

# **Safety in Mines Research Advisory Committee**

## **Final Report**

### **Provisional assessment of the impact of adding sputum screening to existing active case finding methods for tuberculosis in a gold mining workforce**

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## Executive summary

Tuberculosis (TB) rates amongst gold miners in South Africa continue to rise despite well implemented TB control programmes. The human immunodeficiency virus (HIV) prevalence amongst miners is high and is partly the cause for the increasing TB incidence. Case finding with annual radiographs is done routinely but the yield from radiological screening has remained constant since the advent of the HIV epidemic. A cross-sectional study was conducted amongst gold miners in the Free State. The main aims of the study were to identify appropriate screening methods in active case detection of TB, to determine the point prevalence of active TB and to identify risk factors for TB prevalence and incidence. Additional objectives were to investigate incidence of TB following intensive screening and to determine the optimum interval between screening.

Approximately 2000 gold miners were enrolled while attending for annual fitness examinations. On recruitment, a questionnaire was administered which included TB symptomatology and demographic details. In addition, two sputum specimens were collected for TB microscopy and culture, a urine specimen was collected for HIV testing, and a miniature chest radiograph was taken. Sputum smears were examined for acid-fast bacilli using microscopy with fluorochrome staining, and then cultured on Löwenstein-Jensen (LJ) medium. Urine samples were tested for HIV using a screening test and a confirmatory test. Individuals with any abnormal findings were investigated further with clinical examination, standard size chestradiograph and three more sputum specimens. Study participants were followed for a year following their date of the annual examinations (date of enrollment) for episodes of pulmonary and extrapulmonary TB. The annual TB incidence for the cohort was calculated for the year preceeding enrollment. Duration of active disease was calculated from incidence and prevalence estimates.

The refusal to participate proportion was 12%. 1978 individuals participated in the study, 580 (29%) of whom were HIV-infected. 48 cases of active TB were diagnosed using clinical features, radiography and culture. Investigation of the screening methods confirmed that the use of a single screening method for the detection of TB is insufficient. Of the four screening methods evaluated, sputum culture was the most sensitive (70%)<sup>1</sup>. The radiological screening programme (RSP), the current standard of active case detection, had a sensitivity of 27%. The proportion of TB cases detected with sputum microscopy (25%) compared with RSP was similar. The addition of sputum microscopy to the existing case finding programme would only have identified a further 7 (15%) cases of active TB. Symptom screening (sensitivity 29%) for TB appeared to give a slightly higher yield than sputum microscopy. The three most significant symptoms were cough, weight loss and night sweats. It was also found that the combination of RSP and symptoms would detect 60% of all smear positive cases.

The prevalence of active TB was 2.5% (95%CI 1.8–3.2%). The only significant risk factor for prevalent TB was age>40y (Unadjusted Odds Ratio (OR) 2.2, 95%CI 1.2–4.3). Prevalence of TB did not vary significantly by HIV status (3.3% vs 2.2% in HIV-infected and -uninfected, Unadjusted OR 1.5, 95%CI 0.9-2.8), or silicosis grade. TB incidence was 2.4/100py(person-years) (95%CI 1.8–3.2); higher for HIV-positive than HIV-negative miners (5.4 and 1.2/100py respectively, crude incidence rate ratio (IRR) 4.4, CI 2.4-7.9). Other significant risk factors for incident TB were silicosis (p<0.001) and age>40y (IRR 2.1, CI 1.1–4.0). The estimated duration of active disease was 0.61 years in HIV-infected individuals and 1.79 years in HIV-uninfected individuals. HIV infection and silicosis are strong risk factors for incident but not prevalent (active) TB, reflecting more rapid progression of TB in the HIV-infected host with major implications for case-finding and TB transmission.

The incidence of self-presentation with TB in the cohort was 2.4/100 person-years, higher in HIV-infected individuals (IRR 5.1, 95%CI 2.5 – 10.6). Other risk factors were silicosis and age. Self-presentation

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<sup>1</sup> Sputum culture was not used as the “gold” standard and hence was not 100% sensitive.

with TB was insignificantly higher in the second six months after screening in both HIV groups. The optimal frequency can't be determined from this study.

We recommend that all persons with either: a new abnormality on the chest radiograph; or any of the three symptoms of cough, night sweats and fever; are identified for further investigation for TB. Further investigations should include at least two sputum specimens for microscopy and culture. HIV-negative individuals are likely to be important sources of TB transmission despite low incidence, because of their long duration of infectivity. TB control strategies in high HIV prevalence areas should not underestimate the importance of HIV-negative TB. As HIV disease and silicosis were shown to be important risk factors for TB incidence, efforts at improving HIV and dust control remain important strategies in the reduction of TB. We recommend that further investigations are conducted to establish the efficacy of intensive screening on a six-monthly basis.

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## Glossary

**Acid-fast bacilli:** Mycobacteria appear as acid-fast (bright red), slender, slightly curved and beaded or pleomorphic rods.

**Active case detection:** Detection of disease, which is usually asymptomatic, during a screening procedure.

**Active TB:** Infection with *Mycobacterium tuberculosis* which has resulted in disease

**Fluorochrome:** The use of auramine-rhodamine fluorescent dyes to examine a slide under low-power microscopy. It requires a fluorescence microscope. It is more sensitive than acid-fast staining, largely owing to the greater ease of specimen examination.

**Incidence:** The number of new events, such as new cases of a disease, in a defined population within a specified period of time.

$$\text{Incidence Rate} = \frac{\text{Number of new cases}}{\text{Total person-time at risk}}$$

**Intensive screening:** Screening for tuberculosis using symptom review, sputum examination and radiological examination

**Kirchner medium:** liquid culture medium for growth of mycobacterium, more sensitive than Löwenstein-Jensen medium

**Löwenstein-Jensen medium:** conventional solid culture medium for growth of mycobacteria

**Negative Predictive Value:** the proportion of individuals with a negative test result who do not have the disease. Negative predictive values are inversely related to the prevalence of the disease in the population. In other words, the negative predictive value of a test decreases as the prevalence of disease in the population increases.

**Passive case detection:** Detection of disease when a person presents with symptoms

**Polymerase Chain Reaction (PCR):** A gene amplification method which identifies mycobacterial DNA.

**Positive Predictive Value:** the proportion of individuals with a positive result who actually have the disease. Positive predictive values are directly related to the prevalence of the disease. In other words, the positive predictive value of a test increases as the prevalence of disease in the population increases.

**Point Prevalence:** The number of events, such as instances of a disease, in a defined population at a designated point in time.

$$\text{Prevalence} = \frac{\text{Number of Cases}}{\text{Study Population}}$$

**Radiological Screening Programme (RSP):** All employees have an annual fitness examination which includes a miniature chest radiograph to screen for active TB.

**Sensitivity:** (of a screening test): indicated by the proportion of truly diseased persons in the screened population who are identified as diseased by the screening test. It is a measure of the probability of correctly diagnosing a case (Synonym: true positive rate)

**Self-presentation:** presenting to the health service with symptoms [and signs] of illness

**Specificity:** indicated by the proportion of truly non-diseased persons who are so identified by a screening test. It is a measure of the probability of correctly identifying a non-diseased person with a screening test (Synonym: true negative rate).

**Validity:** means the extent to which a test measures the true value of the variable that we are interested in.

**Yield:** The number or proportion of cases of a condition accurately identified by a screening test

# 1 Introduction

## 1.1 Background

Tuberculosis (TB) is the most important disease among South African mine workers (1). Numerous studies have shown that human immunodeficiency virus (HIV) infection confers the greatest known risk for the development of TB, by accelerating the course of newly-acquired TB and increasing the probability of reactivation of latent infection (2,3). In view of the high prevalence of HIV infection amongst miners, the mining industry faces an unprecedented challenge to existing TB control programmes. TB control measures already in place include radiological screening, contact tracing, preventive therapy with isoniazid (INH) for those who are at highest risk of TB and directly observed therapy regimens. However, it is likely that novel control approaches will be required to contain the current TB epidemic in miners.

The case detection of smear positive pulmonary TB cases and their cure has been identified as the key to any effective TB control programme (4). Active case detection by the radiological screening programme (RSP) is associated with a significantly lower mortality compared to self-presentation (5). However, as the HIV incidence has increased, the proportion of TB cases detected by the RSP has decreased (6). One method of improving the yield from the RSP may be the introduction of sputum screening into the routine case-finding programme. Sputum screening is most sensitive if smear examination is combined with sputum culture and this approach has previously been used in national TB prevalence studies with pick-up rates of between 0.5 and 6.4% in unselected adults (7,8). However, a high proportion of the total mycobacterial isolates in these prevalence studies were non-tuberculous mycobacteria (NTM) of uncertain clinical significance with *Mycobacterium avium intercellulare* being the most common species (9). Another strategy for increasing case detection would be to include symptom screening. A recent study in Saskatchewan, Canada, showed an increase in the proportion of culture positive TB with a normal chest radiograph. They showed that most of these patients were symptomatic and would have

been identified on symptoms (10). A Kenyan study found cough and weight loss to be the most useful symptoms in active detection of TB cases (11).

Although the impact of HIV infection on TB incidence is well documented, its impact on TB prevalence, which is an important factor in TB transmission, remains unknown. HIV may accelerate the course of TB resulting in earlier presentation of persons with HIV/TB co-infection and a reduced period of active TB disease in these patients. Therefore, the TB prevalence (i.e. number of persons with active disease at a designated point in time) may be similar in HIV-infected and -uninfected persons. This may explain the stable active case detection rate even though TB incidence rates have increased (6)

We investigated the value of sputum screening in 1999 by including the collection of a single sputum specimen for TB smear and culture along side an anonymous HIV prevalence study of 851 mine workers (unpublished data). The HIV prevalence was found to be 25%. The prevalence of active TB as detected by sputum microscopy, culture and RSP was 1%, 2.6% and 1% respectively. The prevalence did not differ according to HIV status. In contrast, 0.6% of HIV negative and 3.2% of HIV positive miners reported being on TB treatment at the time of their interview, suggesting much higher TB incidence rates amongst HIV positive individuals (1.2 per 100 HIV-negative vs 6.4 per 100 HIV positive employees).

These incidence estimates concur with measured TB incidence rates in a retrospective cohort analysis of miners of known HIV status from the same workforce (12). The limitations of this study were that laboratory results did not correlate well with radiological findings, as has been found in previous comparisons of active case-finding strategies (13,14) and it was not possible to confidently distinguish individual false-positive results in the absence of reassessment and follow-up data. Moreover, it was not possible to comment on the long-term impact of this additional active case-finding measure in the absence of any data concerning the average duration of smear/culture positivity before self-presentation. The only way to assess efficacy would be to measure the rate of self-presentation with TB following intensive screening (using sputum, symptoms and RSP) and to compare this to the incidence rate following RSP alone.

## **1.2 Project outputs**

### **1.2.1 Primary outputs**

1. To determine the point prevalence of active TB amongst HIV positive and HIV negative miners
2. To identify target groups in whom sputum screening might be a cost-effective addition to the RSP
3. To compare results of sputum screening with those of the RSP
4. To estimate the impact of the additional sputum screening intervention on subsequent incidence rates of self-presentation with TB amongst HIV positive miners, by comparing incidence rates between the intensive versus standard screening groups.
5. To investigate the effect of time since screening on the incidence of self-presentation with TB, by calculating period-specific incidence rates for time periods 0 to 2 months; 3 to 5 months; 6 to 8 months and 9 to 11 months for both intensive and standard screening groups. This preliminary analysis will provide an indication of the likely impact of increasing the frequency of standard and intensive active screening. The intensive screening group is likely to be too small to allow investigation of the ideal screening interval for HIV negative men.

### **1.2.2 Secondary outputs**

6. To evaluate symptom screening as a tool for active TB case finding.
7. To identify risk factors for TB incidence in miners and to compare the duration of active TB disease (smear positivity) in HIV-infected miners with HIV-uninfected miners.



### 1.3 Enabling outputs and Timetable

1. Planning stage: This comprised obtaining ethical approval, appointment of staff, liaising with relevant authorities, staff training, design of questionnaires, video development and purchase of laboratory equipment.
2. Recruitment: A pilot study was conducted to identify unforeseen logistical problems. During the main study, persons were enrolled while attending for annual fitness examinations. On recruitment, two sputum specimens were collected for TB microscopy and culture, a questionnaire was administered, a urine specimen collected for HIV testing and a miniature chest radiograph taken.
3. Laboratory processing: Sputum smears were examined for acid-fast bacilli using microscopy with fluorochrome staining. Sputum was cultured on Löwenstein-Jensen (LJ) medium. Urine samples were tested for HIV.
4. Review: All study subjects with positive sputum microscopy or culture were reviewed by study staff and investigated for TB.
5. Follow-up: All study participants were followed up for episodes of TB for a year following their screening.

**Figure 1.a Summary of Enabling Outputs and date of completion**

<b>Enabling output</b>	<b>Date completion</b>
Planning	30/06/00
Screening	31/01/01
Laboratory processing	31/05/01
Review	31/12/01
Follow-up	31/01/02

## 1.4 Sample size calculations

We estimated a sample size of 2000 individuals. Below is an outline of the assumptions used and justifications for the sample size.

### **a) Point prevalence of active TB among HIV positive and HIV negative miners**

From results of the previous preliminary study, outlined in the introduction, an estimated 20 HIV positive and 60 HIV negative miners would have positive sputum smears and/or cultures: sufficient to allow accurate prevalence estimate for both HIV status groups.

### **b) Identification of target groups**

The study would have an estimated 80 TB cases. This would be sufficient to enable preliminary investigation into associations between the prevalence of smear/culture positivity and potential risk factors.

### **c) Comparison between RSP and sputum screening findings**

The ability to recall participants would allow verification of positive bacteriological results, and thus would permit investigation into features associated with non-radiologically apparent culture or smear positive TB. Basing our calculations on the results of the previous study, an estimated 60 TB cases that would have been missed by the RSP would be detected by sputum screening.

### **d) Impact of the additional screening intervention on subsequent incidence rates of self-presentation with TB by HIV positive miners**

This analysis would be a provisional one based on routinely collected data from all consenting TB patients concerning method of detection and HIV status. Since data on i) case-detection and ii) date of last screen would be available for all TB patients and, since over 90% of TB patients were thought likely to consent to HIV testing, it would be possible to estimate the incidence of self-presenting HIV-associated TB for the standard screening group with a high accuracy. This analysis would assume that the HIV prevalence and age-distribution data measured directly for the intensive screening group are representative of the whole workforce.

### **e) Distribution of time lag between screening and self-presentation with TB by HIV positive and HIV negative miners**

This sub-analysis would use routinely collected and study data. Data would be analysed for i) the effect of HIV on the distribution of time lag since screening, and ii) the effect of intensified screening on time lag among HIV positive miners. These data are exploratory, and no sample size calculations have been made.

## **1.5 Accomplishments of Project Outputs**

We were able to accomplish the first three primary outputs fully. Because of the high rate of loss to follow up of study participants due to retrenchments, output 4 and 5 have not been accomplished. It would no longer be safe to assume that the HIV prevalence and age-distribution data measured directly for the intensive screening group are representative of the whole workforce. It was therefore decided to restrict the follow-up to persons who had the intensive screening (in whom the HIV status is known) and to describe the rate of self-presentation in this group only.

## **1.6 Structure of the report**

Chapter 2 details the methods of the study (study procedure, laboratory methods and data analysis) and the quality control procedures that were performed. In chapter 3, the results of various methods of active case detection are presented and the yields from the various screening methods for TB are discussed. Chapter 4 describes the prevalence of TB and the risk factors for TB prevalence and incidence. Chapter 5 details the results of the prospective cohort analysis and discusses the effect of the screening process on rates of self-presentation with TB. General discussion and recommendations follow in Chapter 6.

## 2 Methods

This chapter provides an overview of those methods and systems common to all study objectives. Other methods specific to individual sections are presented in the relevant chapters.

### 2.1 Study site

Anglogold Health Service (AHS) provides comprehensive health care for 18 000 miners employed by Anglogold in Welkom, South Africa. The workforce is made up of officials in supervisory positions and manual labourers (largely migrant African men) comprising approximately 10% and 90% of the workforce respectively. The mean age of the workforce was 42 years in 1999. 90% of miners work underground and the majority of migrants live in single sex hostels. The mine hospital (700 beds) provides the sole source of tertiary care for mine employees and manages the TB control programme. The Occupational Health Centre (OHC) provides surveillance for occupational diseases by doing annual fitness examinations on all miners.

### 2.2 Study population

#### Inclusion Criteria:

- i) Miners attending the OHC for their annual medical examination
- ii) Employees of Anglogold
- iii) Employees in job group 3 to 8 category

#### Exclusion Criteria:

- i) Contractors (as follow-up of these persons would be difficult)
- ii) Miners who declined to participate.
- iii) Females

## 2.3 Study procedures

Miners attending the OHC for their annual medical examination were systematically sampled using a sequential numbering system allocated on entry to the OHC. Every person with a number ending in an even digit was invited to participate in the study. Employees who were eligible for the study were shown a video which explained the study procedures and also provided education about TB and sexually transmitted infections. Each potential participant was then given the opportunity to ask questions about the study in a confidential interview with a professional nurse. Written informed consent was obtained from all study subjects.

A simple questionnaire was administered in which personal demographics, including company number, and respiratory symptomatology were recorded (Appendix 1). A manual, which included translations of all questions into local languages was developed to ensure that all questions were asked in a standardised manner. The following symptoms were recorded:

- i) New or worsening cough and duration of cough
- ii) New or worsening sputum production
- iii) Haemoptysis
- iv) Drenching night sweats
- v) Symptomatic fever and duration of fever
- vi) Recent significant weight loss (>5 kg reported in last 6 months)

Two sputum specimens were collected one hour apart for TB microscopy and culture. Where study participants were unable to produce a sputum sample, a saliva sample was collected. Specimens were collected outdoors under supervision of study staff to minimise the possibility of TB transmission within the OHC.

A urine specimen was collected from each study participant for HIV testing. In order to retain confidentiality, urine specimen bottles were marked with only an HIV test number. This was linked to the study number at a later stage, once all identifiers had been removed.

Persons who were found to have either symptoms suggestive of TB or an abnormal radiograph were investigated by the routine health services: The standard work-up for TB includes a standard size chest radiograph, three sputum specimens for microscopy and cultures and review after treatment with broad-spectrum antibiotics for smear-negative cases.

Miners whose screening microscopy and/or culture were positive were recalled to the health service and investigated further by the research doctor. The average time lag between the initial and review examinations were 63 days (0 – 115 days). A standard-sized chest radiograph was done and a further three sputum samples were collected over three consecutive days. Symptoms, signs and radiological features suggestive of TB were recorded. Treatment for TB was started if there were suggestive clinical features. Treatment was deferred for apparently well individuals, until confirmatory smears or culture results were obtained, to minimise the risk of inappropriately treating for false-positive smear or culture results.

All participants were followed from the date of enrolment until their next annual medical examination in order to determine the subsequent incidence and time-distribution of self-presenting with TB.

## **2.4 Information systems**

The information systems available at AHS provide high quality demographic, occupational and health data. All mine employees are issued with unique identification numbers (industry, company and hospital numbers) that facilitate access to individual health records. The medical information system (MEDITECH) was used to access information about routine laboratory investigations using the patient's company number. A TB database, with detailed clinical records for all cases of TB, dates back to 1984.

Study data collected on forms were double-entered into a custom-designed Microsoft Access database. Range and consistency checks were applied. Incompatible data were referred back to the study physician for verification.

## **2.5 Ethical considerations**

Written ethical approval was obtained from:

- 1) The Ethical Committee of the London School of Hygiene and Tropical Medicine, London, United Kingdom (Appendix 2)
- 2) The Ethical Committee of AHS, Orkney, South Africa (Appendix 3)
- 3) The Ethical Committee of the University of the Witwatersrand, Johannesburg, South Africa (Appendix 4)

All study participants gave written informed consent to the study procedures and were provided with an information sheet about the study (Appendix 5 & 6).

### ***2.5.1 HIV testing***

Urine HIV testing was done using a dedicated HIV test number. Two separate files were kept in separate databases. One contained the HIV test number and HIV result and the other file contained the study number and HIV test number. The HIV test results were linked to other data by the study number, once all personal identifiers had been stripped. Data analysis was not performed until this stage. The file linking HIV test number and study number was password protected so that it was accessible only to the Project Manager.

### ***2.5.2 Confidentiality***

All research staff sign a confidentiality agreement when they are employed. All completed questionnaires were filed and kept in a locked cupboard. All databases were protected by double password.

## **2.6 Laboratory methods**

### **2.6.1 Mycobacteriology**

All sputum specimens were transported to the laboratory on site and processed for TB investigations. The specimens were decontaminated using 4% sodium hydroxide (NaOH) and centrifuged at 2000 rpm for 15 minutes. The specimens were neutralised using a freshly prepared phosphate buffer and centrifuged at 2000 rpm for 10 minutes. The sediment was planted onto an LJ slope and a smear made. Slides were dried overnight in the incubator or were heat dried on a hot plate at 55°C for 45 minutes. Smears were stained using a fluorochrome stain and were read by two independent readers blinded to each other's results. The results from a third reader were used when results were discrepant. Inoculated slopes were incubated at 37°C and monitored once a week for growth. Contaminated slopes were decontaminated. Genprobe Polymerase Chain Reaction (PCR) method for *Mycobacterium tuberculosis* was used for speciation. Specimen cultures characteristic of *M. kansasii* (yellow colonies) were identified using a Genprobe PCR method for *M. kansasii*. *M. tuberculosis* and *M. kansasii* probe negative cultures were sent to the South African Institute for Medical Research (SAIMR, now known as the NHLS) in Johannesburg for BACTEC identification. In cases where two specimens had growth and the specimens were similar in appearance, only one specimen was speciated.

### **2.6.2 HIV investigations**

Urine samples were screened for HIV using the immunoglobulin (Ig) G antibody capture particle adherence tests (GACPAT) as a screening test. Positive and equivocal results were confirmed using the IgG antibody-capture enzyme-linked immunosorbent assay (GACELISA) as a confirmatory test (15). This method has been validated in Malawi, with minimum values for observed relative sensitivity and specificity for the GACPAT compared to serology being 96.5% and 98.8% respectively. For GACELISA the observed sensitivity and specificity results were 98.8% and 99.2%. IgG antibodies were measured



in HIV negative urine samples during a previous study, and confirmed that total urine IgG concentrations were sufficiently high in this population to ensure no loss of sensitivity (16).

## **2.7 Quality control procedures**

The following quality control measures were taken: a) the contamination and culture positivity rates were audited during a preliminary run-in period and at three-monthly periods throughout the study for routinely collected clinical specimens with various grades of smear-positivity and for specimens with negative smears; b) independent rereading at the SAIMR of all positive sputum smears and 10% of the negative ones; c) specimens were stored at  $-20^{\circ}\text{C}$ , so that specimens with contaminated cultures could be recultured after a further decontamination step; and d) Kirchner medium was run in parallel with LJ for one month of the study to check for agreement.

### ***2.7.1 Surveys on routine specimens conducted during the study***

Surveys were carried out on all slides that were processed by the hospital TB laboratory during a specific week. Surveys were conducted in June 2000, October 2000 and March 2001. The slides, read by two independent readers who were blinded to each other's reading and the microscopy results, were then compared with culture results. Table 2.a summarises the findings during the three surveys. Reader 1 was a member of the research laboratory staff and Reader 2 was one of the routine laboratory staff. In survey 1 and 2, the agreement between readers was good. Discrepancies of more than one level (e.g. scanty vs 2+) were found in only 0.5% of samples. The proportion of smear positive specimens that were culture negative remained high in all the surveys but was higher with Reader 1, indicating some over reading by the research staff. In survey 3, the contamination rate was lower than expected (standard guidelines 6%), indicating that there was over-decontamination of specimens which may inhibit growth of the TB culture. This would explain the high figure for smear positive specimens that were culture negative in survey 3.

The quality assurance parameters for the study specimens are shown in Table 2.b. In this case, the two readers being compared were both research laboratory staff. The results of the quality control indicate that there may have been over reading as the proportion of smear positive, culture negative specimens was higher amongst research staff than amongst routine laboratory staff. Again, the contamination rate is lower than the standard, but this is due to the additional decontamination step which was carried out for the study and which falsely lowers the contamination proportion. The initial contamination rate was not documented.

**Table 2.a Quality control surveys conducted using routine TB specimens**

	<b>SURVEY 1</b>	<b>SURVEY 2</b>	<b>SURVEY 3</b>
<b>Date of the survey</b>	05–09 June 2000	23 – 27 Oct 2000	06 – 10 March 2001
<b>No of smears read</b>	280	426	346
	%	%	%
<b>Agreement between readers</b>	93.0	95.0	90.5
<b>Discrepancies &gt;1 level</b>	0.4	0.5	0.9
<b>Proportion of s+/c-* Reader 1</b>	42.0	33.8	34.6
<b>Proportion of s+/c-* Reader 2</b>	32.0	28.8	30.2
<b>Contamination</b>	6.4	9.6	1.5

\* smear positive that were culture negative : s+c-/ s+

**Table 2.b Quality control parameters of study specimens**

<b>No of smears read</b>	3906
<b>Agreement between readers</b>	98.4 %
<b>Discrepancies &gt;1 level</b>	0.1 %
<b>Proportion of s+/c-* Reader 1</b>	59.0 %
<b>Proportion of s+/c-* Reader 2</b>	78.0 %
<b>Contamination</b>	2.5 %

\* smear positive that were culture negative : s+c-/ s+

### **2.7.2 Reading of microscopy slides by SAIMR**

There were 490 slides that were sent to SAIMR for rereading. 435 slides had been classified by the research laboratory as negative and 55 as positive. Amongst slides that were classified as negative, the SAIMR was in agreement in 432 (99.3%) cases. Amongst slides that were classified as positive (1+ and above), the SAIMR was in agreement in 9 (56%) cases and amongst slides that were classified as being scanty, the SAIMR was in agreement in 1 (2.5%). The reason for such a big discrepancy with the scanty positive slides is unknown. One possibility is deterioration of the fluorochrome stain as there was a time delay of six months in some cases between the two readings. If these results from the SAIMR are not artefactual, then the results indicate that there was over reading at microscopy during the study. However, since the agreement between study staff and routine staff of slides which were freshly prepared was very high throughout the study, and the agreement between the two study readers was very high, it is unlikely that there was over reading to the degree that these results would indicate.

### **2.7.3 Culture on Kirchner medium**

379 sputum specimens were cultured on Kirchner medium as well as LJ medium. The comparison of LJ and Kirchner results are shown in Table 2.c. Kirchner medium is the more sensitive of the media, therefore the results obtained are consistent with what was expected. These results confirm the quality of the culture medium and technique.

**Table 2.c Comparison of Kirchner and LJ results**

	<b>Kirchner Positive</b>	<b>Kirchner Negative</b>	<b>Total</b>
<b>LJ positive</b>	13 (77%)	4 (23%)	17
<b>LJ negative</b>	8 (2%)	354 (98%)	362
<b>Total</b>	21 (6%)	358 (94%)	379

# 3 Screening methods in the active case detection of pulmonary TB

## 3.1 Objectives

- a) Comparison of results of sputum screening with those of the RSP
- b) Evaluation of symptom screening as a tool for active TB case finding
- c) Assessment of combinations of screening methods for active TB case finding

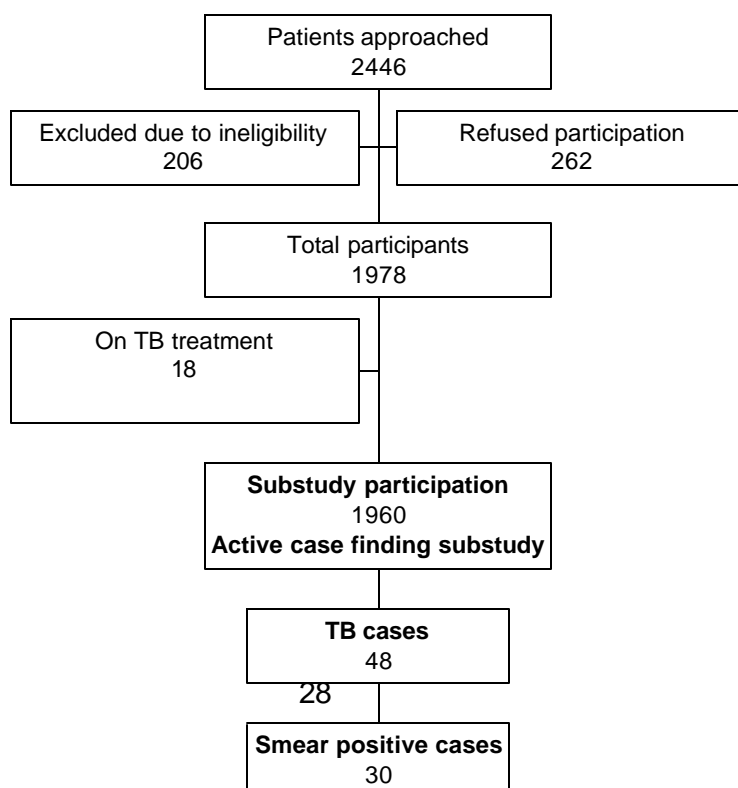
## 3.2 Methods

### 3.2.1 Study population

Persons who were on TB treatment at the start of the study were excluded from this sub-study. All other persons who were enrolled onto the study as in 2.2 and 2.3 above were included in this sub-study.

The algorithm below depicts the study participation.

Algorithm of participation in case finding study



### **3.2.2 Study procedures**

All persons enrolled onto the study were screened for pulmonary TB using a symptom questionnaire, a mini chest radiograph and two sputum specimens for microscopy and culture (see 2.3). Patients who had any features suggestive of pulmonary TB were investigated further as discussed in Section 2.3. The various screening methods were evaluated in detection of active TB. The gold standard used was clinical, microbiologic and radiological evidence of pulmonary TB (see case definitions).

### **3.2.3 Case definitions**

As patients were investigated thoroughly this allowed the application of stringent case definitions that ensured a minimum of false positive cases. Case definitions included clinical, microbiologic and radiological criteria. Microbiological data at screening and at review were used when applying case definitions. All cases of pulmonary and extrapulmonary TB (confirmed and presumed) were classified as having active TB.

#### **Active Pulmonary TB**

Definite : greater than 5 colonies of *M. tuberculosis* isolated from one sputum and compatible clinical features (2 or more symptoms, fever or radiological evidence). In the absence of compatible clinical features, two sputums that were culture positive for *M. tuberculosis* were considered to be definite TB.

Presumed: compatible clinical features and response to TB treatment within 2 months and either

- i) smear positive, or
- ii) new radiological abnormalities and no response to 5 days antibiotics prior to commencing TB treatment.

## **Smear Positive Pulmonary TB**

Cases who met the case definition for definite or presumed pulmonary TB and were smear positive on at least one smear taken at screening or at review, as prescribed by WHO (17).

### ***3.2.4 Radiographic examination***

The mini chest radiograph taken at the time of screening was read for the presence of TB by an experienced reader, under operational conditions. Chest radiographs were compared with previous miniature chest radiographs to determine the presence of a new or changing radiological lesion. When a radiograph was determined to have evidence suggestive of TB, the patient was referred for further TB investigation and classified as a positive radiological screen.

### ***3.2.5 Statistical methods***

Differences in categorical variables were determined using a chi-squared or Fisher's exact test as appropriate. Miners on TB treatment at the time of screening were excluded. The sensitivity, specificity, positive predictive value and negative predictive value of each screening method was calculated. A McNemar's test was performed to test for significance of difference between the various screening methods. A logistic regression model was used to determine the predictive value of individual and combinations of symptoms.

## **3.3 Results**

2446 persons were approached to participate in the study, 206 were excluded as they were not eligible (not AngloGold employees) and 262 (12%) refused participation, leaving 1978 for analysis. The HIV prevalence of the study population was 29% (95% CI 27.3 – 31.3%). The baseline characteristics of all those enrolled are shown in Table 3.a according to HIV status. HIV-infected individuals were significantly

more likely to be younger, to have a shorter duration of employment, to be from a country other than South Africa, to live in a single-sex hostel and to have had a previous episode of TB.

Table 3.b lists the results of the microscopy and culture on all study participants at screening. 32 persons (1.6%) had either one (6) or both (26) sputum specimens that were positive for acid-fast bacilli on microscopy. One (13) or both (28) sputum cultures were positive for mycobacterial growth in 41 patients (2.1%). Table 3.c describes the organisms isolated from culture specimens. Amongst those with positive cultures on both specimens, the organisms were identical in 35 cases (either both *M. tuberculosis* (26) or both *M. kansasii* (1) or other mycobacteria (8)), and different species of mycobacteria in two cases. 215 (11%) complained of at least one symptom and 50 (3%) complained of two or more symptoms. The frequency of individual symptoms reported is shown in Table 3.e.

Of 1978 miners screened for TB, 18 miners were on TB treatment at the time of screening and were therefore excluded from the analysis. There were 48 cases of pulmonary TB which were identified and these cases were classified as having TB in the analysis.

A summary of the microbiological, clinical and radiological findings of the 48 cases picked up is shown in Table 3.d. 47 cases were classified according to the case definitions as definite pulmonary TB and one was classified as presumed pulmonary TB. In one case the patient had both pulmonary and extrapulmonary TB. No cases of extra pulmonary TB alone were identified at screening. 30 (62.5%) of those who had active TB were classified as having smear positive TB according the WHO definition.

The specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) of individual screening methods for detecting pulmonary TB are shown in Figures 3.a and 3.b. The most sensitive method was TB culture. The sensitivity of chest mini radiography and sputum microscopy were similar (McNemar's test,  $0.1 < p < 0.05$ ). All screening methods were highly specific. Examining two

sputum smears identified only one case of pulmonary TB that would not have been detected had only one specimen been examined.

Sensitivity and specificity for each individual symptom for detection pulmonary TB are shown in Figure 3.c. All symptoms, except fever, were significantly associated with active TB. A logistic regression model was used to determine which of the individual symptoms were independent risk factors for disease. "Night sweats" was the strongest risk factor for TB. The two other independent risk factors were cough and loss of weight. The combination of cough, night sweats and loss of weight is henceforth referred to as the "symptom combination". The presence of one or more elements of the symptom combination had a sensitivity of 29% and specificity of 90% to detect all cases of TB. The symptom combination was more sensitive but less specific when compared with microscopy (McNemar's test,  $P < 0.001$ ) and radiography (McNemar's test,  $p < 0.001$ ).

A comparison of the yield of active TB when one or more of the screening methods are combined is shown in Figure 3.d. If symptom screening was added to the existing RSP, an additional 11 (23%) cases of active TB would be identified, whereas only an additional 7 (15%) cases would have been identified by the addition of sputum screening. If both sputum microscopy and symptom screening were added to the RSP, an additional 17 (35%) cases would be identified.

We investigated the yield of the various screening methods to detect smear positive cases of TB shown in Table 3.f. Culture was positive in 77% of all smear positive cases. RSP detected 40% and symptoms detected 30% of all smear positive TB. The combination of RSP and symptoms would detect 60% of all smear positive cases. We compared the screening methods in HIV-positive and HIV-negative individuals and the yield was similar in the two groups (Appendix 7).



**Table 3.a Baseline characteristics of all study participants**

	HIV negative (N=1398)		HIV positive (N=580)		P value
	No	(%)	No	(%)	
<b>Age (years)</b>					
<30	70	( 5)	41	( 7)	0.002
30-39	473	(34)	238	(41)	
40-49	637	(46)	228	(44)	
≥50	218	(16)	73	(13)	
<b>Employment duration (years)</b>					
<10	207	(15)	116	(20)	<0.001
10-19	458	(33)	224	(39)	
20 – 29	566	(40)	180	(31)	
30	167	(12)	60	(10)	
<b>Country of Origin</b>					
SA	733	(52)	253	(44)	0.003
Lesotho	531	(38)	257	(44)	
Mozambique	110	( 8)	54	( 9)	
Other	24	( 2)	16	( 3)	
<b>Residence</b>					
Non Hostel	372	(27)	122	(21)	0.009
Hostel	1026	(73)	458	(79)	
<b>Silicosis</b>					
Absent	1006	(73)	421	(74)	0.827
Early	260	(19)	109	(19)	
Advanced	105	( 8)	39	( 7)	
<b>Place of Work</b>					
Surface	94	( 7)	43	( 7)	0.582
Underground	1304	(93)	537	(93)	
<b>Previous TB</b>					
Yes	115	( 8)	95	(16)	<0.001
No	1283	(92)	485	(83)	

**Table 3.b Results of sputum microscopy and culture on screening on all study participants**

	Screening	
	N=1978	
	Positive	(%)
Microscopy A (first specimen)	29	1.5
Microscopy B (second specimen)	28	1.4
Combined Microscopy	32	1.6
Culture A (first specimen)	35	1.8
Culture B (second specimen)	34	1.7
Combined Culture	41	2.1

**Table 3.c Organisms isolated on screening**

	No	%
<i>M. tuberculosis</i>	40	67
<i>M. kansasii</i>	3	5
<i>M. avium</i>	2	3
<i>M. fortuitum</i>	1	2
<i>M. flavium</i>	1	2
Other NTM (rapid growers)	7	12
Mixed <i>M. kansasii</i> / <i>M. tuberculosis</i>	1	2
Mixed <i>M. kansasii</i> / <i>M. xenopi</i>	1	2
Not identified	3	5
Total	59	100

**Table 3.d Summary of microbiological, clinical and radiological findings of the 48 pulmonary TB patients picked up**

No patients in category	Sputum screening	CXR changes	Symptoms or fever	Sputum review	Response to Rx	Status
4	S+C+	New changes	Yes	S+C+	ND*	Definite
4	S+C+	New changes	No	S+C+	ND	Definite
2	S+C+	None	Yes	S+C+	ND	Definite
2	S+C+	New changes	Yes	S-C+	ND	Definite
2	S-C+	New changes	Yes	S+C+	ND	Definite
3	S-C+	New changes	No	S+C+	ND	Definite
2	S-C+	None	Yes	S+C+	ND	Definite
1	S-C+	None	Yes	S+C-	ND	Definite
2	S-C+	New changes	Yes	S-C+	ND	Definite
3	S-C+	New changes	No	S-C+	ND	Definite
3	S-C+	None	Yes	S-C+	ND	Definite
2	S-C+	None	No	S-C+	ND	Definite
3	S-C+	New changes	Yes	S-C-	ND	Definite
2	S-C+	New changes	No	S-C-	ND	Definite
1	S-C+	None	Yes	S-C-	ND	Definite
5	S-C-	New changes	No	S+C+	ND	Definite
2	S-C-	New changes	Yes	S+C+	ND	Definite
2	S-C-	None	Yes	S+C+	ND	Definite
2	S-C-	None	Yes	S-C+	ND	Definite
1	S-C-	New changes	Yes	S+C-	Yes	Presumed

\*ND = Not determined

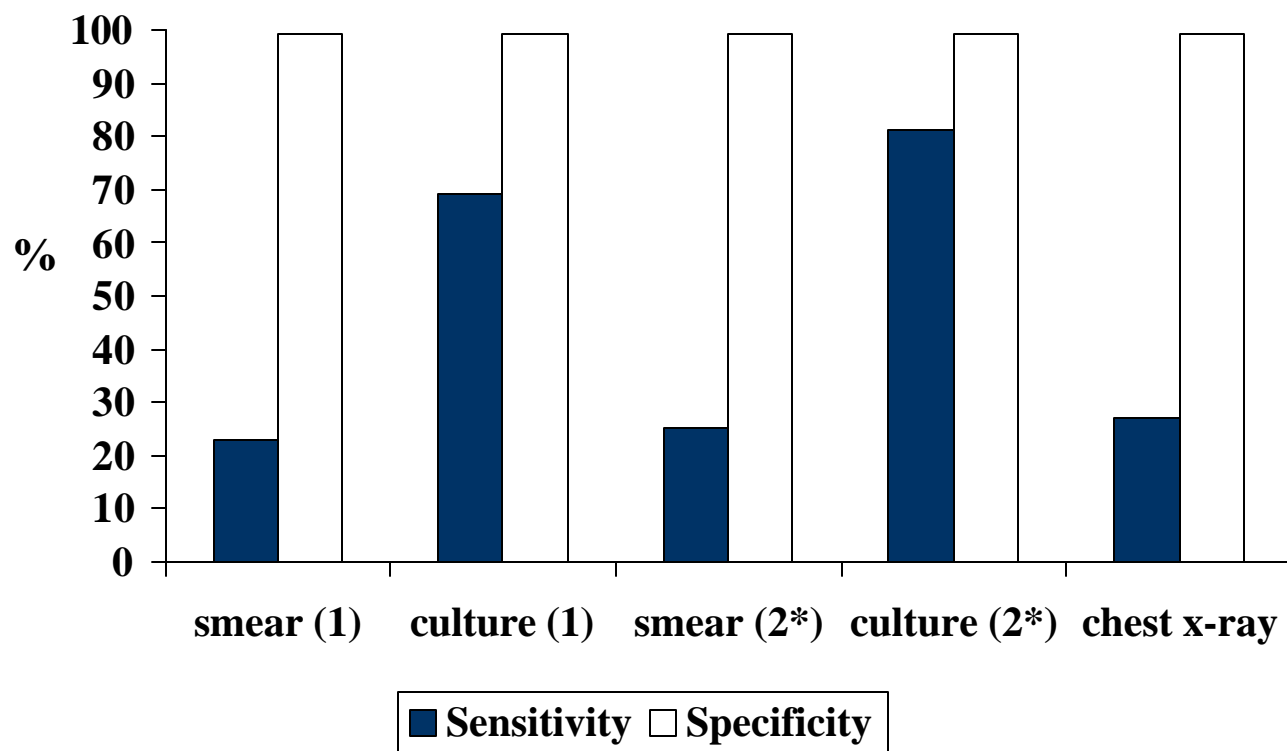
**Table 3.e Frequency of symptoms reported at screening**

Symptom	Frequency	Proportion
Total	1960	100%
Cough	50	2.5%
Sputum production	25	1.3%
Haemoptysis	14	0.7%
Night sweats	122	6.2%
Fever	30	1.5%
Weight loss	106	5.4%
Cough > 3 weeks	24	1.2%
Fever >3 weeks	15	0.8%
<i>Symptom combination</i>	199	10.1%

**Table 3.f Performance of screening tools for the diagnosis of *smear positive* pulmonary TB**

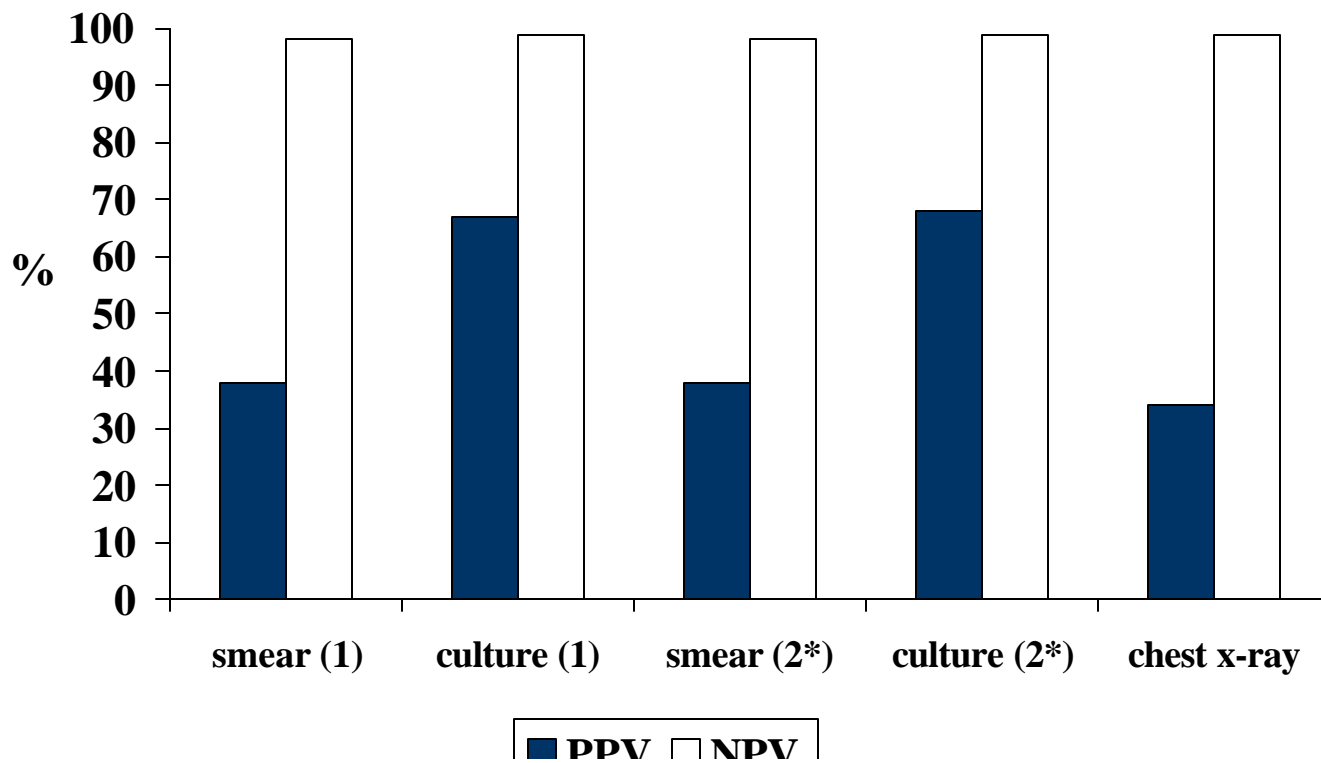
	Sensitivity %	Specificity %	PPV %	NPV %
<b>Symptom combination</b>	30	90	85	99
<b>Culture</b>	77	98	40	100
<b>RSP</b>	40	99	32	99
<b>Microscopy</b>	40	99	38	99
<b>RSP and symptom combination</b>	60	89	8	99

**Figure 3.a Sensitivity and Specificity of smears, cultures and chest radiographs in the detection of all pulmonary TB**



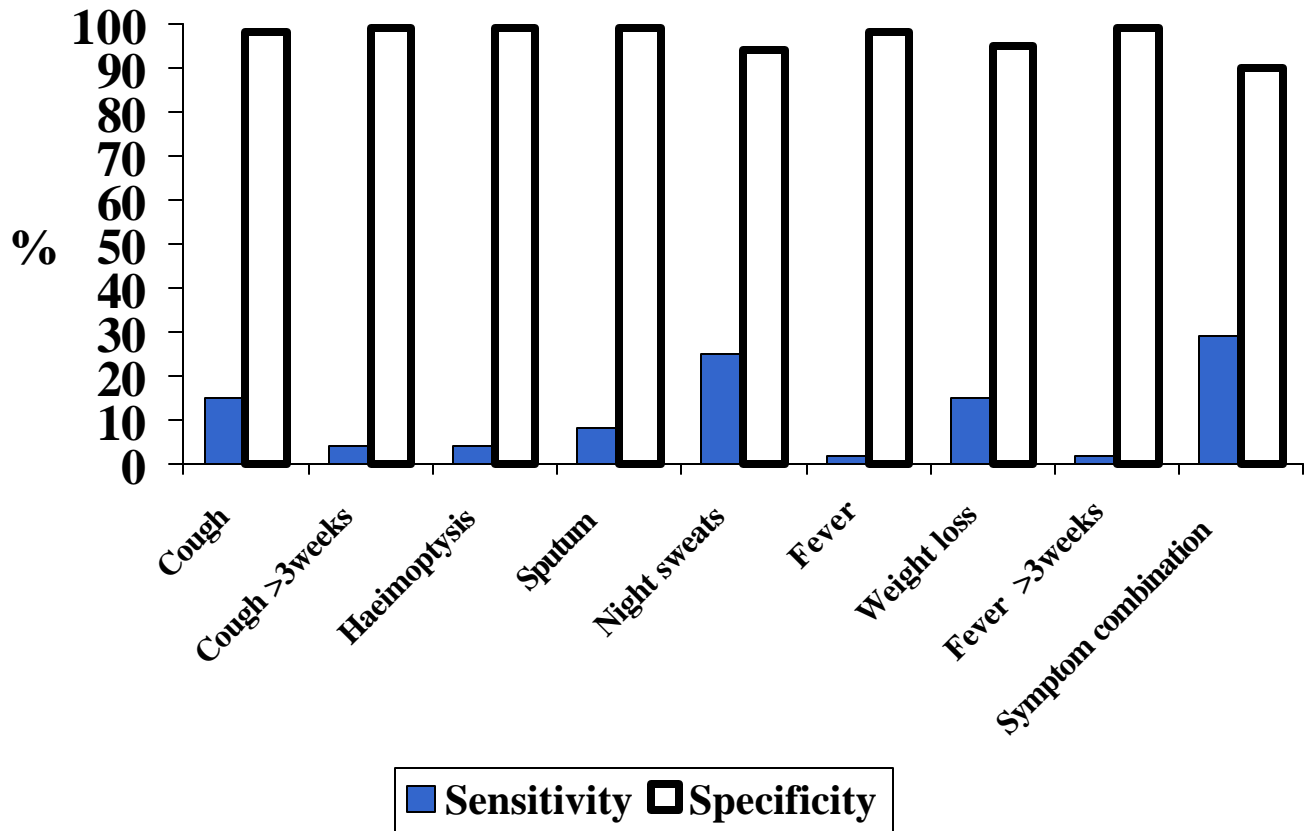
\* positive on either first or second sputum specimen or both

**Figure 3.b Positive Predictive value and Negative Predictive value of smears, cultures and chest radiographs in the detection of all pulmonary TB**

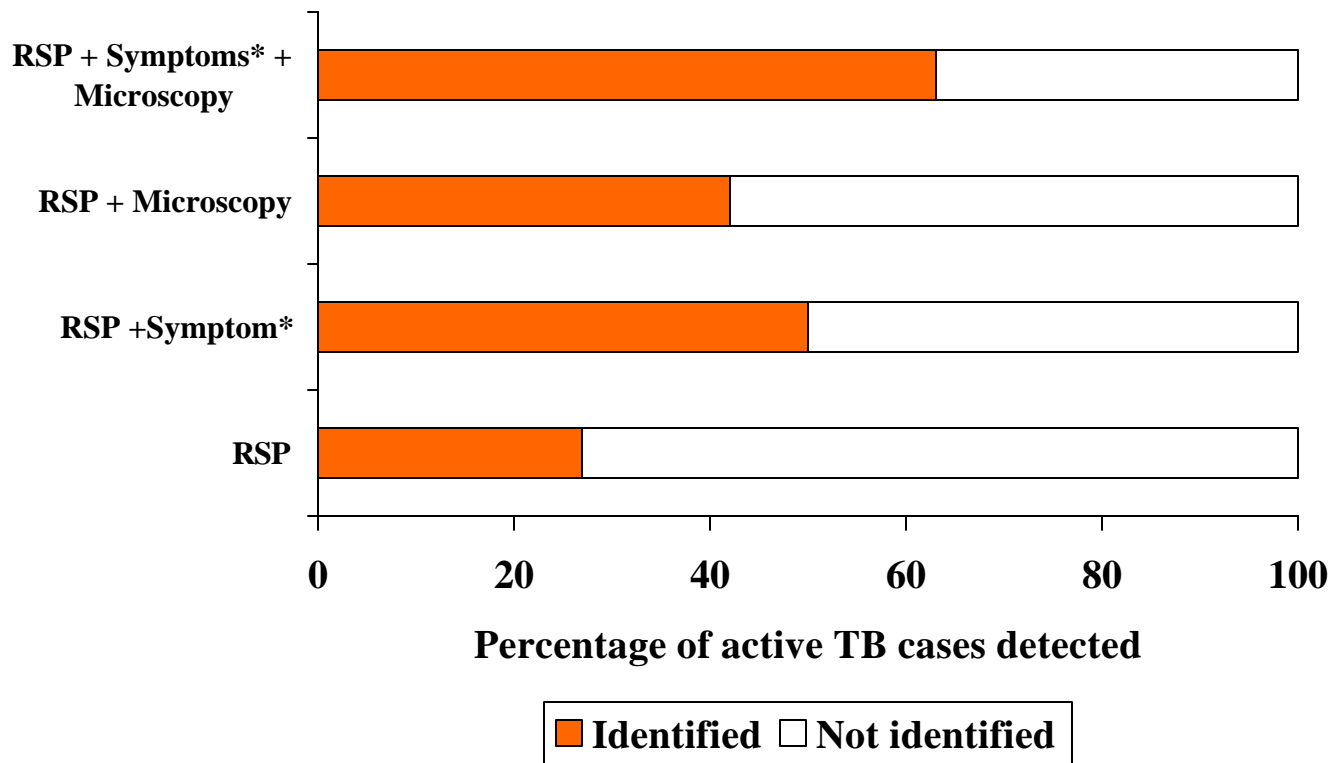


\* positive on either first or second sputum specimen or both

Figure 3.c The sensitivity and specificity of symptoms reported at screening in the detection of all pulmonary TB



**Figure 3.d The sensitivity of combined screening methods in the detection of all pulmonary TB**



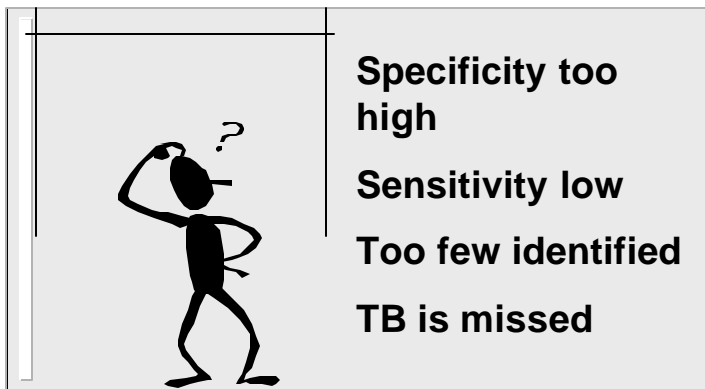
\* any of cough, weight loss or night sweats (symptom combination)



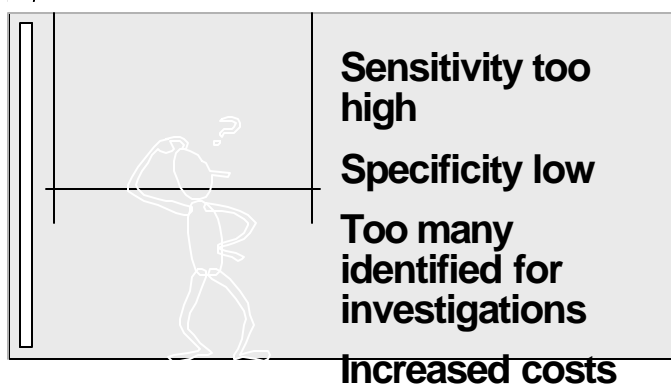
### 3.4 Discussion

To identify the most appropriate screening method or combination of screening methods for the detection of pulmonary TB, one needs to balance a screening test that would identify too many TB suspects many of which do not have the disease, with one which would identify fewer TB suspects with a higher proportion with the disease but result in many cases being missed. The ideal screening test would have a high sensitivity and specificity. One can use the analogy of the test as being a bar of a high jump. The pictures below illustrate, using this analogy, consequences of using a screening system with high specificity but low sensitivity (bar too high) and a screening system with high sensitivity and low specificity (bar too low).

#### Bar too High



#### Bar too Low



The results suggest that the use of a single screening method for the detection of TB is insufficient. Of the four screening methods evaluated, sputum culture was the most sensitive. If sputum culture were not possible, the combination of sputum microscopy, symptoms and radiology would yield the most cases of TB.

The RSP, the current standard of active case detection, detected only a quarter of all cases of TB amongst mineworkers. The advantages of the RSP is that it has a high specificity and detected a larger number of smear positive TB cases than symptom review. Also, radiological screening is already in operation and it can also be used to monitor other occupational lung diseases.

The proportion of TB cases detected with sputum microscopy compared with RSP were similar. The addition of sputum microscopy to the existing case finding programme would have identified only a further 7 (15%) cases of active TB. The advantages of sputum microscopy are that the positive predictive value of the sputum microscopy was higher than that of symptom review indicating that a lower number of false positive patients would be identified with sputum microscopy. Another advantage of sputum microscopy would be that infectious cases of TB are more likely to be identified. The disadvantages are that sputum microscopy is time consuming and requires specialised facilities and trained staff, and there are additional costs of the sample collection i.e. supervision, collection bottle etc. that need to be considered.

TB culture detected the largest proportion of TB cases (81% overall and 77% identification of smear positive TB). As with sputum microscopy, TB culture requires specialised facilities and trained staff and in addition it also requires a waiting period of up to eight weeks, which may delay detection of cases considerably. Ligase chain reaction has been shown to offer speed and discrimination in the early stages of TB disease, with sensitivity of 94% when compared to culture (18). Another method that is being investigated is the amplification by PCR of a fragment of the insertion sequence IS6110 which has

been shown to have a sensitivity of 95% and a specificity of 93% as compared to culture on LJ medium (19).

Symptom screening for TB appeared to give a slightly higher yield than sputum microscopy. The three most significant symptoms were cough, weight loss and night sweats. It needs to be considered that the high frequency of symptom reporting will lead to an increase in the number of persons investigated for TB from 2% (currently positive on radiology) to 10% of persons screened. However, the use of symptom screening in addition to chest radiography will double the identification of active TB cases and, as symptom screening is relatively inexpensive, we recommend that this method be added to the routine RSP of TB.

A limitation of the study was that we were not able to confidently determine the value of using two specimens instead of one. The study participants were required to provide two sputum specimens for microscopy to ensure that, if specimens were lost, there would be duplicate specimens available. Another reason for requesting two samples was to evaluate the value of examining two sputum samples instead of one. Unfortunately the laboratory staff were not blinded to the identity of the specimens and there was a very high agreement (99.6%) between the two microscopy results.

## 4 Duration of active TB disease

### 4.1 Objectives

For HIV-infected and HIV non-infected workers, to:

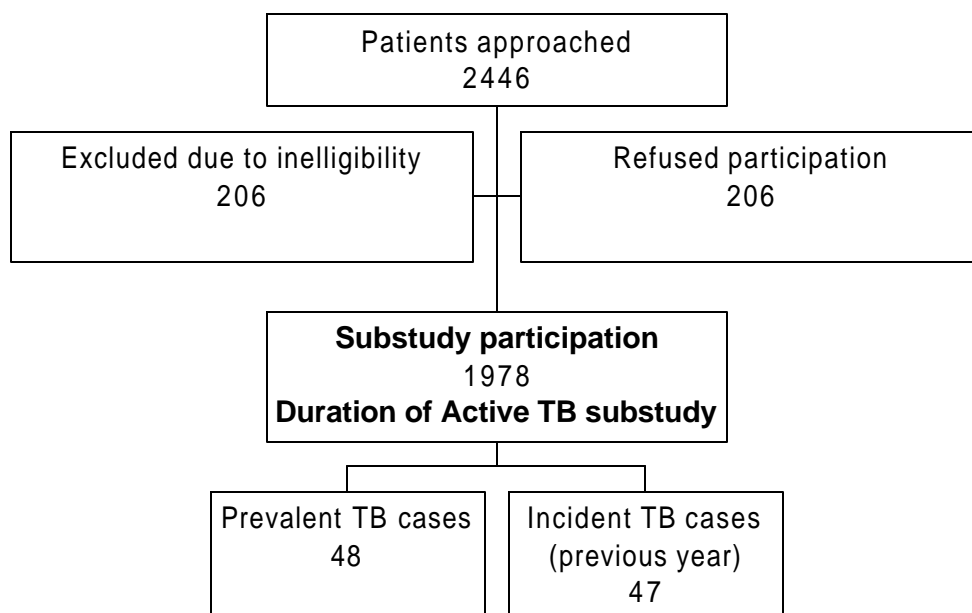
- a) Determine the point prevalence of TB
- b) Determine the factors associated with TB incidence
- c) Determine the duration of active TB

### 4.2 Methods

#### 4.2.1 Study population

All patients enrolled onto the study were included in this sub-study. (i.e. inclusion and exclusion criteria as in 2.2. above). As all but one patient had been in employment for more than a year, no patients were excluded from the analysis. The algorithm below illustrates study participation in this substudy.

Algorithm of participation in Duration of Active TB study



## **4.2.2 Study procedures**

An incidence for TB was calculated by collecting data on episodes of pulmonary or extrapulmonary TB in the year preceding the date subjects were enrolled. The prevalence of TB was based on the number of all definite or presumed cases of pulmonary or extrapulmonary TB at the time of screening.

## **4.2.3 Case definitions**

### **a) Prevalence of TB**

#### **Pulmonary TB**

As for Active TB in 3.2.1

#### **Extrapulmonary TB**

Confirmed ETB: Compatible clinical features and >5 colonies of *M. tuberculosis* isolated from relevant site

Presumed ETB: Compatible clinical features and clinical response to TB treatment plus evidence of TB on histology or cytology from appropriate specimens.

### **b) Incidence of TB**

Case definitions used in the retrospective analysis were as follows:

Definite Pulmonary TB: sputum culture positive for *M. tuberculosis* with >5 colonies or two or more sputum specimens smear positive for AFB.

Presumed Pulmonary TB: single sputum smear positive for AFB, or both smear and culture negative, and chest radiograph suggestive of TB and improvement on TB treatment.

Case definitions for extrapulmonary TB were the same as above.

Case definitions for prevalence were more stringent than for TB incidence. The incidence data was a retrospective analysis for which we were reliant on routinely collected data for the case definitions. In the cross-sectional study, by which prevalence is calculated, the subjects were investigated more thoroughly. We felt it inappropriate to use the same case definitions as this would underestimate number of cases in the retrospective analysis. If the incidence was underestimated this would also underestimate the calculated duration of active TB disease.

#### **4.2.4 Risk factors**

The risk factors examined were age, silicosis, HIV infection, hostel residence, country of origin, place of work and previous TB. HIV status was determined from the linked anonymous urine testing as described in 2.3.2. Information about age, hostel residence, country of origin and place of work were collected during the patient interview (see 2.2). Mini radiographs were graded for nodularity suggestive of silicosis on a six-point scale modified from the International Labour Organization (ILO) guidelines (20). For the purpose of the analysis silicosis was categorised as absent (ILO grades 0/0), early silicosis (0/1 and 1/0), or advanced silicosis (1/1, 2/2 and 3/3). The TB database was used to ascertain a history of previous TB and to determine which patients were on treatment at the time of screening.

#### **4.2.5 Statistical methods**

The data from all 1978 patients were used for this analysis. All patients were followed retrospectively from the date of enrolment to a year preceding the date of screening to the date that TB treatment was commenced. All cases of TB (definite and presumed) were used in the analysis. Odds ratios were calculated for risk factors for prevalence of TB. Poisson regression was done to analyse risk factors for incident TB. The duration of active TB disease was calculated using the formula  $P(\text{prevalence}) = I(\text{incidence}) \times D(\text{duration})$ . The significance of the difference in the duration of active TB disease was calculated using the difference of two proportions.

## 4.3 Results

Of 1978 miners screened for TB, 48 patients met the case definitions for active TB (47 definite, 1 presumed) at the time of screening and all the cases were included in the calculations. The calculated prevalence overall was 2.5% (95% confidence interval (CI) 1.8 – 3.2). The prevalence in the HIV-infected group was 3.3% (95% CI 2.1 – 5.3%) and in the HIV-uninfected group it was 2.2% (95% CI 1.4 – 2.9%). Risk factors for TB prevalence were analysed to identify target groups where sputum screening might be a cost-effective addition to the RSP as shown in Table 4.a. The only significant risk factor for prevalent TB was age > 40 years ( $p = 0.01$ ).

In the year preceding screening there were 47 cases of TB amongst the study participants. Most cases had pulmonary TB (36) but there were 9 cases of extrapulmonary TB and two cases of both pulmonary and extrapulmonary TB. The algorithm below illustrates the study participation and number of TB cases.

Of the pulmonary TB cases, 29 (76%) were definite and 9 were presumed according to the case definitions. TB incidence was 2.4/100 person years (py) at risk (95% CI 1.8 – 3.2). TB incidence in HIV-infected persons was 5.4/100py, and in HIV-uninfected persons was 1.2/100py: crude incidence rate ratio (IRR) 4.4, 95% CI 2.4 - 7.9). Risk factors for incident TB are shown in Table 4.b. Significant risk factors for incident TB, besides HIV, were silicosis ( $p$  for trend <0.001) and age>40 years (IRR 2.1, 95% CI 1.1–4.0). The duration of active TB disease was estimated and is shown in Table 4.c.

**Table 4.a Risk factors for TB prevalence**

		Univariate analysis			
Characteristic		(%)	OR	95% CI	P value
<b>Overall</b>	48/1978	( 2.5)			
<b>Age</b>					
< 40	12/ 822	( 1.5)	1		0.01
≥ 40	37/1156	( 3.2)	2.23	1.16 – 4.30	
<b>HIV status</b>					
Negative	30/1398	( 2.5)	1		0.15
Positive	19/ 580	( 3.3)	1.54	0.86 – 2.77	
<b>Silicosis</b>					
No	30/1427	( 2.1)	1		0.22**
Early	16/ 369	( 4.3)	2.11	1.14 – 3.92	
Advanced	3/ 144	( 2.1)	0.99	0.30 – 3.29	
<b>Hostel</b>					
No	8/ 494	( 1.6)	1		0.14
Yes	41/1484	( 2.8)	1.73	0.80 – 3.71	
<b>SA origin</b>					
No	25/992	( 2.5)	1		0.18
Yes	30/986	( 3.0)	1.47	0.83 – 2.62	
<b>Place of Work</b>					
Surface	3/ 137	( 2.2)	1		0.82
Underground	46/1841	( 2.5)	1.15	0.35 – 3.73	
<b>Previous TB</b>					
No	42/1768	( 2.4)	1		0.42
Yes	7/ 210	( 3.3)	1.42	0.63 – 3.20	

\*\* p –value for trend



**Table 4.b Risk factors for TB incidence**

Characteristic	Univariate analysis				Multivariate analysis*	
	TB (No)	TB (Rates)	IRR**	95% CI	IRR**	95% CI
<b>Age</b>						
< 40	12	1.47	1		1	
≥ 40	35	3.09	2.16	1.15 – 4.05	1.69	0.83 – 3.47
<b>HIV status</b>						
Negative	17	1.22	1		1	
Positive	30	5.35	4.37	2.41 – 7.92	4.45	2.43 – 8.16
<b>Silicosis</b>						
No	25	1.77	1		1	
Early	11	3.04	1.71	0.84 – 3.48	1.48	0.72 – 3.08
Advanced	10	7.19	4.06	1.95 – 8.45	3.41	1.56 – 7.43
<b>Hostel</b>						
No	8	1.64	1		1	
Yes	39	2.67	1.63	0.76 – 3.49	0.99	0.43 – 2.26
<b>SA origin</b>						
No	28	2.87	1		1	
Yes	19	1.95	0.68	0.38 – 1.22	0.85	0.45 – 1.62
<b>Place of Work</b>						
Surface	2	1.47	1		1	
Underground	45	2.48	1.69	0.41 – 6.97	1.56	0.37 – 6.56

\* Adjusted for age category (<40 or greater than 40), HIV, silicosis>1/0, hostel dwelling, country of origin (SA or not), place of work

\*\* IRR = Incidence Rate Ratio

**Table 4.c The estimated duration of active TB disease**

	<b>Duration of active TB disease (years)</b>	<b>95% CI</b>	<b>P value</b>
<b>HIV positive</b>	0.61	0.26 – 0.96	P = 0.038
<b>HIV negative</b>	1.79	0.67 – 2.90	

## **4.4 Discussion**

The prevalence of TB using radiological, clinical and microbiological data in the general population of miners was found to be 2.5% and did not differ significantly in HIV-infected and HIV-uninfected individuals. A true prevalence of TB in the mining population has never been reported before. Studies on prevalence of TB in Korea, which is a country of relatively low HIV prevalence, found, as we have, that age was the only significant risk factor for TB prevalence (21). The TB incidence in the year preceding the study was 2.7/100 person-years and was found to be significantly associated with age, HIV status and silicosis. These findings are consistent with those from other retrospective studies of incidence of TB using routine HIV test results (12).

Using the prevalence and incidence data, we were able to calculate the mean duration of TB before diagnosis, which was significantly shorter in HIV-infected individuals. This reflects more rapid TB progression in compromised hosts and has major implications for both case-finding and TB control. Even in high HIV prevalence areas the importance of HIV negative TB should not be underestimated, as it may contribute disproportionately to transmission owing to the long duration of disease activity before diagnosis. An increase in case-finding of HIV negative persons with TB is likely to have a significant impact on TB transmission.

A limitation of the study is the representativeness of the study sample. A sequential number of men were recruited while attending for annual fitness examination as this was logistically easier than doing a randomised sample of all the persons in the workforce. As persons who are on TB treatment are discouraged from going on leave and the annual fitness examinations are mostly done on persons as they return from leave, it is possible that the incidence rate in this cohort is underestimated. The study sample would also have excluded the small number of employees in hospital at the time of the screening study and this would have slightly underestimated the prevalence of HIV. The effect of these factors on the study results and information about risk factors is unlikely to be significant.

Another limitation of the study is the use of a retrospective incidence cohort. Because of the intervention (i.e. intensive screening) we could not use the cohort prospectively to determine an incidence. A retrospective cohort has the disadvantage of excluding people who may have been lost in the "period of follow-up" either due to death or due to retrenchment etc. The reason for the loss may well have been related to TB. These would have resulted in an underestimation of TB incidence which would have resulted in an over-estimation of the period of active disease. As HIV-infected individuals are known to have a higher mortality rate from TB, it is possible that the underestimate is more marked in the HIV-infected group.

## **5 The effect of the screening process on the rate of self-presentation with TB in the follow-up period**

### **5.1 Objectives**

- a) To estimate the impact of intensive screening on subsequent incidence rate of self-presentation with TB.
- b) To calculate period-specific incidence rates to determine the optimum period between case detection.

### **5.2 Methods**

#### ***5.2.1 Study population***

##### ***Inclusion Criteria:***

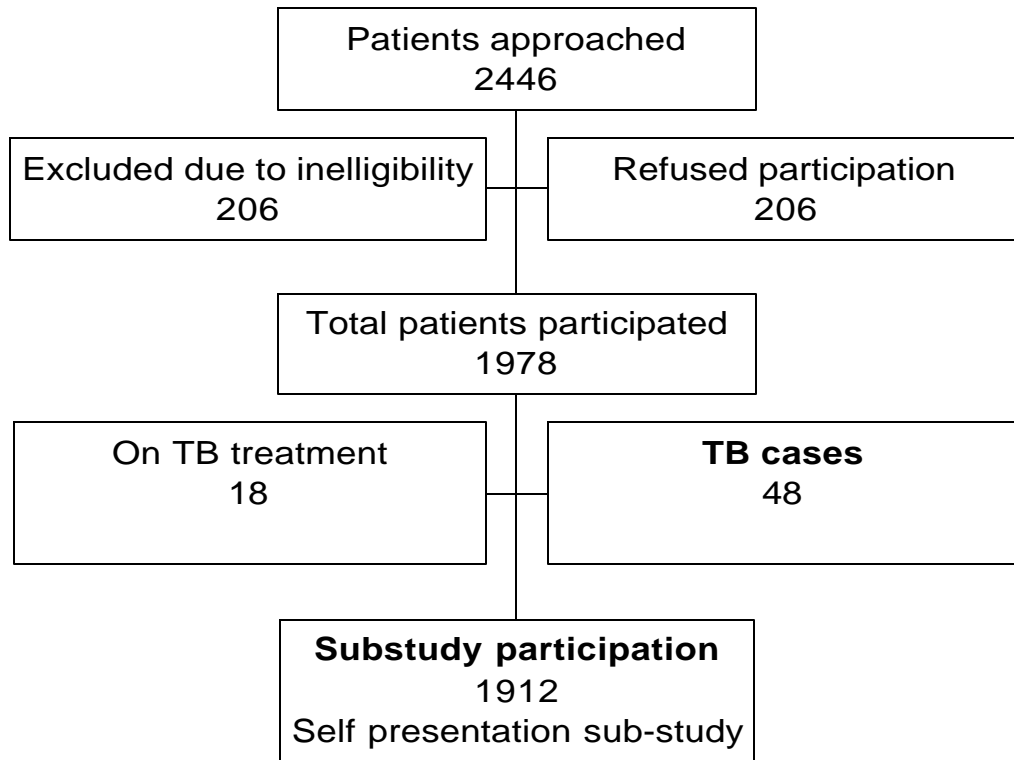
All study participants as in 2.2 above

##### ***Exclusion Criteria:***

- i) Study participants found to have active TB at the time of screening
- ii) Study participants who were on TB treatment at the time of screening

Persons who were enrolled onto the study and did not have the above exclusion criteria were followed until their next radiological screen (either their annual fitness examination or their research radiological examination on the GEN 524 study) for an episode of TB. An algorithm of participation in this sub-study is shown below:

## Algorithm of participation in self presentation study



### **5.2.2 Case definitions**

Case definitions used in this prospective analysis were identical to those used in the retrospective incidence analysis (Section 4.2). All cases of TB that fitted the case definitions for confirmed and presumed pulmonary and extrapulmonary TB were included in the analysis.

### **5.2.3 Data collection**

To determine whether TB was detected by screening or self-presentation an algorithm designed for another SIMRAC study was used (GEN524). The algorithm uses the date of first positive sputum and the date of abnormal x-ray to determine whether the case was detected by a periodical x-ray (active detection) or by self-presentation. All cases of active TB detected through intensive screening were classified as being actively detected.

## **5.2.4 Data analysis**

All persons who were enrolled into the cohort were followed from the date of screening until their next radiological examination (annual or research radiograph) for an episode of TB. Those who had not had another annual fitness examination by the time of analysis were followed until a year after enrollment. The follow up period was terminated when the person developed TB, was lost to follow up or died. The incidence of TB in this cohort was calculated using the date of TB treatment commencement as the date of TB. The incidence of self-presentation during the study period was plotted on Nelson-Aalen graphs to illustrate the point where self-presentation increases. Rates for self-presentation in the first six months of follow-up were compared to those in the second six months of follow up using Mantel-Haenzel significance testing. Comparison was made with the incidence of self- presentation with TB amongst those on INH preventive therapy using poisson regression.

## **5.3 Results**

1912 persons were followed until their next radiological examination, a total of 1375 person years at risk. Mean duration of follow up was 0.7 years. 62 persons had received INH preventive therapy in the past. During this follow-up period, 32 (15 Definite, 18 presumed) cases of TB were diagnosed. 22 cases were in the HIV-infected group and 11 cases in the HIV-uninfected group. 88% of cases had pulmonary TB alone (29), 3 cases had extrapulmonary TB and one case had pulmonary and pleural TB.

The incidence of self-presentation with TB in the cohort was 2.4/100 person-years. The incidence in the HIV-infected group was 5.1/100 person-years and in the HIV-uninfected group was 1.1/100 person-years. Significant risk factors for self-presentation following intensive screening were : HIV infection (crude IRR 5.1, 95% CI 2.5– 10.6) and silicosis (crude IRR 2.6, 95% CI 1.5 – 4.5). Of borderline significance age greater than 40 years (crude IRR 2.3, 95% CI 1.0 – 5.2) was also associated with an increased risk of TB following intensive screening.

Table 5.a shows the rates of self-presentation with TB in HIV negative and HIV positive groups and compares the rates in the first six months and the second six months. There is a non-significant increase in rates after 6 months of follow up in both HIV positive (IRR 1.282, 95% CI 0.548 – 2.99) and HIV negative individuals (IRR 2.083, 95% CI 0.636 – 6.83) was shown.

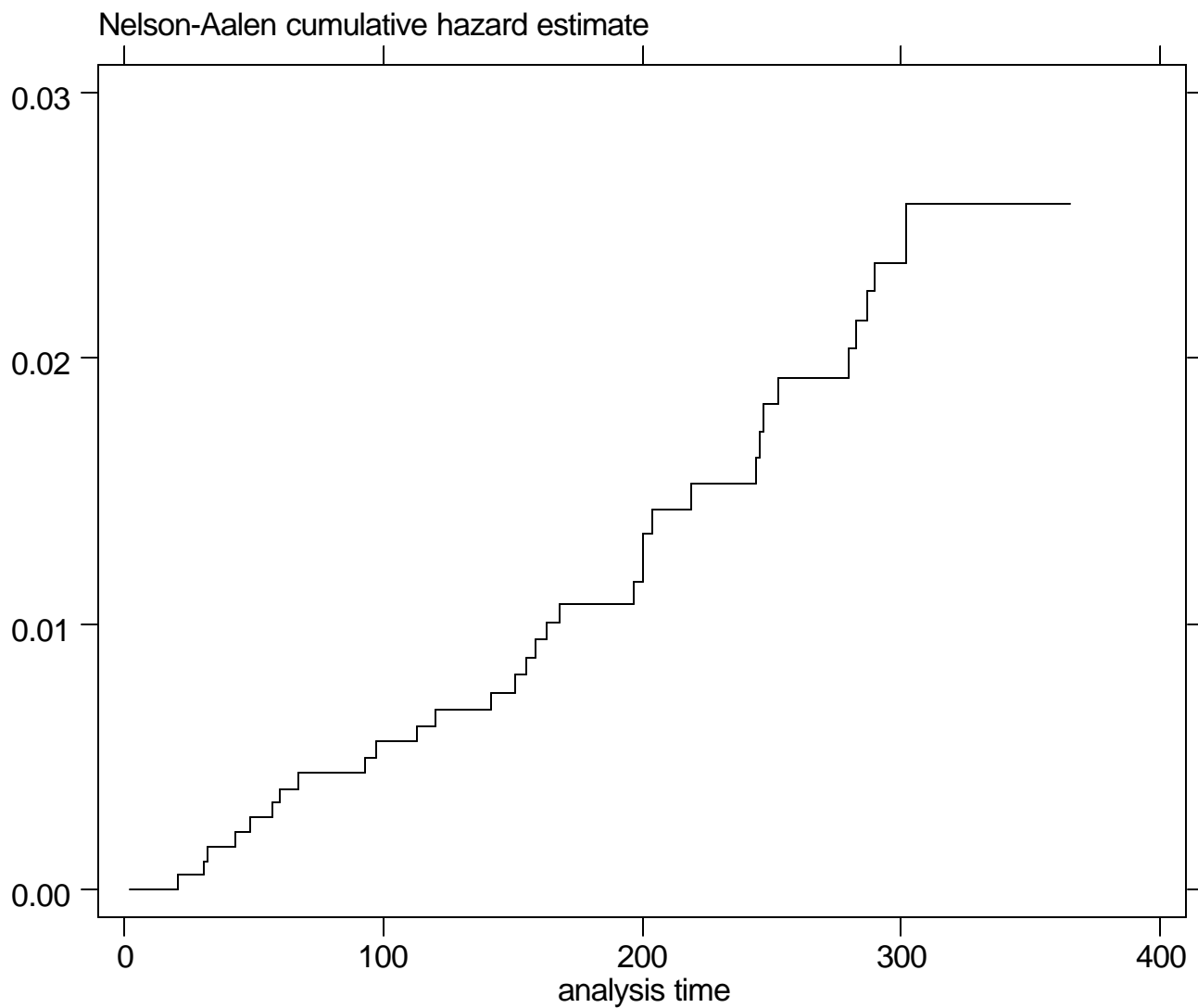
Figure 5.a shows the incidence of self-presentation of TB regardless of HIV status. The graph shows tendency towards a higher incidence of TB cases after 180 days. The incidence of self-presentation according to HIV status was compared in Figure 5.b and 5.3.c.

An incidental finding was that the rates of TB in the HIV-infected group were lower in those who had previously received INH (1/38 py, 2.6/100 person years) compared with to those who had not (21/347py, 6.0/100 person years). This finding was not significant (IRR 0.43, p=0.38).

**Table 5.a Incidence rates of self-presentation with TB according to length of follow-up**

		<b>Rates/100py</b>	<b>95% CI</b>
HIV negative	< 6 months	0.87	0.34 – 1.96
	>6 months	1.83	0.87 – 3.83
HIV positive	< 6 months	5.68	3.36 – 9.58
	> 6 months	6.70	3.61 – 12.45

Figure 5.a Cumulative cases of self-presentation of TB in cohort





**Figure 5.b Cumulative cases of self-presentation of TB in the HIV-uninfected cohort**

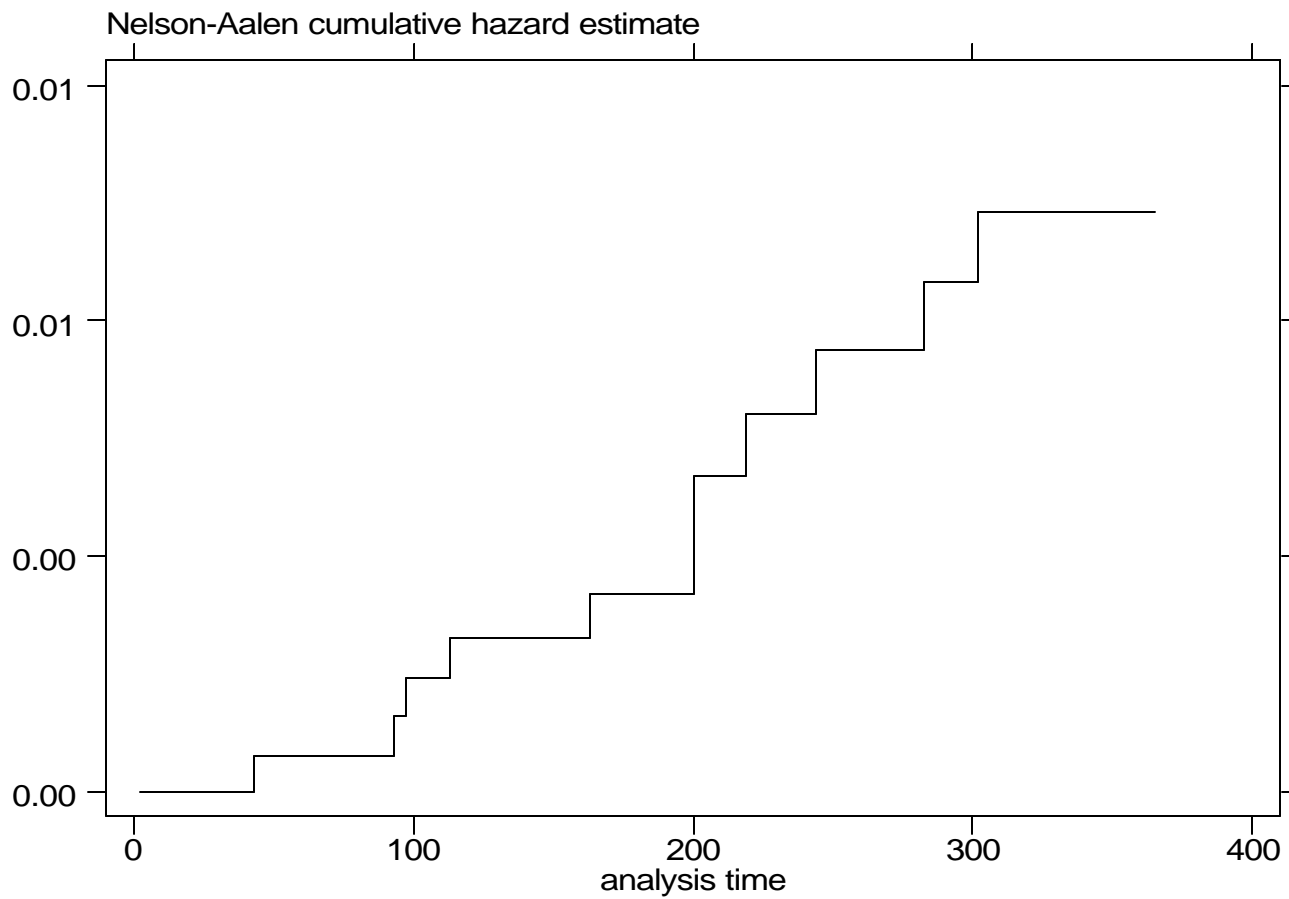
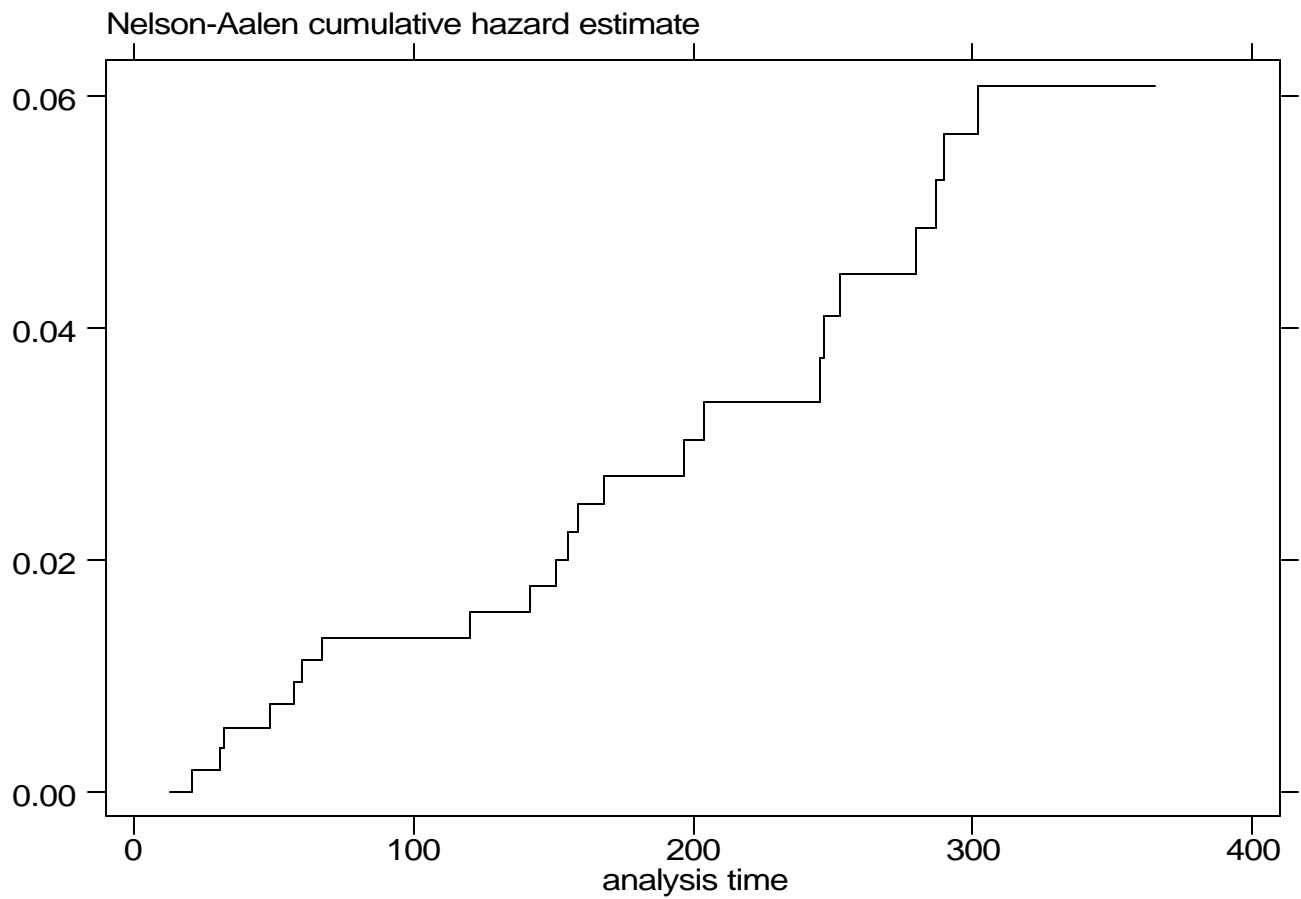


Figure 5.c. Cumulative cases of self-presentation of TB in the HIV-infected cohort



## 5.1 Discussion

The follow up of persons enrolled in this study was done to investigate the incidence of TB following intensive screening and to determine the appropriate time interval for active case finding. It was found that the incidence of self-presentation with TB following intensive screening is higher in HIV-infected individuals. Other risk factors were silicosis and age. Self-presentation with TB was higher in the second six months after screening in both HIV groups, suggesting that six monthly screening may be an appropriate interval for active case finding.

A limitation of the study was that the mean follow up period was reduced due to the high retrenchment rate in this workforce. Also, as patients were followed up to their next radiological screening, the occurrence of another study which administered radiological examinations six months after screening, meant that in some patients the period of follow up had to be terminated at the research radiograph. The reduction in follow up time resulted in insufficient person time of follow up to accurately assess the findings.

An interesting finding is the increase in TB presentation after six months which is greater in HIV-uninfected individuals. After intensive screening there was still a high incidence of TB presentation in HIV-infected individuals which lends support to the findings in the duration of active disease sub-study about a shorter duration of active disease in HIV-infected compared to -uninfected individuals.

A larger study is needed to accurately determine the value of intensive screening six monthly. The results of a randomised study comparing six-monthly and annual radiological screening are awaited, however, screening with six-monthly radiographs alone may not be as effective as intensive screening.

## 6. Conclusions and Recommendations

This study provides valuable information about the epidemiology of TB and role of active TB case finding in gold miners. The high TB and HIV prevalence confirms that urgent strategies are required to control these epidemics. The emphasis of the directly observed treatment strategy (DOTS) which is recommended by WHO is on identifying prevalent cases of TB and rendering them non-infectious with treatment. TB control programmes in the mining industry need to be strengthened by improving active case detection.

Four screening methods for tuberculosis, i.e. radiography, symptom review, sputum microscopy and sputum culture were investigated. The yield of radiological screening was low, which suggests that additional methods need to be introduced to increase detection of TB. Screening with sputum microscopy was similar to chest radiograph and after considering the high cost and complex logistics with introducing sputum testing, it cannot be recommended at present. Symptom screening was found to be of substantial benefit and is recommended as an adjunct to radiological screening. Sputum culture yielded the most cases but the delay in diagnosis and costs associated, do not warrant doing sputum culture in all persons attending for annual medical examination. Sputum culture will need to be re-evaluated once cheaper, more sensitive methods of sputum screening are available.

We recommend that all persons with either: a new abnormality on RSP; or any of the three symptoms of cough, night sweats and fever; are identified for further investigation for TB. Further investigations should include at least two sputum specimens for microscopy and culture. A profile for the investigation of TB using this algorithm is shown in Figure 6.a. If this screening algorithm had been used on the study population it would have identified 12% of persons needing investigation for TB. These patients would then be investigated further with sputum microscopy and culture. The initial sputum microscopy and culture would have yielded 31% (15/48) of the TB cases and further investigation would have identified a

further 18% (9/48). A symptom screening form (Appendix 7) that can be customised to different occupational settings has been developed

Risk factors for TB incidence are well established while those affecting TB prevalence are not well understood. As TB prevalence is a major determinant of transmission, identification of risk factors for prevalence are important for TB control. HIV infection and silicosis are strong risk factors for incident but not prevalent (active) TB, reflecting more rapid progression of TB in the HIV-infected host with major implications for case-finding and TB transmission. HIV-negative individuals are likely to be important sources of TB transmission despite low incidence, because of their long duration of infectivity. TB control strategies in high HIV prevalence areas should not underestimate the importance of HIV-negative TB.

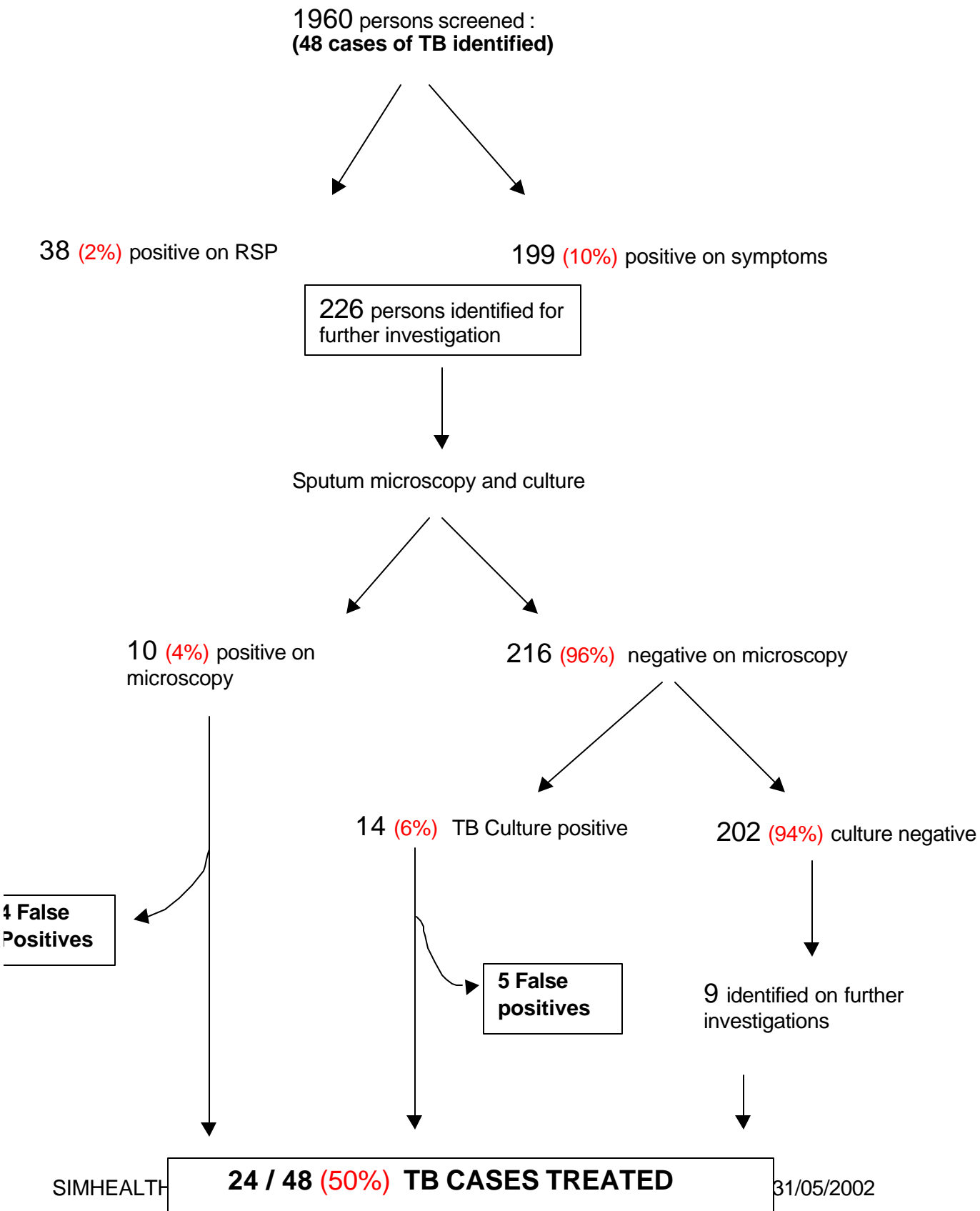
The highest incidence of TB is in HIV infected individuals. The use of INH preventive therapy in the reduction of TB incidence well established in HIV infected individuals (22, 23) and is currently being implemented in this workforce. INH preventive therapy needs to be implemented on a wide scale if it is to have an effect on TB transmission. Its use in HIV-uninfected individuals has not been investigated in this setting. Studies done amongst Alaskan Eskimos in 1970's (24) showed significant reduction in TB transmission after community-wide INH prophylaxis. The use of mass preventive therapy to reduce TB incidence in all miners needs to be investigated.

HIV disease and silicosis were shown to be important risk factors for TB incidence and efforts at improving HIV and dust control remain important strategies in the reduction of TB. Surveillance of HIV infection rates in this population needs to be ongoing. Primary HIV preventive interventions such as education and voluntary counselling and testing need to be strengthened. Secondary HIV interventions aimed at reducing the burden of HIV disease among those already infected (including preventive therapy to reduce the incidence of TB and opportunistic infections) need to be implemented throughout the industry.

The prospective study was not able to determine whether the introduction of intensive screening may reduce the subsequent incidence of TB. We recommend that further investigations are conducted to establish the efficacy of intensive screening on a six-monthly basis.

In summary, the high TB prevalence and incidence, confirm that strategies to control the TB epidemic have failed. Active case detection using chest radiographs alone is insufficient. The improvement of case detection by further investigation of all those with symptoms of TB is recommended. Additional strategies to reduce TB incidence, such as INH preventive therapy in HIV-infected persons, need to be implemented widely. Preventive therapy in HIV-uninfected persons and six-monthly screening need to be investigated.

**Figure 6.a Profile of the performance of screening for TB using chest radiograph and symptoms**



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