done	MDR	Unknown
120	No culture	Unknown	No
120	Done	Sensitive	Yes
129	No culture	Unknown	Yes
141	Done, result n/a	Unknown	No
150	No culture	Unknown	Yes
155	Unknown	Unknown	Unknown
166	Unknown	Unknown	Unknown
172	Unknown	Unknown	Unknown
175	Unknown	Unknown	Yes
210	Done, result n/a	Unknown	Yes
211	No culture	Unknown	Yes
236	Done	MDR	Unknown
500	Done	MDR	Unknown
619	Done	MDR	Chronic TB
720	No culture	Unknown	Unknown
900	Done	MDR	Unknown
900	No Culture	Unknown	Unknown

* Focal TB

3.4.2.3 Miscellaneous cases

There were an additional 8 cases who did not fit into either of the preceding groups.

*2 men died in the rural areas (Lesotho, Transkei), having left the mines several months previously with no mine history of TB

*2 patients refused all medical treatment, both had a clinical diagnosis of TB

*3 patients were brought in dead, the duration of treatment for TB could not be established in 2, one had been treated for 10 days.

*1 patient who was on treatment for TB for 30 days, was readmitted with advanced AIDS

and was being processed for medical discharge when he died.

3.4.3 Autopsy findings

The autopsy findings are shown in Table 12. Miliary TB was present in 17% of patients, all but one of whom were newly diagnosed. 33% of the patients had PTB plus another disorder.

TABLE 12 AUTOPSY FINDINGS IN PTB CLINICALLY POSITIVE : AUTOPSY POSITIVE PATIENTS (N=64)

Pathology	Number of patients
PTB pattern:	
Focal	5
Miliary	11
Extensive bronchopneumonic and fibrocaseous	48
PTB and pleural TB	2
PTB and another lung disease	21
Infective:	11
Non-specific pneumonia	8
Cryptococcus	3
Non-infective	
Lymphoma	1
Interstitial pneumonitis	1
Silicosis	6
Embolus	1
Emphysema	1

3.5 Comparison of Clinically negative:autopsy positive and Clinically positive:autopsy positive groups

3.5.1 Comparison of features which may have influenced the diagnosis of TB

Table 13 shows that both miliary TB and the simultaneous presence of another additional lung disease were significantly ($p < 0.05$) more frequent in patients in whom clinicians failed to diagnose TB antemortem, than they were in patients in whom TB was correctly diagnosed. On the other hand, a history of previous TB was significantly ($P < 0.05$) less frequent in clinically undiagnosed patients.

TABLE 13 COMPARISON OF FEATURES IN DIAGNOSED AND UNDIAGNOSED TB PATIENTS WHO DIED IN HOSPITAL

Autopsy finding	Clinically negative: autopsy positive (n=33)		Clinically positive: autopsy positive (n=31)		
	Yes	No	Yes	No	
Miliary PTB	23	10	10	21	$X^2=8.9$ $P=0.003$
Additional lung disease	14	19	6	25	$X^2=7.5$ $P=0.006$

Case histories and photographs of the lungs illustrating the risk of transmission of undiagnosed TB to the community

Case 13 – Patient who died on the mine

Case 14 – Patient who died off the mine

Case 15 – Nosocomial risk

3.6 PTB CLINICALLY POSITIVE : AUTOPSY NEGATIVE

Patients in this category were those in whom the clinicians had recorded PTB as a major factor in the cause of death but TB was not present at autopsy. There were 46 medical records adequate for analysis in this category.

3.6.1 Patient on treated for TB for longer than 30 days

72% of patients for whom TB was clinically incorrectly ascribed as the cause of death, had been treated for longer than 30 days. The initial diagnosis of PTB was bacteriologically confirmed in 51%, was empiric in 40% and in the rest, the mode of diagnosis could not be ascertained. Most (72%) showed an initial clinical response and had been discharged from hospital only to deteriorate subsequently.

27% of these patients were clinically assessed as having predominantly nervous system disease and in 2 patients, Cryptococcal meningitis was diagnosed. In 27%, the clinical cause of death was ascribed to respiratory failure and the clinical differential diagnosis included multi-drug resistant TB, *Pneumocystis carinii* and non-specific bacterial pneumonia. For some of the remaining patients, their deterioration was ascribed to progressive advanced AIDS. Nevertheless, PTB was included on the death certificate in all of these patients as a major factor in the cause of death.

3.6.2 Patient on treatment for TB for less than 30 days

22% of patients in this category had been treated for 30 days or less. In 7%, neither treatment duration or mode of diagnosis could be accurately ascertained.

A similar spectrum of lung disease was present at autopsy for patients treated for less than 30 days as well as for those treated for more than 30 days (Table 14). Infections predominated of which non-specific pneumonia was most frequent, followed by Cryptococcal and *Pneumocystis carinii* pneumonia.

**TABLE 14 AUTOPSY FINDINGS IN THE PTB CLINICALLY POSITIVE:
AUTOPSY NEGATIVE PATIENTS**

Pathology	Number of patients
PTB	0
PTB plus another lung disease*	
Infective:	
Non-specific Pneumonia	16
Cryptococcal pneumonia	10
<i>Pneumocystis carinii</i>	8
Aspergillus	1
Non-infective:	
Kaposi's sarcoma	3
Lymphocytic interstitial pneumonitis	2
Silicosis	8
Embolus	1
Emphysema	1
Pulmonary oedema	3
Metastatic cancer	3

* Some patients had more than one lung disease

Case histories & photographs of lungs illustrating patients who died while on TB treatment with no PTB found at autopsy

Case 16 – Empirically treated for recurrent TB for 26 days

At autopsy: Aspergillus & *Pneumocystis carinii* pneumonia

Case 17 – Treated for smear positive TB for 183 days

At autopsy: Cryptococcus and pneumonia

Case 18 – Treated for smear positive TB for 84 days

At autopsy: Kaposi's sarcoma and cryptococcal pneumonia

Case 19 – Empirically treated for TB for 148 days

At autopsy: *Pneumocystis carinii* pneumonia and Kaposi's sarcoma

Case 20 – Empirically treated for TB for 100 days

At autopsy: Extensive malignant tumour of unknown primary origin

Case 21 – Treated for smear positive TB for 62 days

At autopsy: Bacterial pneumonia

4. DISCUSSION

“Hic locus est ubi mors gaudet succerrere vitae : this is the place where death delights to help the living” anon

4.1 Introduction

In this study of 350 South African miners who came to autopsy during 1999, we found that clinicians failed to diagnose PTB as the cause of death in 44% of cases, correctly ascribed PTB as the cause of death in 27%, and incorrectly ascribed PTB as the cause of death in 29%. We acknowledge that the study involved mainly failures in the TB control programmes, and realise that around 90% of TB patients are successfully treated (Murray, 1999a; Churchyard, 2000a). Nevertheless, even a few undiagnosed PTB cases represent a considerable public health risk and, in evaluating possible reasons for discordant diagnoses, areas which might be amenable to improved clinical management were identified. Poor clinico-pathological correlation is not unique to the mine medical services, but also occurs even in developed countries with very well resourced medical care.

Numerous clinico-pathological correlation studies have shown how important autopsy is in quality control, medical education and research (Nemetz, 1987; Scottolini, 1983; Cameron, 1981; Goldman, 1983). Clinically important diagnoses are missed, despite improved medical knowledge, experience, and diagnostic tools, and previous studies have emphasised the importance of autopsies for recognising disorders that have not been clinically suspected. In both general and HIV-infected populations, infectious and other diseases are frequently missed, and diagnostic discrepancies have been observed in up to 75% of cases. (Cameron, 1981a&b; Hui, 1984 ; Wilkes, 1988; Klatt, 1988). Only a limited number of autopsy studies relating to HIV infected patients have been reported from Africa, and few of these have included clinical correlation (Lucas, 1991; Lucas, 1993; Rana, 1997; Nelson, 1993; Abouya, 1992; Murray, 1999a)

Unsuspected TB as a cause of death has been described in both AIDS (d'Arminio Monforte, 1996; Flora, 1990) and general populations (Bobrowitz, 1982; Edlin, 1978; Enarson, 1978). In one large general autopsy series, TB was clinically diagnosed in only 50% of the cases in which it was judged to be the main diagnosis at autopsy (Naalsund, 1994).

4.2 The natural history of TB

In order to evaluate the aspects identified in this study which might lead to a reduction in missed, delayed and misdiagnosis of PTB, the natural history of PTB is briefly outlined:

Exposure → Infection → Disease → Diagnosis → Treatment →
Outcome →

- cure
- treatment failure including multi-drug resistance
- recurrence
- death

Infection occurs when susceptible persons are exposed to infectious patients, not all of whom have detectable TB bacilli in their sputum. To break the chain of transmission, the cornerstone of all TB programmes is early case detection and successful treatment.

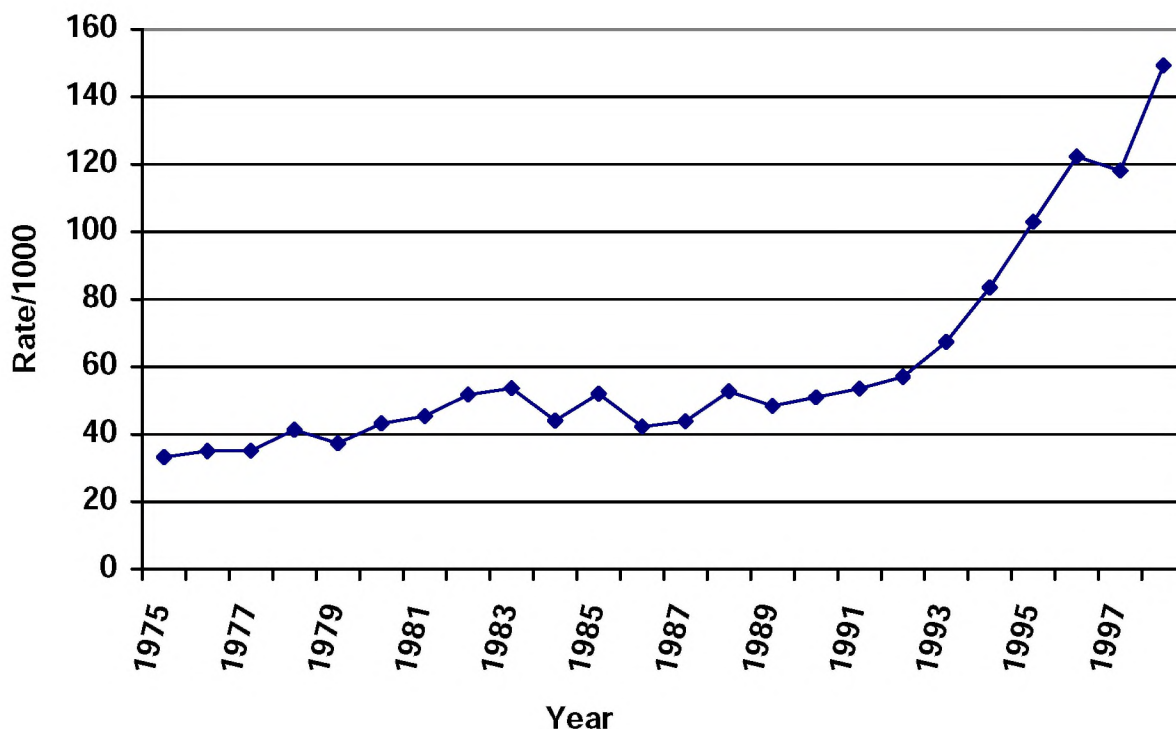
The factors responsible for progression from TB infection to disease are not all known but include conditions which impair immunity such as co-existent HIV infection, alcoholism and silica dust exposure (Murray, 1996). The control of these disorders is outside the scope of this study, but clearly a reduction in them would impact on the incidence of TB.

4.3 The burden of TB due to HIV

There is a 10% life time incidence of developing TB disease in an HIV negative person who is infected with TB bacilli versus a 50% life time incidence of TB disease in an HIV infected person (Narain, 1992). Not only does HIV infection increase susceptibility to TB infection but it also results in reactivation of TB and rapid progression of infection to active TB disease. (Chaisson, 1987; Daley, 1992; Small, 1993).

The profound impact which HIV has had on TB in Africa (De Cock, 1992; Nunn, 1994), has not spared the mining industry. In this study, 76% of cases were known to be HIV infected. As the rate of HIV infection increased during the 1990's, so did deaths in miners from TB and this is reflected in the autopsies performed at NCOH:

FIGURE 8 RATES OF PTB AT AUTOPSY 1975 – 1998 (NCOH PATHOLOGY DATABASE)



4.4 Case finding

4.4.1 Surveillance programs

The routine medical surveillance of miners includes annual medical examinations and chest radiography for the early detection of PTB. However in this study, autopsies showed lungs with advanced disease even though surveillance radiographs taken only months prior to death were normal. This demonstrates that TB in HIV infected persons may have a rapid course whether from new infection, re-infection or reactivation. In this study, 64% of the patients who were correctly clinically diagnosed with PTB presented with extensive disease and had a rapidly terminal course, dying within 10 days of hospital admission. Many of the clinicians who participated in the study believe that an annual surveillance examination is no longer sufficient. Two SIMRAC projects (GEN 524 and HEALTH 705) are currently investigating various other methods of screening for improved early detection of PTB.

4.4.2 Passive case finding

The role of the primary health nurse is considered to be of great importance in all TB programs (South African Tuberculosis Control Program, 2000). The nurse is usually the first health care worker whom the patient contacts and thus clinical acumen, awareness and interest of nursing staff can contribute to early diagnosis. This study noted instances where patients were being seen regularly at the clinics by nurses (e.g. for dressing of wounds) and who were then admitted to hospital and died within days with advanced PTB. Doctors in wards may not always consider TB in their differential diagnosis. Initiatives such as recording of weight and involvement of mine workers' unions have been successful at one centre. Most nurses whom the study team encountered during the course of this study were unaware of research projects undertaken by SIMRAC.

4.4.3 Frequency or missed TB and diagnostic delay

64% of miners with clinically undiagnosed PTB and 39% of those in whom TB was diagnosed shortly before death had attended the mine health care facilities on at least one occasion within 3 months of death. These figures exclude a primary clinic visit that resulted in a hospital admission, as well as the terminal hospital admission.

At a majority of these prior attendances, respiratory symptoms and signs were present. Health service delay in diagnosis occurred at both clinics and in hospital. Missed 'windows of opportunity' to have made a timely diagnosis have been described in many other settings (Marrero, 2000; Salaniponi, 2000; Taylor, 2000).

The study data did not enable ascertainment of patient delay i.e. time elapsed from the onset of symptoms to medical consultation, but several studies have shown that health system delays may be longer than patient delays (Stean, 1998; Lawn, 1997; Lawn, 1998; Aoki, 1985).

4.4.4 The importance of undiagnosed PTB and diagnostic delay

For the individual patient, delayed or missed diagnosis of PTB may result in disability or death. Unrecognized TB may be even more dangerous in HIV infected people because untreated TB may increase viral replication (Nakata, 1997) and accelerate the progression of HIV/AIDS (Whalen, 1995; Perneger, 1995).

Undiagnosed and untreated PTB also poses a substantial threat to public health resulting in transmission to health care workers, family, friends and co-workers.

Nosocomial transmission is important especially, but not only, with regard to HIV infected contacts. In this study, patients with clinically undiagnosed TB spent a total of 907 days in hospital before dying, and even patients who were diagnosed with TB during their terminal admission had spent a total of 361 days in hospital before TB treatment was started. This suggests a substantial risk to health care workers and other patients. A study from Malawi showed a higher incidence of TB in nurses in medical and TB wards as opposed to other hospital departments (Harries, 1997). Nosocomial outbreaks of TB have been well described in the USA (MMWR, 1991). A recent outbreak of MDR-TB in a South African hospital resulted in the deaths of 6 HIV infected women, with a mean survival of 43 days (Sacks, 1999).

In a survey in Baltimore in the early 1960s, 44 per cent of cases of TB first recognised at death were considered to have been communicable (Simpson, 1965). More recently, it has been estimated that an untreated patient with sputum smear-positive TB may infect between 10 and 14 people every year (Murray, 1990). Where diagnosis is delayed or missed, the pulmonary disease may progress to become smear positive. In addition, patients with smear-negative but culture positive PTB are also responsible for transmission: they accounted for 17% of all TB transmission in San Francisco (Behr, 1999). The situation may be even worse in the mining industry, given the high background of HIV infection as HIV infection increases susceptibility to TB infection.

A molecular epidemiology study of PTB in South African miners showed that despite a high cure rate, ongoing transmission of TB (rather than reactivation of latent infection) accounted for at least 50% of the TB cases – higher than in any other study (Godfrey-Faussett, 2000). It was suggested that improved active case finding and shortening delays in the diagnostic process were among the measures needed to interrupt transmission of TB.

Thus patients with undiagnosed PTB or in whom the diagnosis is delayed, represent a major public health problem and may be one of the reasons why the TB rate continues to escalate on the mines. A recent study from Cuba illustrates how an intervention which reduced delay in diagnosis attributable to the health care system from 56.9 days to 14.2 days contributed to a reduction in the incidence of TB (Marrero, 2000).

4.5 Management of patients with suspected PTB

4.5.1 Diagnostic tests

In this study, reasons for failing to make the diagnosis of PTB in hospitalised patients with respiratory signs and symptoms included omission of laboratory tests such as sputum smears and culture, as well as mistaking radiographic or clinical signs and symptoms of PTB for those of pneumonia and other conditions.

Similar reasons for failing to diagnose TB accurately and timeously have been described in other settings for patients with and without HIV infection, and management errors have been noted in around half of the patients (Bobrowitz, 1982; Katz, 1985; Flora, 1990; Kramer, 1990).

In the subjects of this study, two other factors contributed to the difficulty in clinical diagnosis: the high frequency of miliary PTB and the simultaneous presence of an additional lung disease. At autopsy, both miliary TB and the simultaneous presence of another additional lung disease were significantly more frequent in patients in whom clinicians failed to diagnose TB antemortem, than they were in patients in whom TB was correctly diagnosed.

4.5.2 Sputum smear for TB bacilli

Sputum smear examination for TB bacilli is a cornerstone of TB diagnosis: it is rapid, simple and cheap and detects those patients who are most infectious. South African gold miners are at risk for disease due to non-tuberculous Mycobacteria, *M. kansasii* in particular (Cowie, 1990; Corbett, 1999). Nevertheless, a prospective study of miners showed that the predictive value of a positive smear being *Mycobacterium tuberculosis* and not a non-tuberculous mycobacterium, was 91% (Sonnenberg, submitted).

4.5.2.1 Sputum smear negativity in HIV infected PTB patients

In our study, even patients with extensive PTB at autopsy had been sputum smear negative. HIV infection is associated with an increased prevalence of smear negative PTB and up to 60% of HIV infected patients may be smear negative (Klein, 1989 ; Elliott, 1993). In a South African study, 23% of HIV infected patients were unable to produce any sputum and the overall yield of sputum smears was 43% (Hudson, 2000). The rate of sputum smear negativity is related to the degree of immunosuppression as shown in Table 15.

**TABLE 15 CLINICAL FEATURES OF 182 HIV INFECTED PATIENTS
ACCORDING TO CD4+ COUNT**

CHARACTERISTIC		CD4 categories			P VALUE
		>500 (n=27)	200-500 (n=66)	<200 (n=89)	
POSITIVE SPUTUM SMEAR	n (%)	24 (88.9)	43 (65.2)	59 (66.3)	0.079
CHEST RADIOGRAPH Atypical	n (%)	9 (33.3)	9 (14.1)	50 (56.2)	0.001
CHEST RADIOGRAPH Cavitation	n (%)	14 (51.9)	30 (46.9)	17 (19.1)	0.001
CHEST RADIOGRAPH					
No/Minimal change	n (%)	5 (18.5)	15 (23.4)	32 (36.0)	0.015
Moderate change	n (%)	13 (48.1)	29 (45.3)	40 (44.9)	
Extensive change	n (%)	9 (33.3)	20 (31.3)	17 (19.1)	
DRUG RESISTANCE					
None	n (%)	23 (88.5)	59 (90.8)	74 (85.1)	0.150
SDR	n (%)	3 (11.5)	6 (9.2)	19 (10.7)	
MDR	n (%)	0 (0)	0 (0)	3 (1.7)	

From Murray, 2000a

4.5.2.2 False negative sputum smears

Our study found that negative sputum smears were associated with diagnostic delays, even in those patients who were correctly clinically diagnosed as having PTB during their terminal hospital admission (1.7 days to make the diagnosis in smear positive patients vs 6.1 days in smear negative patients), a finding which has been noted elsewhere (Kramer, 1990).

Thus every effort should be made to increase the yield of sputum smear specimens. False-negative results, rather than genuinely smear negative PTB disease, may arise from a number of correctable reasons:

- inadequate numbers of specimens: three high quality sputum specimens are required to reliably detect smear positive PTB. A study from Malawi showed that examination of three sputum smear specimens detected 21% more cases than would have been detected if only one specimen had been sent to the laboratory (Harries, 1996).
- inadequate quantity (Warren, 2000) and quality of specimens: specimen quality can be improved by physiotherapy and sputum induction (Anderson, 1995).
- poor laboratory technique: in our study some of the laboratories did not participate in a quality control scheme, and the quality of the sputum specimen was not always

commented on in the laboratory report. Nearly 1/3 of sputum specimens defined as smear negative in a local laboratory in Tanzania were found to be smear positive in a reference laboratory (Chum, 1996). In the laboratory, the use of techniques such as fluorochrome-stained smears and homogenisation and concentration of sputum increases the diagnostic yield.

4.5.3 Sensitivity of sputum smear versus sputum culture for TB bacilli

The yield from sputa is increased dramatically if the sputum is submitted for culture. However, in this study clinicians sometimes omitted to send sputa for culture, even at centres which, according to their questionnaire responses, were routinely doing cultures.

This omission may in part reflect the ethos of the South African National Tuberculosis Control Program (South African Tuberculosis Control Program, 2000) which de-emphasises sputum culture as a tool for the diagnosis of TB. The consequences of omitting sputum culture examination for the management of TB were stressed at the clinico-pathological meetings held during the course of the study, and the mine medical services appear to have subsequently tightened up on their practice.

Under optimal conditions, about 10,000 TB bacilli per ml are required for detection by smear, versus around 500 viable bacilli per ml for culture. Under operative conditions smear sensitivity for TB ranges from 40 to 65%, using culture as the gold standard (Toman, 1981). Procedures need to put in place to ensure that culture result are collected and acted upon.

Thus in both HIV and non HIV patients, if the diagnosis of PTB relies on smear microscopy alone, a good number of patients will be missed, many of whom will be a source of infection in the community and in whom diagnosis will be delayed until the disease is advanced.

We acknowledge that cost of culture is a consideration. However, in the interests of public health and also because PTB is a scheduled occupational disease, these additional costs are justifiable in the mining industry. Indeed, there have been cogent arguments for the wider availability of culture for the diagnosis and management of PTB even in resource-poor countries (Heifets, 1999).

4.5.4 New diagnostic techniques

Because of the lower sensitivity of sputum smears and the delay in cultures (2-4 weeks for a result), a variety of new technologies have been developed for the more rapid and sensitive detection of PTB. The appropriate utilisation of these was a lively source of debate at the clinico-pathological meetings.

It was hoped that the polymerase chain reaction (PCR) technique, which can be performed on sputum smear specimens, would provide a more sensitive diagnosis than smears stained with conventional methods and a more rapid diagnosis of TB than sputum culture. However, it has become clear that PCR, which is an expensive test, is no more sensitive than properly performed smears stained by routine methods and there are significant rates of false-positive results (Heifets, 2000) Rapid serological tests for antigen and antibody detection are not recommended in South Africa. They have not been adequately evaluated in high prevalence

TB settings, false-negative results are common in HIV infected persons, and antibody tests cannot distinguish between active TB and mere infection (Weyer, 1999). Sputum culture examination is still considered to be the gold standard for laboratory diagnosis.

4.6. Management of smear negative PTB

Although TB may be missed: "Won't Get Fooled Again" (by Tuberculosis)" (Ashkin, 1999) and the reasons for this failure sometimes are obvious in retrospect (Tattevin, 1999), management and diagnostic problems arise in patients with negative sputum smears.

Clinical decision making is even more complicated in HIV/TB settings because of the increased incidence of smear negative PTB, atypical chest radiographs and because HIV co-infection broadens the differential diagnosis and likelihood of co-existing respiratory conditions. Numerous algorithms for diagnosing smear negative PTB, with and without resort to culture, have been developed based on clinical symptoms, response to antibiotic trials and chest radiographs (Colebunders, 2000; Hudson, 2000; Elliott, 1992; Wilkinson, 2000).

In trying to outline an approach to the problem of a patient with negative smears, the patient's clinical features should direct further investigations and action.

4.6.1 Chest radiographs

This study found at autopsy, a high frequency of miliary TB, additional diseases and atypical TB with pneumonic type consolidation in patients in whom TB had not been clinically diagnosed. Over-reliance on chest radiographic findings may not improve diagnostic accuracy

It is well known that the chest radiograph in HIV infected patients with PTB is often atypical with less apical disease and more basal infiltrates (Abouya, 1995; Pozniak, 1995; Pitchenik, 1985). Atypical radiographs occur more frequently as CD4+ counts decrease (see Table 15), and positive smears and cultures are even seen in some patients with normal chest radiographs (Murray, 1999a; Post, 1995).

All the doctors who participated in this study indicated, in response to a questionnaire, that they would like formal training in interpreting radiographs. The proposed new project to research, develop and evaluate such a training program (SIMHEALTH 803) is awaited.

4.6.2 Trial of antibiotics

Bacterial pneumonia is the main differential diagnosis in both HIV infected and non-infected patients and patients in this study frequently had a trial of antibiotics. However, antibiotics trials may be a source of multiple errors:

- PTB patients may show a partial response either because of successful treatment of a superimposed bacterial infection, or because of fluctuations in TB disease
- Non-TB patients may not respond because of a non-infective condition e.g. Kaposi's sarcoma, or because the antibiotic used is ineffective for example against *Pneumocystis carinii*, *Nocardia* or *Cryptococcus*
- Non-TB patients may respond to TB therapy because of the broad antibacterial effect of rifampicin

The adoption of a policy of following all patients with pulmonary infiltrates to radiological resolution may help. A patient whose radiograph does not resolve completely following antibiotic treatment for pneumonia, should undergo further investigation.

4.6.3 Extra-pulmonary TB

TB may not be limited to the respiratory system. A search for extra-pulmonary involvement may often confirm the diagnosis. This is particularly true of patients with concomitant HIV infection.

4.6.3.1 Pleural involvement

Rupture of a sub-pleural caseous focus into the pleural space elicits an immune response culminating in a pleural effusion. HIV co-infection doubles the probability of a patient developing a tuberculous effusion. Either biopsy or culture can confirm the diagnosis.

HIV infection and the degree of immune suppression alter the yield from pleural fluid culture. In a retrospective study, pleural fluid cultures were shown to be positive for TB in 32% of HIV negative patients, this figure increased to 72% for those HIV positive patients with low CD4 counts (Hopley, 2000a).

The system used to culture the pleural fluid may also affect the yield. In a prospective study of 35 HIV sero-positive patients with tuberculous pleural effusions, the standard laboratory method cultured TB from 40% of the patients. The BACTEC lytic Myco/F system had a significantly higher yield of 83% (Hopley, 2000b).

4.6.3.2 Pericardial effusion / constriction

Involvement of the pericardium, when it occurs, is easily demonstrated by echocardiography. Culture and biopsy are not often undertaken due to the invasive nature of the sampling techniques.

4.6.3.3 Lymph nodes

Many HIV infected PTB patients with negative smears have lymphadenopathy and, in these patients, fine-needle lymph node aspirates have a high yield for TB bacilli (Bem, 1993; Pithie, 1992). Direct staining of aspirated material is often positive for TB bacilli. A South African study found that lymph node aspiration was the most cost-effective diagnostic test in smear negative PTB (Hudson, 2000). In HIV persons with TB, lymph nodes may be diagnostic even when nodes are symmetrically enlarged, in contrast with tuberculous lymphadenitis in HIV negative patients (Bem, 1997; Hudson, 2000).

4.6.3.4 Blood and bone marrow

Both blood culture and bone marrow biopsy may be helpful. The BACTEC lytic Myco/F system was developed specifically to culture Mycobacteria from blood and has the advantage of identifying non-tuberculous mycobacteria (Pettifer C, M.Med report submitted to WITS University, 2000).

4.6.3.5 Liver

Liver biopsy will often confirm a diagnosis of TB in patients with evidence of hepatic infiltration (raised alkaline phosphatase and gamma-GT).

4.6.3.6 Central nervous system

There should be a low threshold of clinical suspicion for performing a lumbar puncture. In patients with changes in their CSF, empiric therapy should be started if TB is suspected.

4.6.3.7 Genitourinary tract

The genitourinary tract is frequently involved in patients with disseminated TB. This is true even in the absence of pyuria and urine cultures for TB may be positive in up to 77% of patients (Shafer, 1991).

4.7 Miliary TB

The presentation of miliary TB is frequently subtle and non-specific. Symptoms often reported are fever, weight loss and malaise; cough may not be present and an altered mental status is often found (Prout, 1980; Kim, 1990). Up to 30% of patients have normal chest radiographs (Al-Jahdali, 2000) and doctors may fail to consider the diagnosis. There is a high mortality, often associated with diagnostic delays. If the sputum is negative for TB, blood and urine cultures may be useful. Liver needle biopsy and lymph node aspirates are also sensitive diagnostic tests (Al-Jahdali, 2000; Maartens, 1990; Monie, 1983; Kim, 1990).

4.8 Other lung diseases in patients with TB

In this study, there was a high rate of other lung diseases occurring simultaneously with PTB at autopsy and this complicated clinical decision making. Non-specific bacterial pneumonia was most frequent, followed by Cryptococcal and *Pneumocystis carinii* pneumonias.

HIV co-infection broadens the differential diagnosis of respiratory conditions to include diseases such as pulmonary Kaposi's sarcoma, lymphoma, Nocardia (Miller, 1996). All these conditions must be added to diseases long-known to enter the differential diagnoses, such as carcinoma and silicosis.

4.9 Advanced AIDS

About 70% of people with HIV will have at least one respiratory episode in the course of their disease. If fever, weight loss and malaise are mistakenly ascribed to progressive HIV infection alone, the possibility of TB may be overlooked and not investigated.

In this study, most patients were HIV infected with advanced AIDS. Men who retire on grounds of ill-health have an exit medical examination which always includes a chest radiograph as laid down in the ODMW Act. The problem surrounding further investigation and treatment of TB in these men is clearly an important one both for the patient, his family and the community. A system to ensure continuation of care is urgently required, possibly through The Employment Bureau for Africa (TEBA). Efforts should also be made to ensure

that the lungs of deceased ex-miners are sent to the NCOH to ensure that compensation of occupational disease, if present, is paid to their families.

4.10 Management of patients while on treatment for PTB

4.10.1 Directly observed treatment strategy (DOTS)

Once diagnosed, the quality of treatment affects outcome. Compliance is a central issue to which DOTS is the recognized key. Nurses have an important role to play, not only in ensuring compliance, but also in the early recognition of clinical deterioration such as may be due to adverse drug reaction or, in HIV infected patients, the sequential development of another opportunistic disease.

4.10.2 Failure to improve and deterioration while on treatment

We found that in 29% of the study subjects, the clinicians had recorded PTB as a major factor in the cause of death but TB was not present at autopsy. These patients were all on TB treatment. 72% of them had been treated for longer than 30 days. Most of them had clinically improved and been discharged from hospital, only to deteriorate subsequently and die. They appear to have responded to treatment for TB and sequential development of other diseases accounted for many of the discrepancies between pre-mortem and post-mortem diagnoses. Those in whom the initial diagnosis of TB was not laboratory confirmed may have had TB misdiagnosed from the start (e.g. cancer was found at autopsy) or the diagnosis of TB may have been correct and they also developed a second disease.

At autopsy, non-specific pneumonia was most frequent, followed by Cryptococcal and *Pneumocystis carinii* pneumonia.

Mortality among HIV infected TB patients is rarely due to TB after the first month of treatment, when death from other infections occurs more frequently. A study of South African miners was the first to provide autopsy data to support the contention that much of the excess mortality of HIV infected patients who die while on treatment for tuberculosis is due to non-tuberculosis AIDS related conditions (De Cock, 1992; Nunn, 1992). Autopsy examination showed that early mortality (within one month of diagnosis of PTB) was due to TB while late deaths were most commonly due to other infection.

In another autopsy study of 119 deaths in HIV infected South African miners, 47 patients were on treatment for PTB at the time of death. Of the 34 patients who had been treated for more than 30 days, only 3 had extensive TB at autopsy (Murray, 1999b)

Deterioration in a patient who has received treatment for PTB for more than 30 days should thus prompt an aggressive search for reasons, including additional infections, non-compliance with treatment and drug resistance. If TB was diagnosed empirically, then it should be considered whether or not TB is the correct diagnosis.

4.11 Multi-drug Resistance

In this study, few patients were known to have died from MDR-TB. It seems unlikely that MDR was a factor in those patients who had never been previously treated for TB. Two recent studies of TB drug resistance in South African gold miners showed that the rate of primary

MDR was less than 1%, and was not associated with HIV infection (Murray, 2000a; Churchyard, 2000b).

However, the most powerful predictor of MDR organisms is a history of treatment for TB and patients who have previously undergone therapy should be presumed to harbour drug resistant organisms until proven otherwise (Iseman, 1993). Regardless of a history of previous TB, MDR also becomes a possibility in any patient who still has extensive TB disease after 30 days of treatment. In a prospective study of gold miners with PTB, acquired multidrug resistance was 18.1%: 6.5% for recurrent disease and 33.9% in treatment failure cases (Murray, 2000a).

We found that many of the study subjects who were at risk for MDR TB had not had a sputum specimen sent for drug susceptibility testing. The emergence of MDR due to doctors' errors in the treatment of PTB has been described in two recent studies from America, where up to 3.9 'management errors' per patient were documented (Mahmoudi, 1993; Rao, 2000).

4.12 Risk factors for death from PTB

4.12.1 HIV infection

This study found that most deaths occurred in patients known to be HIV infected: 76% were known to be HIV infected and, of those who had had CD4+ counts, 90% were profoundly immunocompromised (CD4+ count <200).

Although those HIV positive patients on treatment for PTB who survive respond as well to treatment as do HIV negative patients, even if they have advanced immunosuppression, HIV positive patients have a higher mortality during treatment for PTB. The high mortality rate in HIV positive patients with tuberculosis is well known (Nunn, 1992; Wilkinson, 1996; Small, 1991; Churchyard, 2000a). In a prospective study of South African miners, mortality in HIV positive patients was 26 times that in HIV non-infected patients. (13.7% vs 0.5%). The overall fatality rate was 7.4% (Murray, 1999a). Most of the excess mortality is, as has been discussed, due to non-tuberculous AIDS related conditions. However, HIV infected patients are also more likely to die of TB. Despite a similar radiological severity of disease at presentation, 5/49 HIV positive patients with extensive disease died of autopsy proven tuberculosis in the first month, compared with 0/46 in HIV negative patients (Murray, 1999a).

The last-mentioned study also showed that the degree of immunosuppression is the strongest predictor of survival in HIV infected TB patients while they are on treatment for TB. In patients with a CD4+ lymphocyte count of less than 200, the case fatality rate was 22.1%, compared to 7.7% in those with a count of between 200 and 500. There were no deaths among patients with a normal CD4+ count.

4.12.2 Silicosis

Some studies (Churchyard, 2000a; Ng, 1992) but not others (Murray, personal communication) have shown that silicosis is associated with an increased TB case fatality rate.

4.12.3 Other factors including quality of medical service

In addition to miliary TB, the severity of TB disease on chest radiographs, increasing age and MDR are well documented factors associated with death (Reider, 1999).

It has also been shown that the TB case fatality may vary depending on the expertise of the medical doctor (Borgdorff, 1998). The mine medical service in our study with the least proportion of cases of PTB which were clinically undiagnosed (23%) has several features which may have been a factor: for decades, the senior management has considered TB to be a major problem requiring adequate funding. This resulted in the appointment of a dedicated doctor experienced in both the clinical management and epidemiology of TB to head this program. Computer programs were installed, laboratories upgraded and research projects undertaken on a regular basis. A study in 1994 highlighting the problem of undiagnosed TB resulted in many improvements, including better adherence to local protocols.

Yet, even this at this medical service, the study showed that in some instances routine tasks had not been performed.

4.13 Limitations of study

We acknowledge that the clinical data in this retrospective study was not complete. However, the proportion of medical records reviewed from the selected eight medical centres (65%), is comparable to a landmark autopsy study in which 63% of clinical records were reviewed (Wilkes, 1988). The autopsy rate in miners is around 85%, which is much higher than the 50% in most of the studies showing the value of autopsy (Wilkes, 1988; Cameron, 1981a; Lucas, 1993). The inconsistency with which different clinicians may have recorded their clinical actions is unavoidable in a retrospective study such as ours.

We were unable to perform cultures at autopsy and, although the pathologic features were not those of *Mycobacterium intracellulare*, we could not definitively exclude the possibility that other mycobacteria such as *M. kansasii* may have been present. However, miners with advanced AIDS do not have an increased incidence of non-tuberculous mycobacteria when compared with miners who are not HIV infected (Sonnenberg, 2000).

5. CONCLUSION

We retrospectively reviewed the findings of miners who clinically were assessed as having PTB as a major factor in the cause of death and/or in whom PTB was present at autopsy. Most patients' were HIV infected. We showed that PTB was accurately ascribed as the cause of death by clinicians in only 27% of cases. The absence of a diagnosis of TB during life could be attributed to a high proportion of miliary TB, the simultaneous presence of other lung diseases and the omission of accurate laboratory tests. In many of the patients in whom PTB was correctly clinically ascribed as a cause of death, previous windows of opportunity to have made an earlier diagnosis were missed. Some of the patients who died while on TB treatment appeared to have recovered from TB and subsequently developed another disease. Autopsies continue to provide important information for the management of patients despite advances in medical knowledge and technology.

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7. TECHNOLOGY TRANSFER

“Keep doing what you’ve always done and you’ll get what you always got”
Dixie Snider

7.1 Clinico-pathological conferences

Clinico-pathological conferences were held to disseminate the study findings, present illustrative cases, and discuss best practice clinical strategies. A wide range of mine health care workers attended the conferences which were held at different centres, as the study progressed. The study findings were illustrated by showing macroscopic and microscopic photographs of the lungs and comparing autopsy findings with the clinical history obtained from record review.

In the presentations, individual mines and patients were not identified. However, each participating doctor received a file containing laminated photographic illustrations of her/his cases as well as a summary of the findings of the study to date.

Seven conferences were held:

- October 1999 at Leslie Williams Hospital for the West Rand mines
- November 1999 at Duff Scott Hospital for their doctors, nurses and laboratory staff
- February 2000 at Afrox Occupational Health for their doctors and nurses
- March 2000 at St Helena Hospital for the Gold Fields, Duff Scott and Harmony Free State centres health care workers
- April 2000 at Fochville for the West Rand mines’ medical station staffs’ annual meeting.
- May 2000 at Rustenburg for the platinum mines health care workers
- May 2000 at Secunda for the coal mines health care workers.

Invited speakers:

- Dr Mark Hopley from Chris Hani - Baragwanath Hospital: an approach to the management of sputum-smear negative patients with respiratory disease.
- Dr Lucille Blumberg from the South African Institute for Medical Research: laboratory aspects of TB management.
- Dr La Grange from the Chamber of Mines: the problems of TB in the mining industry.
- Dr Mary Ross from SIMPROSS: an overview of SIMRAC research.

The meetings were attended by about 250 people. Medical doctors (these included surgeons and radiologists), laboratory staff, clerks, nurses from the primary clinics as well as hospital wards, radiographers and students attended. Positive and enthusiastic feedback was received including comments like: “It is the first time we have ever had a participatory report back from a SIMRAC project”.

7.2 Hand-out for medical staff

A hand out which will include a summary of the study findings, selected references, and illustrative cases for distribution to health care workers will be compiled. This will be submitted to SIMRAC. It is anticipated that this will provide data to assist clinicians with the process of performance review of individual cases in the future.

7.3 Chamber of Mines

The findings have been reported to the TB Committee tasked with development of a new policy document for the industry.

7.4 Performance review on individual cases

The process of feedback on individual cases which was initiated during the study will become part of the routine autopsy service. With few exceptions, doctors indicated that they found this useful and have used the opportunity to initiate the process of performance review.

Deciding when current diagnostic and management strategies are no longer good enough and need to be changed is a key issue. Self-assessment of one's own performance has been shown to be one of the most effective and efficient ways of achieving this (Sackett, 1991). A crucial step in initiating performance review is feedback to clinicians on what they are actually doing, compared with a confirmatory gold standard. Autopsy findings are such a 'gold standard'.

Performance review is time consuming, and the process should concentrate on crucial items in the history, physical examination and tests ordered which are key determinants of outcome. In setting up performance review one will also have to begin by improving the documentation in clinical records and consider the introduction of standard protocols. The findings of this study suggest that elements the review should cover include previous visits to the medical facilities, radiographs, with particular emphasis on miliary TB, and sputum for TB culture. This will form part of the hand out (see above). It is also important to be aware that 'bad' outcomes may be the result of factors beyond the clinician's control (such as financial constraints) so that spurious conclusions about clinical performance are not drawn.

Performance review is a lot of work – there is evidence it does actually improve subsequent performance (Sackett, 1991) – but, for the process to be successful, it requires time and it is too early to determine the success of this SIMRAC project with regard to TB management in the mining industry.

8. EVALUATION OF THE STUDY

To evaluate the study, a questionnaire (Appendix 2) together with a personal letter (Appendix 3) was sent to selected mine health care workers. The selection of respondents was based on attendance at the clinico-pathological conferences, personal involvement in TB programs, and mine commodity. Fifteen questionnaires were sent and 12 replies were received from gold, platinum and coal mining groups. Most knew of health related SIMRAC projects and would like to receive these reports. All felt that this study was interesting and useful and would participate in future research projects initiated by SIMRAC.

8.1 Surveillance

Several medical officers thought that the frequency of radiographic surveillance should be increased, particularly in the high risk groups of HIV infected persons and those with previous TB. Low dose digital radiographs were mentioned. All believed that nurses involved in primary health care should play an active role in the early detection of TB and should be encouraged to obtain sputa for TB bacilli examination. However, there was no consensus whether nurses should order chest radiographs or sent sputa for TB cultures. All but one thought that a formal training program for nurses should be introduced.

8.2 Diagnosis

All mines have a formal TB control program based on the national guidelines, and one mentioned that the proposed Chamber of Mines guidelines would be adopted.

The need for formal training in the interpretation of chest radiographs was felt and copies of the ILO radiographs on occupational chest disease were requested by most respondents. SIMHEALTH has responded by commissioning a project to research, develop and evaluate a training package for chest radiograph interpretation.

The poor sensitivity of sputum smears for TB was recognised and most centres stated that cultures were routinely performed for all patients admitted for TB investigation. Financial constraints and laboratory overload were the reasons why others do cultures only on selected patients.

Patients retired on grounds of ill-health were all required to undergo chest radiographs and to have a clinical examination. Difficulties were encountered in doing further investigations as most patients wanted to leave the mine as soon as possible. Treatment for suspected TB was often started prior to discharge.

8.3 Treatment

Patients who failed to improve on TB treatment were all reinvestigated and cultures routinely performed. All believed that MDR cases should be treated at a dedicated centre.

8.4 Autopsy

All but one would like to receive autopsy reports on their cases together with regular summaries of industry data.

9. RECOMMENDATIONS

9.1 Introduction

The optimum management of TB on the mines requires measures that are additional to the national guidelines. The following recommendations are intended to supplement, not replace, the national guidelines. While some of the recommendations have financial implications, these additional costs are justifiable in the mining industry in the interests of public health and also because PTB is a scheduled occupational disease. The Chamber of Mines initiative to recommend practice standards for the management of PTB on mines, which incorporates many findings of this study, is strongly supported.

9.2 Active & passive case finding

Cases with advanced TB had surveillance chest radiographs interpreted as normal performed during the year preceding death. Groups at high risk for TB, such as those with previous TB, HIV infection and high silica dust exposure should be identified and examined at more frequent intervals. The results from two current SIMRAC projects which are evaluating methods to improve surveillance for TB are awaited.

Many patients with either undiagnosed TB or delayed diagnosis of TB had recently attended mine primary clinics and hospitals. The role of nurses in the primary health care setting should be strengthened and in many centres nurses should be enabled to request investigations for TB, including sputum smear examinations. Formal training programs in TB control are recommended for nurses.

For patients admitted to hospital with respiratory signs and symptoms, TB should be actively excluded (see below) in all, even if they show some response to treatment for bacterial pneumonia.

9.3 Sputum smear examination for TB bacilli

The poor sensitivity of sputum smear examination for TB bacilli is well known and even multiple tests will only result in positive results in around 60% of cases. Laboratories should be formally accredited, report on sputum quality and volume, and have a quality control program in place.

9.4 Sputum cultures for TB bacilli

Sputum cultures for TB are the gold standard for the laboratory diagnosis of TB and should be routinely performed on all cases admitted for investigation of respiratory disease.

9.5 Additional diagnostic tests

Expensive tests for the diagnosis of TB such as PCR are not recommended.

Other tests such as fine needle aspiration of lymph nodes and culture of pleural fluid and blood in Bactec (Myco-F) media are recommended in sputum-smear negative patients suspect for TB.

9.6 Chest radiographs

Chest radiographs should be routinely performed on all patients admitted to hospital, especially to the medical wards. Difficulties in interpretation of x-rays were common, and a training course on the interpretation of chest radiographs which was requested by many medical officers is recommended.

9.7 Miliary TB

Many cases died from miliary TB and most were undiagnosed in life. Chest radiographs read as 'clear' should be carefully scrutinised. The difficulties in making this diagnosis are acknowledged. Specimens from extra-pulmonary organs such as lymph nodes are often helpful in making the diagnosis of TB. Empirical treatment (whilst awaiting culture results) is advised when the diagnosis is suspected.

9.8 Drug Resistance

The prevalence of drug resistance is unknown in several centres, and failures on prolonged treatment for TB suggest that this may be a problem. All re-treatment cases and treatment failures must have drug susceptibility tests performed, as in the national guidelines. Regional specialized centres should be established (for industry cases) for those cases with multi-drug resistant TB.

9.9 Management while on TB treatment

Patients who have been on TB treatment for longer than 30 days, and in whom drug resistance has been excluded, seldom die of TB. Many treatable conditions such as bacterial and *Pneumocystis carinii* pneumonia contributed to the mortality in this study.

The DOTS program provides the treatment supervisor an ideal opportunity to monitor the general well-being of the patient, and guidelines on when to re-investigate patients who deteriorate while on treatment for TB should be made. In addition to the presence of TB bacilli in sputum smears, patients with clinical features such as failure to gain weight and pyrexia should be actively investigated to exclude drug resistance as well as the development of other diseases.

9.10 Advanced AIDS and medical incapacity

Patients who leave mine employment due to ill-health should be actively investigated for TB before termination. Cases of advanced AIDS require special attention as they are particularly susceptible to TB. Ideally, the intensive phase of treatment for TB should be given on the mine before discharge. A system to ensure continuation of care should be established, perhaps through the TEBA regional offices.

9.11 Recurrent TB

Cure following treatment of the first episode of TB should be established by sputum culture as several cases of 'recurrent' TB were identified within months of treatment completion.

9.12 Performance review

The unique South African law (ODMWA) allows clinicians access to autopsy results on all their cases and a mechanism is now in place to ensure this will occur, if requested by the doctor. Only clinicians can institute change in their programs but performance review using autopsies as the gold standard will enable them to measure both positive and negative outcomes in their institution and to measure their performance against industry norms. This study has established a baseline against which performance improvement can be evaluated.

HOSPITAL ADMISSION	
MEDICAL STATION	
TB DATA	
LABORATORY DATA	
XRAY: MX	
LP	

P NO _____

STUDY NO _____

BUREAU NO _____

1. DEMOGRAPHIC DATA

SURNAME _____

FIRST NAMES _____

COMPANY NO _____

INDUSTRY NO _____

ID NO _____

MINE _____

HOSPITAL _____

HOSP NO _____

AGE _____

YEARS SERVICE _____

DEATH DATE

--	--	--	--	--	--	--	--

DEATH PLACE

in hospital	casualty	bid	other
-------------	----------	-----	-------

2. PATHAUT DATA

CATEGORY:

CI+Path+	CI-Path+	CI+Path-
----------	----------	----------

Clinical Data:

Cause Of Death: _____

Clin Other _____

Pathology Data:

TB:

Yes	No
-----	----

 Severity:

Focal	Moderate	Marked
-------	----------	--------

AFB:

Pos	Neg
-----	-----

Path Other _____

X-rays Submitted With Organs

Yes	No
-----	----

3 HOSPITAL RECORDS

ADMITTED

Yes

No

HOSPITAL

WARD

TB

Medical

Surg

Trauma

ADMISSION DATE

DEATH DATE

DURATION OF HOSP STAY

CLIN CAUSE OF DEATH:

CHEST DISEASE

Main finding

☐

Secondary finding

☐

Absent

☐

Mild

☐

Moderate

☐

Marked

☐

Admission Xray:

Yes

No

Xray Reading

Yes

No

Chest Diagnosis:

Chest Lab Investigations

TB: Smear:

Yes	No
-----	----

 No. Of times _____ Results:

Pos	Neg	N.A.
-----	-----	------

Culture:

Yes	No
-----	----

 No. Of times _____ Results:

Pos	Neg	N.A.
-----	-----	------

Drug Resistance:

Yes	No
-----	----

Sensitive	MDR
-----------	-----

Other chest lab investigations: _____

Treatment in hospital

TB Continues with previous treatment ☐ Starts in hospital ☐

Date TB rx started

--	--	--	--	--	--	--	--

No of days rx _____

< 30 days	> 30 days
-----------	-----------

Other chest related rx _____

OTHER IMPORTANT CLINICAL FINDINGS

HIV

Pos	Neg	Unk
-----	-----	-----

Date

--	--	--	--	--	--	--	--

CD4 count

Date

--	--	--	--	--	--	--	--

4. TB HISTORY

Previous TB

Yes	No
-----	----

Date rx stopped

--	--	--	--	--	--	--	--

If on Treatment on Admission:

How was TB diagnosed:

Empiric	Smear	Culture
---------	-------	---------

Drug Resistance:

Not done	Done
----------	------

Sensitive	MDR
-----------	-----

5. SURVEILLANCE MX

Date

--	--	--	--	--	--	--	--

< 1 year of death ☐ > 1 year death ☐

Reading _____

6. MEDICAL STATION VISITS IN YEAR PRECEDING DEATH

Dates:	Reason
1. _____	_____
2. _____	_____
3. _____	_____
4. _____	_____
5. _____	_____
6. _____	_____
7. _____	_____
8. _____	_____
9. _____	_____
10. _____	_____
11. _____	_____
12. _____	_____

no of visits _____ No chest related visits _____

Tb investigated

No	Yes
----	-----

 If yes: Date

--	--	--	--	--	--	--	--

smear results _____
cultures results _____

7. CASE SUMMARY 1

TB RX duration _____

TB

Extensive

Focal

CATEGORY 1 CLIN+PATH+: rx < 30 days: extensive ie late presentation
rx> 30 days : drug resist / poor compliance

CATEGORY 2 CLIN- PATH +: Rx usually < 30 days / fulminant course: Sputum sent for TB yes / no Sputum not sent died too soon / comatose // x-rays: Not done / not read as TB TB not considered

CATEGORY 3 CL+ PM-: >30 DAYS: TB confirmed microbiologically (smear/culture) & patient recovered // TB not confirmed (query wrong clinical diagnosis)
<30 DAYS: Incorrect clinical diagnosis:

-
-
-
-
-
-
1. Failure to present early e.g. Coughing is not considered to be a disease symptom
 2. Primary health care workers do not investigate patients with early symptoms
 3. Surveillance program failed MMX's not taken / Not read correctly/ Not acted on
 4. Admitted to hospital with extensive, fulminant disease and dies even though on TB treatment
 5. Admitted to hospital with extensive, fulminant disease and dies before can be adequately investigated (Inadequate diagnostic procedures)
 6. Clinical error in judgement e.g. Acute infections such as pneumonia or meningitis dominate the clinical features also e.g. Inadequate diagnostic procedures e.g. non-TB disease dominates e.g. diabetes, cardiac failure
 7. MDR organisms; not detected as no culture and sensitivity tests are performed
 8. Autopsy lesions focal and diagnostic procedure may have failed to detect them
 9. Subclinical course of disease with few clinical symptoms

APPENDIX 2 EVALUATION QUESTIONNAIRE

Monday, November 06, 2000 14h30

Date:

Mine/hospital:

STATUS OF RESPONDENT/S

- * Are you involved in the design, implementation and/or evaluation of the TB program in your hospital.
- * Did you attend a clinico-pathological seminar on the correlation between ante and post mortem diagnosis of TB
- * Did you read the hand-out
- * Please supply your position in the hospital

EARLY RECOGNITION OF DISEASE

Surveillance

- * Most surveillance x-rays were normal – even in patients with advanced disease on presentation- would you alter your surveillance programme in any way

Medical Station

Prior to hospital admission many patients had visited mine clinics on several occasions where they were seen by nurses for example for diabetes management, surgical dressings.

- * Is there a role for primary health care nurses in the early detection of TB

What decision making is the nurse currently allowed, and would you like her to be able to do the following on men she suspect of having PTB:

- * Bring to attention of doctor
- * Send for sputum smear / culture
- * Order chest x-ray
- * Education of the health care worker in TB – is there any formal programme / do you think such a programme would be useful

DIAGNOSIS

Protocol

Most centres we visited did not have a TB protocol, particularly so for the investigation of suspected cases.

- * Do you have a formal written protocol / informal protocol / follow National guidelines

Radiology

- * Most but not all centres had as standard practice to take a chest x-ray on admission to medical wards – what is / was your practice (eg also before general anaesthetic)
- * Many x-rays were incorrectly interpreted as being normal eg with miliary TB at autopsy. Do the medical officers have any formal training in x-ray reading? Do you have access to a radiologist?
- * Previous x-rays for comparison: are they readily available? Are they routinely examined
- * At one centre the ILO x-rays were prominently and permanently displayed.
Would this assist you and other responsible for reading and interpreting x-rays?
Do you have the ILO x-rays – do you use them – would it be helpful to have them
- * Would you like x-ray training – in what form

Sputum

Many centres relied on sputum smear for the diagnosis of TB and did not do cultures:

- * Did the finding that sputa smear tests alone are such poor tests/lack sensitivity for the diagnosis of TB surprise you
- * Has your laboratory been instructed to report on the quality of the sputum specimen (5mls early morning significantly increases the yield)

- * If you did not routinely do cultures previously for diagnosis of TB are you now doing cultures (if not why not eg costs)
- * Will you continue to put sputum smear negative patients onto treatment without sending a culture.
- * Do you regularly follow the SANTBP guidelines for sputum culture ie cases with recurrent TB and treatment failure
- * Will you continue to use other more expensive diagnostic tests such as PCR / TB antibodies
- * If patients are put onto treatment for empiric TB – are any special steps taken – do you keep them under the personal care of the medical officer, are they managed in the general TB programme
- * Many patients in the study had been previously admitted with pneumonia – if the x-ray does not resolve (by 6 weeks) what steps do you take
- * Will the finding that the TB yield of pleural fluid, gland aspirate and blood be significantly improved when material is directly inoculated into bactec/myco-f bottles at the bedside change your practice
- * Many patients with pulmonary disease admitted to hospital for other reasons were not investigated – how can this be rectified

ADVANCED AIDS

- * Many patients with advanced aids had undiagnosed TB (and are a danger to others) – should a programme be instituted to ensure that TB is investigated in these patients prior to medical discharge: actively exclude TB on smear / culture; is the exit sufficient and do you have time to read it

ON TREATMENT

The study found that many patients who had been on treatment for >30 days had undiagnosed / uninvestigated bacterial pneumonia and / or PCP.

- * How will this assist you in managing TB cases who deteriorate while on treatment for TB.
- * What observations should the nurse administering Dots make and when should the patient be referred to the doctor for investigation e.g. loss of weight, pyrexia, haemoptysis ?
- * An isolated case of non-compliance while on Dots was noted: how can Dots be improved and do you think that compliance testing should be part of your programme? If so urine colour only / drug tests.

MULTI-DRUG RESISTANCE

- * Many cases that died of TB having been treated for longer than 30 days had MDR – in the others drug testing had not been done – will this encourage you to perform cultures more frequently: as per national guidelines; on all patients, recurrences only, treatment failures.
- * Should MDR TB be treated at a dedicated centre

BARRIERS TO IMPROVED CLINICAL PRACTICE IN MANAGING TB

What barriers exist in your practice which detract from performance

- * Financial : laboratory costs / staff (e.g. 1 day in hospital vs cost of culture)
- * Motivation: fatigue and burnout
- * Knowledge: NB access to 'experts' e.g. laboratory person such as Lucille Blumberg, Prof. Solomon for x-rays
- * Experience: high staff turnover (doctors and other health care workers)

AUTOPSIES

- * The study found that around 50% of cases of TB were undiagnosed – did this surprise you, did you think that this applied to your centre
- * Did the autopsy details of miners' influence you in reassessing your TB programme and assist in performance review?
- * What use did you make of the photo hand outs – e.g. general education / bed letter review

Would you like to:

- * be supplied with autopsy reports concerning all TB cases – with/without photos
- * receive autopsy results on interesting or unusual cases only
- * receive autopsy data on a named patient basis, requested by you

What use will you make of this – be specific

- * receive regular summaries of industry data e.g. autopsy prevalence of TB, concordance between clinical and pathologic diagnosis

How can we improve the number of autopsies on * miners in service
* ex-miners

COMMENTS ON STUDY / SIMRAC

- * How can we disseminate the findings of the study to doctors who mainly treat white miners and ex-miners and mine doctors in isolated regions?
- * Would you agree to participate in future SIMRAC projects
- * What comments, criticisms or suggestions/ recommendations (where to from here) would you like us to report on in the final SIMRAC report
- * Are you aware of other SIMHEALTH projects – name them
- * Get some feedback on Lucille / Mark
- * Has the study motivated you to improve the management of TB:
- * Did you fine the study:
 - * Not interesting and not useful
 - * Interesting but of little practical use
 - * Interesting and useful

APPENDIX 3 – LETTER SENT TO DOCTORS FOR AUTOPSY REPORTS

NATIONAL CENTRE FOR OCCUPATIONAL HEALTH

Tel: 011 720 5734 Fax: 011 720 6103 Email: murraj@health.gov.za

Date:

To: Dr
Title
Hospital
Tel
Fax
Email

CONFIDENTIAL

You may be interested in the findings of the autopsy on the below mentioned deceased worker.

Name:

Mine:

Co No:

MBOD No:

Date of death:

Industry No:

Pathology No:

Organs received:

Clinical history received:

The autopsy of the cardio-respiratory organs showed:

If you would like further details please contact me. Please remember that the findings in no way mean that compensation is guaranteed

Yours sincerely

Dr J Murray
Senior Pathologist
signed on computer