PULMONARY TUBERCULOSIS IN RELATION TO LUNG FUNCTION LOSS.

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EXECUTIVE SUMMARY

Pulmonary tuberculosis (TB) has been associated with obstructive airways disease. The incidence of TB is high among gold miners, due to the high prevalence of Human immunodeficiency virus (HIV) and silicosis in the workforce.

A study was undertaken among Black South African gold miners to determine whether an episode of pulmonary TB, even though treated, i) causes an accelerated loss of lung function in comparison to miners of the same age who had not had TB during the study period and ii) cause chronic respiratory symptoms.

The study was conducted in a single gold mining company in the Free State Province of South Africa. There were 185 miners in each group. There was no significant difference between the 2 groups with respect to age, duration of employment and baseline lung functions. Miners who had had TB had significantly more silicosis (18.4% versus 10.8%) and were more likely to be current or ex-smokers (82.7% versus 61.6%) than miners who had not had TB.

Miners who had had an episode of TB compared to miners who had not had TB had a 40 ml per year greater loss of both the forced vital capacity (FVC) and the volume exhaled in the first second of a forced vital capacity manoeuvre (FEV1). Among miners who had had TB during the study period the following characteristics at baseline were associated with a greater annual loss of FEV1; sputum smear positive status, self presentation compared to detection by the radiological screening

programme, extensive radiological disease and bronchiectasis. The radiological presence of extensive post TB scarring and bronchiectasis at the end of TB treatment was also associated with a greater annual loss of FEV1. At the time of follow-up lung function testing miners who had had TB, compared to those who had not had TB, had more than a two fold greater risk of having respiratory symptoms of cough, breathlessness and wheezing and a ten fold greater risk of having restrictive lung disease, but were not at greater risk of having obstructive lung disease.

TB is an important cause of loss of lung function in this workforce. Strategies to detect TB earlier or reduce susceptibility to TB by intensifying HIV and dust control programmes are required. TB preventive therapy would reduce the incidence of TB among susceptible miners and may lead to improved lung health in these miners by preventing deterioration in lung function associated with having an episode of pulmonary TB.

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GLOSSARY

Lung function testing

The term lung function testing covers a range of tests designed to assess the function and integrity of different parts of the respiratory system. In this report all testing is confined to the use of *spirometry*, which measures the mechanical ventilatory capacity of the lung.

Spirometry

FVC	The total volume the subject can exhale in a forced expiratory manoeuvre
FEV1	The volume the subject can exhale in the first second of a forced expiratory manoeuvre
$FEF_{25-75\%}$	The mean forced expiratory flow over the middle half of the FVC
FEV1 / FVC ratio	The percentage of the FEV1 to FVC
BTPS	BTPS is body conditions: normal body temperature, ambient pressure, saturated with water vapour.
Coefficient G	Pulmonary function tests are continuous, normally distributed variables. It is well recognised that lung function tests are prone to measurement errors. These errors can be broadly categorised as systematic errors of measurement and random errors of measurement. Systematic error may be due to procedural changes, e.g., a technician effect or seasonal variability. A systematic error changes mainly the mean, i.e. it shifts the

distribution. Random error of measurement is due to the random error in measurement procedure itself and more importantly, random fluctuation in the measured quantity that reflects the variability in pulmonary function within an individual subject. This fluctuation can be due to factors such as subjects fatigue, bronchoconstriction, diurnal or seasonal variation, acute response to allergens, etc. By definition, the random error of measurement does not change the mean, but can change the size of the variance. When testing the reliability of a pulmonary function measurement, we estimate the size of the random error of measurement, relative to the total variation in the measurement across subjects, i.e., we compare the amount of the within-person variability relative to the between-person variability. The statistic that measures the relative size of the random error of measurement is the reliability coefficient G.

Microbiology

HIV	Human immunodeficiency virus
LJ	Lowenstein-Jensen TB culture medium
NTM	Non-tuberculous mycobacteria
ZN	Ziehl-Neelsen
TB	Disease due to *Mycobacterium tuberculosis*

Occupational

ILO	International labour organisation

Study design

TB case	Miners who had an episode of pulmonary TB during the study period
Control	Miners who did not have an episode of TB during the study period

1 INTRODUCTION

Pulmonary tuberculosis (TB) has been associated with airflow obstruction at diagnosis (1, 2, 3), during (4) and at the completion of treatment (5) . Studies with longer follow-up periods have shown that a large proportion of cases with treated pulmonary TB had evidence of permanent airflow obstruction or restrictive impairment (6, 7). There are no published studies in which the effect of TB on lung function impairment was evaluated longitudinally comparing pre and post treatment lung functions while controlling for the presence and extent of silicosis.

The South African gold mining industry employs over 300 000 miners. The risk factors for TB among gold miners include silica dust exposure (8, 9), silicosis (10, 11) and HIV infection (10, 12). Prior to 1992, the incidence of TB among working gold miners was stable but high (in the order of 500 smear and/culture-positive cases per 100,000 person years) (12). With the advent of HIV, TB rates have risen and currently exceed 2,000 per 100,000 per year (12). The TB control programme includes standard treatment regimens, combination tablets administered under direct observation and active case detection through the radiological screening programme.

In a cross-sectional study (13), (i.e. one in which each subject was studied only on one occasion), we established that the loss of lung function was related to the number of TB episodes and the time period between TB diagnosis and lung function testing. The lung function loss was greatest after 6 months and had stabilized after

13-18 months of follow up. Thus, the residual effect was measured from 18 months onwards. The study established that the percentage of subjects with residual airflow impairment (FEV1<80% of predicted) was 18.4% after one episode of TB, 27.1% after two episodes of TB, and 35.2% after three or more episodes of TB. HIV status was not related to lung function loss due to TB.

For prevention of chronic obstructive lung disease in occupational settings, it is important to determine the factors that are associated with significant airflow limitation and their possible combined effects. The effects of silicosis on airflow limitation among Black gold miners has previously been studied (14). The effect of TB on airflow limitation among Black gold miners has not previously been studied in a longitudinal study.

2 AIMS

The aims of this study were to determine among Black South African gold miners:

1. The longitudinal loss of lung function following an episode of pulmonary TB after controlling for confounding variables, in comparison to age matched controls without any history of TB, and
2. The association between pulmonary TB and respiratory symptoms in TB cases after completion of TB treatment, in comparison with age matched controls without any history of TB.

3 METHODS

3.1 *Study design*

This is a longitudinal study in which the change in lung function preceding and following an episode of pulmonary TB was assessed and compared to age matched control subjects who did not have TB during the study period.

3.2 *Study population and site*

The study was conducted at a single gold mining company in the Free State Province of South Africa. The workforce consists of officials in supervisory positions (largely White men) and manual labourers (largely migrant Black men) comprising approximately 10% and 90% of the workforce respectively. The Black migrant workforce is recruited from rural South Africa and neighbouring states and constitutes the study population.

The gold mining industry has undergone major downsizing over the past decade as a result of declining ore reserves and profitability. The workforce of the mining company decreased from approximately 86,000 in 1990 to 20,000 in 2000. Changes in labour recruitment policies have resulted in a more stable and therefore older workforce than was the case a few decades ago. The mean age of the workforce increased from 34 years in 1990 to 42 years in 1999.

Ninety percent of miners work underground. The majority of the migrant miners live in single sex hostels at the mines and return home once a year for leave. Typically, hostels accommodate 2 - 3000 men with 2 to 6 men per room.

The mine hospital (760 beds) provides the sole source of tertiary care for mine employees and manages the TB control programme. Clinics situated at most of the surrounding mine shafts provide primary health care to miners. The occupational health centre provides surveillance for occupational diseases.

3.3 *TB control programme*

A comprehensive TB control programme was introduced in 1977. The TB control programme includes standardisation of diagnostic criteria, rifampicin-based short-course chemotherapy regimens and the use of combination tablets. Directly observed therapy was introduced in 1993. The TB control programme also incorporated both active case-detection through a miniature radiography screening programme and passive detection of those men who self present with symptoms. In 1995, treatment regimens were changed in line with World Health Organisation (WHO) and national recommendations to include ethambutol in the intensive phase of TB treatment and routine smear evaluation of treatment outcomes of smear positive cases.

3.4 *Cohort selection*

Lung function screening was introduced in 1994. Lung function testing is performed on entry into employment, every three years thereafter, and on exit from employment. In a reliability study we established that lung function tests were most

reliable between January 1995 and August 1996. The reliability coefficient G during this period was 0.94. Miners who had had a lung function test during this period who were still currently employed on the 12th December 1999 were eligible for inclusion in the study.

Comparison of the cohort of eligible men with the computerised TB database identified those miners who had had an episode of pulmonary TB at least 2 months after the date of their baseline lung function test. Miners who had had TB diagnosed within two months of the date of their baseline lung function test were excluded as the presence of TB at the time of the lung function test could not be confidently excluded. Miners who had successfully completed TB treatment were included in the study.

Age-matched controls were selected from the cohort of eligible miners who had no history of TB recorded on the TB database, prior to the baseline lung function tests or during the study period. All study subjects were evaluated between April and July 2000. After written informed consent had been obtained from all study subjects, each had a repeat lung function test and a respiratory, smoking and occupational questionnaire administered

3.5 *Mycobacteriology*

Miners with suspected mycobacterial disease are investigated using a standard protocol with 3 sputum specimens taken over 2 days. Smears are made from concentrated sputum and stained with auramine for fluorescent microscopy. Positive

smears are confirmed with Ziehl-Neelsen (ZN) staining. Following decontamination with 4% sodium hydroxide, sputum is inoculated onto Lowenstein-Jensen (LJ) slopes and incubated for up to 8 weeks. An initial identification step for *M. tuberculosis* is carried out on LJ slopes with more than 5 colonies, using a colorimetric ribosomal RNA hybridisation test (Accuprobe® *M. tuberculosis* complex probe kit, Gen-Probe, San Diego, CA). Positive cultures are sent directly to the South African Institute of Medical Research (SAIMR) mycobacteriology laboratory for biochemical species identification of non-tuberculous mycobacteria and drug susceptibility testing of *M tuberculosis* strains.

3.6 *Case definitions.*

The following definitions were used for a case of TB, method of detection, treatment category, site of disease, drug resistance and treatment outcome.

A case of culture-positive TB was diagnosed if there were compatible clinical features and the sputum culture was positive. Culture-negative TB was diagnosed if there were compatible radiographic changes plus two of the following: smear positive; no response to amoxycillin; radiological response to anti-tuberculous drugs;

Method of detection. *Self presentation* – spontaneous presentation with symptoms; *Active* – detection through the radiography screening programme (RSP).

Treatment category. *New case* - defined as a person who had never previously been treated for TB; *retreatment TB* - defined as a patient who had previously been treated for TB and then presented with active TB requiring re-treatment.

Site of disease. Patients were classified as having either Pulmonary TB alone (PTB) or in combination with extra-pulmonary TB, (PTB+ETB).

Drug resistance. *Drug resistant* - resistance to one or more of the primary TB drugs, i.e., isoniazid (H), rifampicin (R), streptomycin (S) or ethambutol (E).

Treatment outcome.

The following case definitions were used to define outcome for initially smear positive men: *Cure*:- Completion of treatment with documented smear conversion from positive to negative and / or negative smears within a month of completing treatment. *treatment completion*:- completion of treatment without bacteriological confirmation of cure, *failure*:- smear or culture positive at end of treatment.

3.7 *Annual occupational health medical examination*

Mine employees are required by law to have a medical certificate of fitness to do risk work, i.e., dust-exposed work. All miners under-go an annual medical examination at the occupational health centre to determine fitness to do risk work. Lung function testing and radiological screening for mycobacterial disease and silicosis form part of the annual medical examination. The results of these annual medical examinations

are captured onto a separate database, maintained by the occupational health centre.

3.8 *Lung function testing*

Maximal forced expiratory manoeuvres, performed in the seated position, were recorded in a computerised database using a Hans Rudolph pneumotachograph (Flowscan, Electromedical Systems Inc). The system software requires and validates calibration with a 3,0 L syringe. Barometric pressure and temperature are entered via the keyboard for correction of volumes to BTPS. During testing, flow versus volume tracings are displayed. A minimum of three acceptable and reproducible forced expiratory manoeuvres were obtained according to the standards recommended by the American Thoracic Society (ATS). All testing was done by nursing personnel trained in the techniques of performing spirometry to ATS standards. Height, in stockinged feet, was measured to the nearest centimetre. Data recorded for each test included date of test, date of birth, height, weight, the largest forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and forced expiratory flow rate in the middle half (25 to 75%) of the forced vital capacity ($FEF_{25-75\%}$). The reference equation by Louw for Black South African males was used. Lung functions were categorised as obstructive if the FEV1 / FVC ratio was <70% of predicted and restrictive if the FEV1 / FVC ratio was $70% of predicted and the FVC was <80% of predicted.

Lung function tests done at baseline were reviewed by a professional nurse experienced in lung function testing and a respiratory physician. Only those men

whose lung function tests met ATS criteria for an acceptable lung function test were included in the study.

3.9 *Silicosis grading*

Mini chest radiographs taken during the annual medical examination were routinely reviewed by a single reader for new abnormalities suggestive of mycobacterial disease and the presence of compensable silicosis (moderate to advanced). However, no formal silicosis grading was done. Serial mini chest radiographs are stored at the occupational health centre for all currently employed miners and are kept for at least 5 years after miners leave employment.

The mini chest radiographs of study participants, taken at the time of the baseline lung function, were assessed by a single reader for the presence and grade of silicosis using a modified International Labour Organisation (ILO) scoring system. The ILO system was designed for use with standard sized films, but use of mini-radiographs has been validated in a separate study involving the same workforce (15). For the purposes of this study silicosis was deemed to be present if the ILO category was 1/1 and above and absent if the ILO category was 0/0, 0/1 or 1/0.

3.10 *Radiological pattern and severity of TB*

Standard sized chest radiographs were taken on all miners presenting with suspected pulmonary mycobacterial disease at diagnosis, after 2 months of treatment and at the end of treatment. All standard sized radiographs were stored in

the radiology department. Standard size chest radiographs of TB patients included in the study were graded for radiological pattern and extent of TB at the time of diagnosis and at completion of treatment. The radiological pattern of disease was classified as cavitary, fibrosis, nodular or infiltrate. The presence and extent of pleural abnormalities and bronchiectasis were also recorded. The radiological extent of disease was determined by the reader dividing the lung on each side into 3 equal zones and allocating a score according to the total number of zones involved. The chest radiographs were read by two readers and a consensus score was derived for each variable. The chest radiographs for each TB patient at diagnosis of TB and completion of treatment were read in chronological order.

3.11 *HIV tests*

HIV-testing, with pre and post test counselling, was offered to all patients presenting with suspected mycobacterial disease. The uptake of HIV testing among patients with suspected mycobacterial disease was greater than 90%. HIV test results were kept confidential to the health service. In accordance with WHO recommendations, HIV-infection was diagnosed if both the screening (Enzymun-Test® Anti-HIV 1+2+subtype O, Boehringer Mannheim Immunodiagnostics) and confirmatory ELISA (IM®$_x$ system HIV-1/HIV-2 III Plus, Abbott diagnostics) tests were positive.

3.12 *Symptoms*

A modified ATS respiratory questionnaire was administered to all study participants at the time of follow-up lung function testing.

3.13 *Occupational history*

Date of first employment and dates of contract renewal were obtained from The Employment Bureau of Africa (TEBA) for each miner. Miners were interviewed at the time of follow-up lung function testing to validate the TEBA occupational history and provide job descriptions for each contract period.

3.14 *Ethics approval*

Ethics approval was obtained from the Anglogold Health Services Medical Ethics Committee and the University of the Witwatersrand Committee for Research on Human Subjects.

3.15 *Data analysis*

SAS (SAS Institute Inc., Cary, NC, USA, Version 8) and STATA 6.0 (STATA Corporation, Texas, USA) software were used for analysis. The outcome variable investigated was change in height adjusted pulmonary function (PF) per year of follow-up, $\Delta PF=PF_{2000} - PF_{1995\text{-}6}$. The adjustment for average height was $PF*(1.69^2/ht^2)$, where ht is the individual's observed height. The General Linear Model (GLM), SAS Proc GLM, was used to compare the adjusted longitudinal differences in pulmonary function by explanatory variables. In all comparisons, adjustment was made for the presence of silicosis at baseline and age, duration of gold mining dust exposure, pack-years of smoking, and asthma at the time of follow up lung function. The adjusted least square means and the 95% Confidence Intervals are presented in the results and tables.

Conditional logistic regression was used to test for a significant difference between paired categorical variables. Results were expressed as odds ratios (OR) with 95% confidence intervals (95% CI) or a significance value (p value). Multiple logistic regression was used to investigate confounding between categorical variables. Likelihood ratio tests were used to test for overall significance for inclusion of each variable in the logistic regression model. Student's t-test was used to test for differences in means of continuous variables between groups.

4 RESULTS

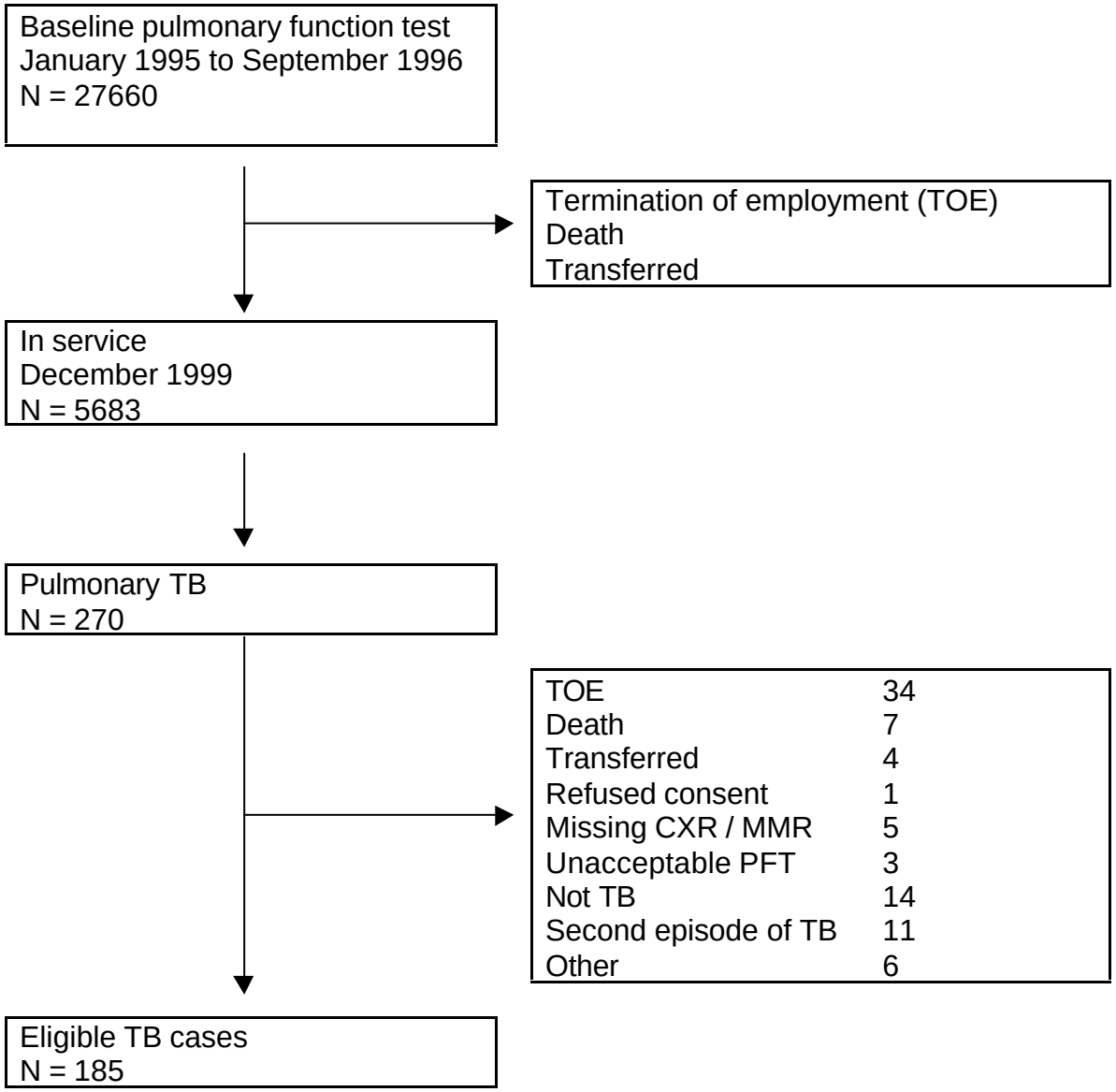
4.1 *Selection of study subjects*

The selection process is shown in Figure 1. During the period of reliable lung function screening between January 1995 to September 1996, 27660 miners had lung function tests, of which 5683 miners were still in service on the 12/12/1999. 270 miners had had an episode of pulmonary TB after the date of the baseline lung function test of whom 185 were eligible for the study. An age matched control, who had not had TB following the date of the baseline lung function, was selected from the computerised payroll records, as outlined in the methods section. Of the 27660 miners in service between January 1995 to September 1996, the mean age of the 270 study subjects, on the 1st January 1996, was slightly younger than that of non study participants (Mean age 39.5 years versus 41.7 respectively, p=<0.0001)

4.2 *Cohort characteristics*

Characteristics of the TB cases and controls at baseline are shown in table 1. There was no significant difference between TB cases and controls with regard to baseline age group, duration of employment and forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and forced expiratory flow (FEF). There were significantly more TB cases with a history of previous TB than controls due to the selection criteria that were applied (23.2% versus 3.2%, p=0.001).

Figure 1. Trial profile.



The prevalence of silicosis at baseline was significantly greater among TB cases compared to controls (p=0.03). A significantly greater proportion of controls had never smoked compared to TB cases (38.4% versus 17.3% respectively, p=0.0001). The length of follow up was slightly longer among controls than TB cases. The majority of the study subjects were working underground at the time of baseline lung function (90.8% [168/185] versus 90.3% [167/185] for TB cases and controls respectively). During the study period, 4 cases and 2 controls were transferred from underground to surface work.

4.3 *Laboratory and radiological characteristics of TB cases*

Of the 185 TB patients, 74.6% were new and the remainder were retreatment cases. Just over half were detected by the radiological screening program (54.6%) and the remainder self presented with symptoms. Of the 168 men who had had an HIV test, 58.3% were positive. Only a minority of patients had evidence of concurrent extra-pulmonary involvement (11.4%). The majority of patients were cured (73.0%), and the remainder completed TB treatment. The majority of TB cases were smear or culture positive at diagnosis (73% [135/185] and 77.3% [143/185] respectively). *Mycobacterium tuberculosis* was isolated in 127 patients. The combined resistance of pre-treatment isolates of *M. tuberculosis* to any of the primary TB drugs was 10.3% [12/116].

Standard sized chest radiographs were available in 184 TB patients at diagnosis and completion of treatment. Extensive radiological disease ($4 zones) was present in a

quarter of patients at diagnosis but occurred significantly less commonly at the end of treatment (25.5% and 15.8% respectively, p=0.002). Cavitatory disease was present in 149 (81%) patients at diagnosis but was considered to be the primary parenchymal disease in only 35 (19%). Among patients who had evidence of cavities, infiltrates, pleural blunting, thickening or effusions at diagnosis, significantly fewer patients had evidence of these abnormalities following completion of treatment (Table 2). In contrast, significantly more patients had evidence of fibrosis, bronchiectasis and hilar elevation following completion of treatment than at the the time of TB diagnosis (Table 2).

The odds of having extensive radiological disease ($4 zones) was significantly greater among TB cases who self presented compared to those detected by the radiological screening programme (OR 2.7, 95% CI 1.4 – 5.4) and among smear positive compared to smear negative patients (OR 7.1, 95% CI 2.1 – 24.1).

4.4 *Factors associated with loss of lung function*

Among *controls* the adjusted average longitudinal loss of lung function was not associated with age, duration of occupational dust exposure, or pack-years of smoking as recorded at baseline (Table 3). Among controls with silicosis (ILO grade $1/1) compared to those without silicosis (ILO grade #1/0) there was a significant decline in FVC (46 versus 6 mls/year, p=0.01) and FEV1 (106 versus 69 mls/year, p=0.02) but not in the FEV1/FVC ratio or FEF (Table 3).

TB cases, compared to controls, had a significantly greater loss of FVC (53 versus 13 mls/year, p<.0001), FEV1 (116 versus 76 mls/year, p<.0001) and FEF (296 mls/year versus 234 mls/year, p=0.001) (Table 4). There was no significant change in the FEV1 / FVC ratio compared to controls. TB cases had a similar mean loss of FEV1 / year to that of controls with silicosis (FEV1; 116 mls / year versus 106 mls / year) (Table 3 and 4, Figure 2). Among TB cases with silicosis compared to those without silicosis the mean loss of FEV1 / year was not significantly different (FEV1 119 versus 115 mls / year) (Figure 2).

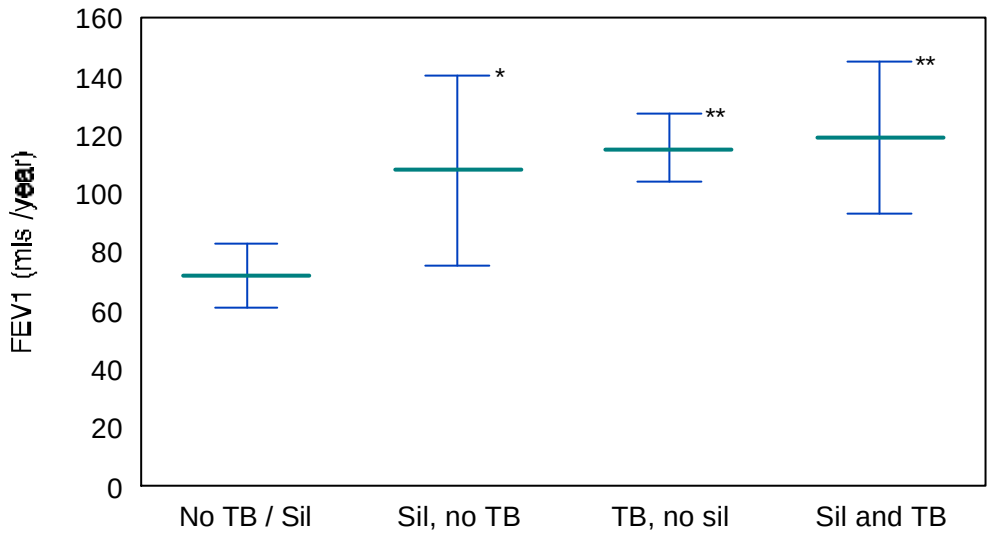


Figure 2. Differences in mean longitudinal loss of FEV1 / year stratified according to presence of silicosis at baseline and an episode of pulmonary TB during the study period. FEV1 adjusted for age, height, duration of employment, smoking history, previous TB history and history of chronic lung disease. * p<0.05, ** p<0.001. Sil = silicosis.

4.5 *Factors associated with loss of lung function among TB cases*

The adjusted mean loss of lung function among TB cases according to clinical characteristics (treatment category, site of disease, method of detection, treatment outcome, HIV status and duration of follow up from date of TB diagnosis) are shown in table 4. The adjusted mean loss of lung function according to bacteriological status and radiological characteristics at diagnosis and end of treatment are shown in tables 5, 6 and 7 respectively.

4.5.1 Clinical variables

TB cases who self presented with symptoms had a significantly greater loss of FVC and FEV1 compared to those detected by the radiological screening programme (FVC: 69 mls versus 39 mls, p=0.009 and FEV1: 131 mls versus 102 mls, p=0.008, respectively) (Table 4). None of the other clinical variables i.e., treatment category, site of disease, treatment outcome, HIV status at diagnosis of TB and duration of follow up after TB diagnosis were associated with loss of lung function (Table 4).

4.5.2 Bacteriological status

Sputum smear positive TB cases, compared to smear negative cases, had a significantly greater mean loss of FVC, FEV1 and FEF (Table 5) (FVC: 64 mls/yr versus 26 mls/yr, p=0.003; FEV1: 129 mls/yr 95% versus 89 mls/yr, p=0.001**;** FEF: 317 mls/year versus 244 mls/year, p=0.009). Smear negative cases did not have a significantly greater loss of FEV1 than did controls (89 mls/year versus 76 mls/year, p=0.2) (Tables 4 and 5). Culture positive cases did not have a significantly greater

loss of lung function than did culture negative cases (Table 5). Drug resistant cases were not associated with a greater loss lung function than fully susceptible cases (Table 5).

4.5.3 Pattern and severity of radiological TB disease

Extensive radiological TB disease (zone score $4) compared to less extensive TB disease (zone score #3) at diagnosis was associated with significantly greater loss of FEV1 (153 mls/year versus 103 mls/year, p<0.0001) and FEF (389 mls/year versus 265, p<0.0001) (Table 6). There was a significantly greater decline in the FEV1 / FVC ratio among cases with extensive disease compared to cases with less extensive disease (2.6%/yr versus 1.6%/yr, p<0.0001) (Table 6). Extensive scarring at the end of treatment was also associated with significantly greater loss of FEV1 (p=0.03) and FEF (p=0.02) than was less extensive scarring (Table 7).

TB cases who had radiological evidence of bronchiectasis at diagnosis or at the completion of treatment, compared to those TB cases who did not, had a significant reduction in FEV1 (at diagnosis; 142mls/year versus 108 mls/year, p=0.01 and completion of treatment; 143mls/year versus 104 mls/year, p=0.0009) (Table 6 and 7). Similarly, among cases with bronchiectasis at diagnosis and at end of treatment there was a significant decline in the FEV1 / FVC ratio compared to those cases without bronchiectasis (At diagnosis; 2.4%/yr versus 1.7%/yr, p=0.005; at end of treatment: : 2.2%/yr versus 1.7%/yr, p=0.03, respectively (Table 6 and 7).

Among TB cases, none of the radiological patterns of disease was associated with a significantly greater loss of lung function at diagnosis or at completion of treatment (Table 6 and 7). The presence of pleural abnormalities at the end of treatment, compared to their absence, was associated with a significant decline in FEV1 (127 mls/year versus 99 mls/year, p=0.01) and FEV1/FVC ratio (21% versus 16%, p=0.02). The presence or absence of pleural abnormalities at diagnosis was not associated with loss of lung function (Table 6).

4.6 *Pattern of lung function abnormality and compensation*

The proportion of TB cases and controls that had obstructive and restrictive lung functions at baseline and follow up are shown in Table 8. There was no significant difference in the proportion of cases and controls that had obstructive or restrictive lung functions at baseline. At follow up, the proportion of TB cases and controls that had obstructive lung functions had increased significantly from baseline ($p<0.0001$ for both). There was, however, no significant difference at follow up in the proportion of TB cases and controls that had obstructive lung functions (p=0.5).

Among *controls*, at follow up, current smokers had significantly greater odds of obstruction than non-smokers (adjusted OR 4.3, 95% CI 1.3 – 9.3, p=0.007). None of the other factors adjusted for, i.e., age group, employment category and silicosis status, were significantly associated with obstruction among controls.

TB cases older than 40 years had a significantly greater odds of obstruction compared to those younger than 40 years of age (adjusted OR 3.4, 95% CI 1.4 –

10.6, p=0.02). Extent of radiological disease at diagnosis, but not at follow up, was significantly associated with obstruction at follow up (Adjusted OR 2.9, 95% CI 1.1 – 8.2, p=0.04). None of the other factors adjusted for, i.e., silicosis status, employment category, smear status, method of detection and smoking category was significantly associated with obstruction among TB cases.

TB Cases had a significantly greater odds of restriction at follow up than controls (Adjusted OR 10.3, 95% CI 1.3 – 88.7, p=0.03). There were no exposure or clinical factors among TB cases that were associated with greater odds of restriction.

At follow up, TB cases were significantly more likely to be eligible for compensation for occupational lung disease under the Occupational Diseases in Mines and Works Act than controls based on a criterion of having an FEV1 $_{\text{percentage predicted}}$ #65% or an FEV1/FVC ratio <65%, (20.5% versus 8.7% respectively; adjusted OR 2.4, 95% CI 1.2 - 4.9, p=0.02).

4.7 *Association between TB and respiratory symptoms*

TB cases compared to controls, at the time of follow up lung function testing, had significantly greater odds of having symptoms of cough (p=0.007), breathlessness (p=0.07) and wheezing (p=0.006), but not production of phlegm (0.07) (Table 9). Among TB cases none of the clinical variables, bacteriological status or extent of radiological disease were associated with a significantly greater odds of respiratory symptoms (Tables 10, 11, 12).

5 DISCUSSION

5.1 *Summary of results*

The association between TB and loss of lung function has been studied in cross sectional (1, 2, 3, 4, 6, 7, 13, 16) and cohort studies (5, 17, 18). TB has been associated with a reduced FEV1 and FVC at diagnosis (1, 2, 3, 5, 16, 17), during treatment (4), end of treatment (5, 16, 17) and with long term follow up (6, 7, 18). A positive relationship between extent of radiological disease and rate of decline in FEV1 has been shown in numerous studies (1, 2, 5, 6, 7, 17). This is the first study to report changes in lung function comparing spirometric values preceding and following an episode of pulmonary TB in contrast to age matched controls without TB followed up for the same period.

Pulmonary TB was an important cause of loss of lung function, after controlling for other exposure variables associated with loss of lung function, and with respiratory symptoms post treatment. The rate of loss of lung function was directly related to the extent of radiological disease at diagnosis and end of treatment. Loss of lung function was also independently associated with self-presentation and sputum smear positive status, both of which were associated with extensive radiological disease at diagnosis. Significantly more cases had restrictive lung functions, but not obstructive lung functions compared to controls at follow up.

5.2 *Limitations*

A large proportion of miners who were screened in 1995 / 1996 were no longer in employment at the time of follow up. This may have resulted in a healthy survivor effect particularly among the older miners. As a result the loss of lung function due to TB may have been underestimated. The baseline lung functions were done as part of the routine annual medical examination whereas the follow up lung functions were done under research conditions. It is suspected that the FVC at baseline was not measured at full expiration, which would have resulted in a smaller FVC than would have been anticipated, and subsequently the loss of FVC would have been overestimated. This would also have resulted in a larger FEV1 / FVC ratio than expected and as a consequence the proportion of patients with obstructive lung function impairment at baseline may have been underestimated.

5.3 *TB and loss of lung function*

The relationship between radiological extent of TB disease and loss of FEV1 and FVC has been reported in cross sectional studies at the time of diagnosis (1, 2), during treatment (4) and with long term follow up (6, 7). Cohort studies have shown that the FEV1 and FVC are significantly reduced at the time of TB diagnosis but show significant improvement by the end of short course chemotherapy (5, 17). However, patients, particularly those with more extensive disease at diagnosis, may be left with chronic residual radiological changes and airflow limitation at the end of treatment (5), which may continue to progress despite bacteriological cure (18). The extent of radiological TB disease is thought to reflect the extent of endobronchial TB disease, which results in airflow limitation (7, 17). Our results confirm and expand the

finding of previous studies by quantifying the decline in FEV1 and FVC from baseline lung functions among TB patients in comparison to age matched controls. After controlling for other exposure variables, TB patients in contrast to controls, have an additional loss of FEV1 and FVC of 40mls/year each.

Furthermore, new insights into the interrelationship of extent of disease, method of detection and smear status are presented. Patients who self presented, compared to those who were detected by the radiological screening programme, and those who were sputum smear positive had significantly greater loss of FEV1 and FVC. Self presentation and sputum smear positive status were in turn independently associated with extent of disease at diagnosis.

5.4 *Obstructive and restrictive airways disease*

TB associated with obstructive airways disease has previously been described at diagnosis (1, 2, 3, 5), during treatment (4), end of treatment (5) and with long term follow up (6, 7, 18). The prevalence of obstruction has varied from 28% to 68% according to study design, timing of assessment and medical or surgical treatment. A surprising but common finding has been that a positive smoking history among TB patients has not been associated with obstruction (4, 5, 7). , Age greater than 40 years has been associated with obstruction (3). Extensive radiological disease has not consistently been associated with obstruction (5).

The prevalence of obstruction among TB patents in our study at follow up was similar to that reported in another cohort study at the end of treatment (5). Among TB patients in the present study, age greater than 40 years and extensive radiological disease at diagnosis, but not smoking history, were associated with obstruction. Among controls, current smokers had significantly greater odds of obstruction than non-smokers. The contribution of smoking to obstructive airways disease among controls and the dominant effect of TB among cases to the development of obstructive airways disease, may explain why there was no significant difference in the prevalence of obstruction between cases and controls.

The prevalence of restriction among TB cases at follow up in this study was lower (8.7%) than that reported by two other South African studies at the end of treatment (24%) (5) and with long term follow up (15%) (7). In our study, there was a significant difference in the prevalence of restrictive airways disease between cases and controls. TB as a risk factor for restrictive lung disease has largely been ignored. Whereas endobronchial TB is thought to be the dominant causative mechanism of obstruction, restrictive lung functions probably occur when post inflammatory fibrosis (lung and pleural) dominate over endobronchial and emphysematous changes. Controls are unlikely to have had an exposure, other than dust, predisposing them to interstitial fibrosis and consequently had less restrictive lung disease.

As the odds of being eligible for compensation, based on lung function criteria, among TB cases was 2.4 fold greater than that of controls, as a matter of policy all TB cases should have a lung function assessment following completion of treatment.

A cohort study of TB patients who had completed TB treatment and been followed up for 15 years showed that the proportion of patients who developed obstruction progressed significantly over time (18). This has important implications for compensation assessment of former miners with a history of occupational TB.

5.5 *Silicosis and airflow limitation*

Silicosis, in this study, was associated with a similar loss of FEV1 and FVC as that of a an episode of pulmonary TB. In contrast to a previous cross-sectional study done in this mining population which found an additive effect of silicosis and TB on loss of FEV1 (13), there was no significant difference between TB patients with or without silicosis and loss of FEV1 per year. This may be attributable to the small sample size and the fact that the current study was not designed to detect a significant difference between the two.

The specific influence of silicosis on loss of lung function in this population of gold miners has previously been evaluated in a cross sectional (19) and cohort study (14). The cohort was followed up for 5 years after recruitment. Men with silicosis on entry lost 87 mls / year (unadjusted for age) of FEV1 compared to 37 mls / year among miners without silicosis on entry. Among a cohort of granite workers from Hong Kong with simple or complicated silicosis followed up for 10 years, the annual loss of FEV1 was 79 mls / year (20). Granite workers with radiological progression of silicosis compared to those with static silicosis had significantly greater annual loss of FEV1. The annual loss of FEV1 / year among silicotic patients without TB (106 mls / year, 95% CI 77-135) in the present study, adjusted for age and exposure

variables, was similar to that reported for the previous two studies. A limitation of the current study was that progression of silicosis was not controlled for.

The difference between the annual loss of FEV1 (adjusted for age) among miners without silicosis in this study and that found in similar group in a related cohort study (14) is significantly different (69 mls / year, 95% CI 60-79 versus 13 mls/year respectively). Although undetected silicosis due to the use miniature radiographs may be a possible explanation this is unlikely to be a major reason. In a previous study, among former Black miners from the same study site, the correlation between radiological and autopsy diagnosis of silicosis using mini chest radiographs (15) was better than that achieved comparing standard sized chest radiographs with autopsy diagnosis among former White miners (21). The difference between the findings of this study and that of the cohort study remains unexplained.

5.6 *TB, prevention and control*

Among South African gold miners the incidence of TB is greater than 2000 per 100,000 employees per year. The cumulative incidence of TB among currently employed miners is estimated to be 20% (unpublished data). The high prevalence of two powerful risk factors in the workforce, namely silicosis and HIV and their combined effects, which are multiplicative, are responsible for the high incidence of TB (10). Silicosis is also associated with a significant loss of lung function that is similar to that associated with an episode of TB (14, 19, 20, 22).

TB is therefore a common cause of airflow limitation among South African gold miners. Strategies to improve lung health among miners should focus on interventions that will lead to improved TB control. Intensifying dust control and HIV prevention programmes would lead to a decrease in the prevalence of silicosis and HIV-infection and reduced susceptibility to TB. Improved dust control would have the added benefit of reducing the occurrence of chronic airflow limitation associated with chronic dust exposure and silicosis (Figure 3). Introduction of tobacco control programmes are required to reduce the prevalence of tobacco associated chronic obstructive airways disease.

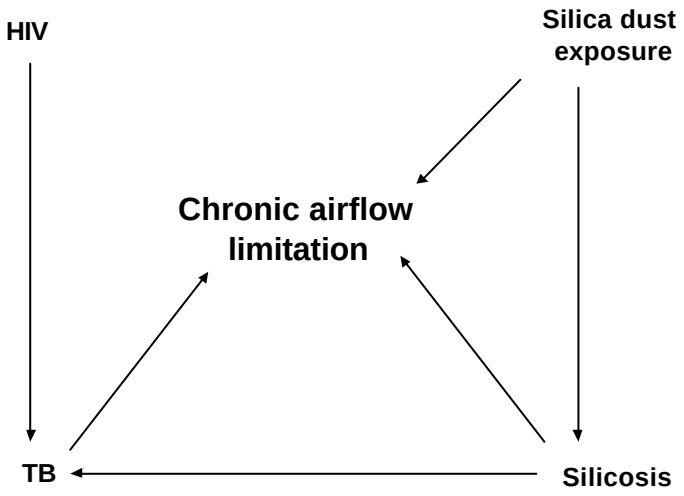


Figure 3. Association between TB, silicosis, HIV and chronic airflow limitation.

Isoniazid preventive therapy (IPT) targeted to miners with silicosis or HIV infection would reduce the risk of developing TB by more than half (23, 24). Miners who receive IPT are therefore less likely to develop chronic airflow limitation that is associated with an episode of TB.

The extent of radiological TB disease has consistently been shown to be an important predicator of loss of lung function. In this study miners who were detected by the radiological screening programme or who had sputum smear negative TB had significantly less extensive disease and airflow limitation. Interventions to detect TB earlier, with less extensive disease, would reduce the risk of developing significant airflow limitation among miners who develop TB. The current radiological screening programme should be maintained. Educational campaigns to improve awareness of TB symptoms among miners and health care staff, to promote earlier presentation and diagnosis, may be of benefit.

5.7 *Conclusion*

TB occurs with a high incidence among South African gold miners and is associated with a significantly greater lung function loss compared to age matched controls. Early detection and treatment of TB are important measures to reduce the likelihood of developing chronic airflow limitation among TB patients. Intensification of dust control and HIV prevention programmes are required to reduce the prevalence of silicosis and HIV infection in the workforce. Miners with silicosis and HIV infection should be offered TB preventive therapy.

Table 1. Cohort characteristics at baseline: cases and controls

	TB cases		Controls		
	N	% / SD	N	% / SD	P value
Age group (years)					
Mean	39.4	(6.5)	39.3	(6.4)	0.9
<30	16	(8.6)	16	(8.6)	
30-39	79	(42.7)	83	(44.9)	
40-49	84	(45.6)	79	(42.7)	
$50	6	(3.2)	7	(3.8)	
Duration of employment (years)					
Mean	18.1	(7.5)	17.5	(7.6)	0.5
<10	31	(16.8)	31	(16.8)	
10-19	68	(36.8)	78	(42.2)	
20-29	77	(41.6)	66	(35.7)	
$30	9	(4.9)	10	(5.4)	
Past TB history					0.001
No	142	(76.8)	179	(96.8)	
Yes	43	(23.2)	6	(3.2)	
Silicosis					0.03
None	151	(81.6)	165	(89.2)	
Present	34	(18.4)	20	(10.8)	
Smoking history (pack years)					
None	32	(17.3)	71	(38.4)	0.0001
1-9	131	(70.8)	97	(52.4)	
10-19	17	(9.2)	11	(5.9)	
$20	5	(2.7)	6	(3.2)	
Baseline PFT's (mean)					
FVC	4.112	(0.57)	4.118	(0.55)	0.91
FEV1	3.411	(0.59)	3.414	(0.50)	0.95
FEF	3.810	(1.38)	3.706	(1.15)	0.43
FEV1 / FVC %	82.9	(0.08)	82.9	(0.06)	0.92
Mean follow up (years)	4.5	(0.5)	4.7	(0.5)	0.002

Height standardised

Table 2. Radiological abnormalities at diagnosis and completion of treatment among TB cases.

Radiologcal abnormality	At diagnosis		End of treatment	
	N	**(%)**	**N**	**(%)**
Total	184	(100)	184	(100)
Extent of disease	47	(25.5)	29	(15.8)
$4 zones				
Parenchymal				
Primary				
Cavities	35	(19.0)	11	(6.0)
Fibrosis	5	(2.7)	119	(64.7)
Infiltrates	122	(66.3)	15	(8.2)
Nodules	13	(7.1)	17	(9.2)
Secondary				
Cavities	119	(64.7)	67	(36.4)
Fibrosis	12	(6.5)	72	(39.1)
Infiltrates	31	(16.8)	3	(1.6)
Nodules	13	(7.1)	20	(10.9)
Bronchiectasis	45	(24.5)	57	(31.0)
Pleural abnormalities				
Present	120	(65.2)	111	(60.3)
Blunting	62	(33.7)	49	(26.6)
Effusion / thickening	19	(10.3)	7	(3.8)
Apical caps	94	(51.1)	93	(50.5)
Central structures				
Tracheal deviation	12	(6.5)	19	(10.3)
Hilar elevation	23	(12.5)	41	(22.3)
Mediastinal shift	3	(1.6)	5	(2.7)
Thoracic lymphadenopathy	86	(46.7)	83	(45.1)
Pericardial effusion	29	(15.8)	32	(17.4)

=<0.05, p<0.01, p<0.001, p<0.0001 Blunting of costophrenic angle

Table 3. Adjusted mean difference in lung function per year among controls according to personal and exposure characteristics

	FVC (mls/yr)		FEV1(mls/yr)		FEV1/FVC Ratio (% / yr)		FEF (mls/yr)	
	M	95%CI	M	95%CI	M	95%CI	M	95%CI
Age group (Yrs)								
<30	29	64-+6	97	63-131	1.6	1.0-2.2	236	152-321
30-39	14	29-+10	70	56-85	1.4	1.2-1.7	221	186-257
40-49	6	22-+1	72	57-88	1.7	1.5-2.0	245	206-284
50+	21	29-+71	70	21-119	2.2	1.3-3.0	292	173-412
Exp Dur (Yrs)								
<10	21	61-+18	70	32-109	1.3	0.6-1.9	267	172-362
10-19	15	33-+4	75	57-93	1.6	1.3-1.9	221	177-265
20-29	6	20-+9	74	60-88	1.8	1.5-2.0	239	205-273
30+	11	40-+17	70	42-99	1.4	0.9-1.9	242	173-311
Smoking (Pack yrs)								
0	+8	26-+41	49	16-81	1.2	0.7-1.8	194	114-274
1-9	24	47-0	94	71-116	2.0	1.6-2.3	271	216-327
10-19	33	71-+6	83	46-121	1.4	0.8-2.1	237	145-330
20+	+10	36-+56	53	9-98	1.5	7-2.3	209	99-320
Silicosis								
No	6	16-+4	69	60-79	1.6	1.4-1.8	233	210-256
Yes	46	16-76	106	77-135	1.9	1.4-2.4	256	184-327

M = mean difference in lung function, Yrs = years, Exp Dur = exposure duration

Indicates a negative value unless prefaced by a + sign.

At baseline

Table 4. Mean loss in lung function per year according to TB clinical variables adjusted for age, height, duration of employment, smoking history, grade of silicosis, previous TB history and history of chronic lung disease.

	FVC (mls/yr)		FEV1 (mls/yr)		FEV1/FVC Ratio (%/yr)		FEF (mls/yr)	
	M	95%CI	M	95%CI	M	95%CI	M	95%CI
TB								
No	13	2-25	76	65-87	1.7	1.5-1.9	234	209-260
Yes	53	42-64	116	105-126	1.9	1.7-2.1	296	271-321
Treatment category								
New	51	39-64	111	99-124	1.8	1.5-2.0	295	267-324
Retreatment	60	38-83	131	110-152	2.2	1.8-2.6	288	238-338
Site of disease								
PTB	51	40-64	116	105-128	1.9	1.7-2.1	298	271-325
PTB+ETB	64	31-96	108	78-140	1.6	1.0-2.1	282	209-354
How detected								
RSP	39	24-54	102	88-116	1.7	1.4-2.0	283	249-317
Self	69	52-86	131	115-146	2.0	1.7-2.3	308	270-345
Treatment outcome								
Cured	47	34-60	107	95-120	1.8	1.5-2.0	286	256-315
Completed	68	46-89	136	116-157	2.0	1.6-2.4	322	274-370
HIV status								
Negative	65	48-83	122	106-139	1.8	1.4-2.1	301	261-341
Positive	47	32-62	116	101-130	2.0	1.7-2.3	306	271-341
Duration of follow up								
<2 years	65	34-96	123	94-152	1.8	1.3-2.4	338	270-407
$2 years	51	39-63	114	103-126	1.8	1.6-2.1	289	262-316

N = number, M = mean loss in lung function / year

PTB = pulmonary TB alone, PTB+ETB = Pulmonary and extra pulmonary TB

Self = self presentation, RSP = radiological screening programme

= Duration of follow up from date of TB diagnosis.

Episode of TB during study period, No = controls, Yes = TB cases

Table 5. Mean loss of lung function per year according to mycobacterial status adjusted for age, height, duration of employment, smoking history, grade of silicosis, previous TB history and history of chronic lung disease.

	FVC (mls/yr)		FEV1 (mls/yr)		FEV1/FVC Ratio (%/yr)		FEF (mls/yr)	
	M	95%CI	M	95%CI	M	95%CI	M	95%CI
Culture								
Negative	36	10-62	105	81-130	1.9	1.4-2.3	268	210-326
Positive	57	44-70	117	105-129	1.8	1.6-2.0	300	271-329
Smear								
Negative	26	5-47	89	69-109	1.7	1.3-2.1	244	198-290
Positive	64	51-78	129	116-141	2.0	1.7-2.2	317	288-346
Drug resistance								
F/S	51	36-65	111	98-124	1.8	1.5-2.0	286	252-320
DR	33	6-72	92	56-128	1.8	1.1-2.5	272	177-367

N = number, M = mean loss in lung function / year

F/S = fully susceptible, DR = drug resistant

Table 6. Mean loss in lung function per year according to radiological pattern and extent of disease at diagnosis adjusted for age, height, duration of employment, smoking history, grade of silicosis, previous TB history and history of chronic lung disease.

	FVC (mls/yr)		FEV1 (mls/yr)		FEV1/FVC Ratio (%/yr)		FEF (mls/yr)	
	M	95%CI	M	95%CI	M	95%CI	M	95%CI
Zone score								
#3	48	35-61	103	92-115	1.6	1.4-1.8	265	237-293
$4	69	47-92	153	132-174	2.6	2.2-3.0	389	341-438
Radiological pattern								
None	34	16-84	69	22-116	1.1	0.2-2.0	206	95-316
Cavities	52	27-78	123	99-147	2.1	1.7-2.6	297	241-354
Fibrosis	64	6-122	136	82-191	2.5	1.5-3.5	236	108-364
Infiltrates	55	41-69	115	102-129	1.7	1.5-2.0	308	277-339
Nodular	46	6-86	120	83-159	2.5	1.8-3.2	278	189-366
Bronchieactasis								
No	51	38-63	108	96-120	1.7	1.5-1.9	285	256-313
Yes	62	38-86	142	119-164	2.4	2.0-2.8	336	283-390
Pleural abnormalities								
No	50	31-69	105	87-123	1.5	1.2-1.9	272	230-313
Yes	55	41-69	122	108-135	2.0	1.8-2.3	310	278-341

N = number, M = mean loss in lung function / year

Extent of radiological abnormalities regardless of cause

Predominant parenchymal pattern

Table 7. Mean loss in lung function per year according to radiological pattern and extent of disease at completion of treatment adjusted for age, height, duration of employment, smoking history, grade of silicosis, previous TB history and history of chronic lung disease.

	FVC (mls/yr)		FEV1 (mls/yr)		FEV1/FVC Ratio (%)		FEF (mls/yr)	
	M	95%CI	M	95%CI	M	95%CI	M	95%CI
Zone score								
#3	50	38-62	111	99-122	1.8	1.6-2.0	282	255-310
$4	71	43-99	143	116-169	2.3	1.8-2.8	366	304-429
Radiological pattern								
None	30	2-62	94	64-124	1.8	1.2-2.4	275	204-346
Cavities	53	10-96	91	50-131	1.4	0.6-2.2	230	135-325
Fibrosis	56	42-70	122	108-135	1.9	1.6-2.2	309	278-341
Infiltrates	31	6-67	95	60-130	1.8	1.1-2.5	226	144-308
Nodular	86	48-123	141	106-177	2.0	1.3-2.7	342	258-426
Bronchieactasis								
No	45	32-59	104	91-117	1.7	1.5-2.0	276	246-305
Yes	71	51-92	143	124-163	2.2	1.8-2.6	344	298-390
Pleural abnormalities								
No	44	27-62	99	83-116	1.6	1.2-1.9	280	241-319
Yes	59	44-74	127	113-141	2.1	1.8-2.3	307	274-340

N = number, M = mean loss in lung function / year

Extent of radiological abnormalities regardless of cause

Predominant parenchymal pattern

Table 8. Proportion of TB cases and controls that had obstructive and restrictive lung functions at baseline and follow up.

	Baseline				Follow up			
	Cases		Control		Cases		Control	
	N	(%)	N	(%)	N	(%)	N	(%)
Obstruction	13	(7.0)	6	(3.2)	52	(28.1)	37	(20)
Restriction	13	(7.0)	7	(3.8)	16	(8.7)	3	(1.6)
Normal	159	(86)	172	(93)	117	(63.2)	144	(77.8)

Table 9. Unadjusted and adjusted odds ratios for associations between TB and respiratory symptoms.

	Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI
Cough	2.4	1.3-4.2	2.4	1.3 - 4.6
Phlegm	1.7	1.0-2.9	1.8	1.0-3.2
Breathlessness	2.4	1.4-4.1	2.7	1.4-5.2
Wheezing	2.3	1.3-3.8	2.3	1.3-4.1

Adjusted for age group, presence of silicosis and duration of employment at baseline and smoking status at follow up.

Table 10. Odds ratios for the association between respiratory symptoms and TB, according to clinical variables.

	Cough		Phlegm		Breathlessness		Wheezing	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Treatment group								
No TB	1		1		1		1	
New	2.1	1.2-3.7	2.0	1.1-3.6	2.6	1.5-4.6	2.2	1.2-3.9
Recurrent	2.2	1.1-4.8	1.4	0.6-3.5	2.0	0.9-4.3	3.0	1.4-6.3
Site of disease								
No TB	1		1		1		1	
PTB	2.1	1.2-3.6	1.8	1.0-3.2	2.4	1.4-4.0	2.1	1.2-3.7
PTB+ETB	2.9	1.1-7.9	2.2	0.7-6.6	3.2	1.2-8.7	4.8	1.8-12.6
How detected								
No TB	1		1		1		1	
RSP	1.6	0.9-3.0	1.7	0.9-3.4	2.1	1.1-3.9	2.1	1.1-3.9
Self	3.2	1.7-5.8	2.1	1.0-4.1	3.1	1.6-5.8	2.9	1.5-5.5
Treatment outcome								
No TB	1		1		1		1	
Cured	2.0	1.1-3.5	1.7	0.9-3.1	1.9	1.1-3.4	2.3	1.3-4.0
Completed	3.0	1.4-6.1	2.4	1.1-5.2	3.7	1.8-7.6	3.0	1.4-6.2
HIV status								
No TB	1		1		1		1	
Negative	2.5	1.3-4.8	1.6	0.8-3.4	1.3	0.6-2.8	2.2	1.1-4.4
Positive	2.2	1.2-4.1	2.0	1.1-3.9	3.1	1.7-5.6	2.6	1.4-4.7
Duration of follow up								
No TB	1		1		1		1	
<2 ys	2.4	0.9-6.4	1.4	0.4-4.5	0.6	0.1-2.6	1.7	0.6-4.9
$2 ys	2.1	1.2-3.7	1.9	1.1-3.4	2.8	1.6-4.8	2.5	1.4-4.3

PTB = pulmonary TB alone, PTB+ETB = Pulmonary and extra pulmonary TB

Table 11. Odds ratios for the association between extent of radiological disease and respiratory symptoms at diagnosis and completion of TB treatment

	Cough		Phlegm		Breathlessness		Wheezing	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Zone score before treatment								
No TB	1		1		1		1	
<=3	2.0	1.1-3.5	1.7	0.9-3.1	2.3	1.3-4.0	2.3	1.3-4.1
>=4	2.7	1.3-5.7	2.2	1.0-4.8	3.0	1.4-6.3	2.5	1.1-5.3
Zone score after treatment								
No TB	1		1		1		1	
<=3	1.9	1.1-3.3	1.5	0.9-2.8	2.2	1.3-3.8	2.3	1.3-4.0
>=4	4.1	1.8-9.6	3.7	1.5-9.0	3.9	1.7-9.2	2.9	1.2-7.0

Table 12. Odds ratios for the association between respiratory symptoms and TB bacteriological status.

	Cough		Phlegm		Breathlessness		Wheezing	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Sputum direct								
No TB	1		1		1		1	
Neg	2.5	1.2-5.2	1.6	0.7-3.6	3.0	1.5-6.2	3.3	1.6-6.8
Pos	2.1	1.2-3.6	1.9	1.1-3.5	2.2	1.3-4.0	2.1	1.2-3.7
Sputum culture								
No TB	1		1		1		1	
Neg	1.8	0.7-4.4	0.7	0.2-2.4	1.7	0.7-4.2	1.4	0.5-3.6
Pos	2.1	1.2-3.7	2.0	1.1-3.7	2.8	1.6-4.8	2.7	1.5-4.6

Neg = Negative, Pos = positive

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