Safety in Mines Research Advisory Committee

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A Randomized Controlled study of the effectiveness of annual and 6-monthly screening with mass miniature radiography (MMR) for the active case-finding of cardiopulmonary TB patients

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EXECUTIVE SUMMARY

Background
Despite an expanded tuberculosis (TB) control programme, TB incidence rates in the gold mining industry have risen progressively during the 1990s to levels of over 3,000 per 100,000 men per year. Deaths while on TB treatment now account for twice as many deaths among gold miners each year than deaths from mine accidents. The increase in TB case and fatality rates among South African gold miners corresponds with the evolving HIV epidemic.

The mining industry has used a radiological screening programme (RSP) to screen for pneumoconioses and mycobacterial diseases for decades. In a gold mining workforce, in the Free State Province, the proportion of TB cases detected by the RSP declined from 77% in 1990 to 49% in 1996. Although radiological screening has been used for decades, the efficacy of the RSP has never been formally evaluated. Both 6-monthly and annual radiological screening were used in different companies and no data were available as to which approach was the more effective, particularly with an emerging HIV epidemic in the workforce.

Aim
The aim of this study was to determine the effectiveness of 6-monthly compared to annual radiological screening.

Methods
Study design
This was a randomised controlled trial. Study participants were individually randomised into one of two arms comparing 6-monthly (intervention arm) with annual screening (control arm) over a period of two years.

Study site and population
The study was conducted among employees, who derive their health benefit from the company provided health service (group 3-8), at a single gold mining company in the Free State Province of South Africa.

Results
A total of 22634 miners were randomised to the intervention or control arms. Of those individuals randomised, 2.7% (622/22634) were excluded from analysis, leaving 10997 and 11015 miners in the intervention and control arms respectively.

Almost a third of miners were lost to follow up, largely due to retrenchments. The two groups were similar with respect to median age, occupational group, duration of follow up and proportion lost to follow up and reason for loss to follow up.

The proportion of TB cases detected by the RSP was similar in the control and intervention arms (28% and 29% respectively, p=0.67). The proportion of sputum culture positive pulmonary TB cases, detected by the RSP or self

presentation, that were smear negative did not differ significantly between the control or intervention arms (16% and 14% respectively, p=0.56).

The prevalence of TB detected through the RSP was not significantly different between the intervention and control arms at the time of the final annual screening radiograph (0.65% [46/7075] and 0.91% [65/7111] respectively, p=0.07). TB incidence was similar in the control and intervention arms (2.72 and 2.90 per 100 per years respectively, p=0.3).

The mortality rate during the first two months of TB treatment was significantly lower in the intervention arm compared to the control arm (10.1 and 22.5 per 100 person years respectively, unadjusted hazard ratio 0.45 [0.22 – 0.92], p=0.024). The mortality rate, from TB diagnosis to end of follow up, was significantly reduced in the intervention arm compared to the control arm (Control arm: 19.0 per 100 person years and Intervention arm: 14 per 100 person years, unadjusted hazard ratio 0.73 [95% CI 0.55 – 0.97], p=0.03).

TB cases in the intervention arm, compared to the control arm, had less extensive radiological disease (based on zone score) at diagnosis (p=0.05), but not at the end of TB treatment (p=0.7)

Discussion

This large individually randomised study, comparing radiological screening once a year to twice a year, has failed to demonstrate a significant difference in the proportion of TB cases detected by the intensified RSP, but did demonstrate a significant reduction in the mortality rate during the first two months of TB treatment. Although the proportion of TB cases detected by the radiological screening programme has decreased over the past decade in parallel with the increasing HIV epidemic, a sizeable proportion of TB continues to be detected by the RSP. Companies doing 6-monthly radiological screening should continue to do so and those using annual radiological screening should consider the cost benefit of deaths averted by doing 6-monthly radiological screening. Intensification of the active case-finding programme through the use of a screening tool with a high sensitivity, such as sputum cultures, warrants further investigation.

ACKNOWLEDGEMENTS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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.

Incidence Rate =   Number of new cases
Total person-time at risk

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.

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.

Prevalence: The proportion of individuals in a population who have a given disease at a specified point in time.

Prevalence =   Number of Cases
Study Population

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

Self presentation: Detection of TB disease when a person presents spontaneously with signs or symptoms to the health service

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)

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).

1 BACKGROUND

1.1 Tuberculosis among southern African gold miners

Gold mining has been an economically important industry in South Africa from the early part of the 20th century. The industry relies on a combination of state-of-the-art technology to ventilate and cool the largest and deepest mines in the world, together with labour intensive drilling and ore collection techniques. Silicosis is a common occupational hazard in South African gold miners, and a potent risk factor for tuberculosis (TB) [1, 2, 3, 4, 5, 6, 7]. With the advent of the HIV epidemic, South African miners now have high prevalence rates of two of the most powerful risk factors for developing TB disease following infection [7, 8] and their combined effect is multiplicative [7]. As a result, HIV is exacerbating (rather than replacing) silica-associated TB. Although difficult to quantify, it is highly likely that the congregate living and social conditions facilitate TB transmission within the workforce. Crowding, and sharing of bedrooms, has been identified as a risk factor for TB in many settings [9]. Exclusively adult male crowding, as occurs in hostels, is likely to be a much greater risk factor than mixed age and sex crowding, since population surveys have shown the prevalence of infectious TB to be much higher in adult males than females, and much higher in adults than children [10, 11, 12].

Incidence rates of TB in gold miners have been unusually high since the early days of the industry [1], but were contained at stable rates of around 500 to 1,000 per 100,000 employees per year until recently by an intensive TB control programme [13]. The programme was unusual in having an active TB case-finding component, annual chest radiography of all employees, as well as more standard passive case-finding and treatment. Diagnosis of TB in men presenting symptomatically (passive case finding), or detected by the active radiological screening programme (active case finding), is based as far as possible on serial sputum smear examination and mycobacterial cultures. TB is only diagnosed in bacteriologically-negative cases if there has been radiological progression unresponsive to standard antibiotics. Treatment is with short course rifampicin-based regimens, administered at the workplace as directly observed therapy using fixed combination tablets.

Despite these measures, TB case rates in this work force have risen progressively during the 1990s from a previously high but stable rate of 600 to 700 per 100,000 men per year to present levels of over 3,000 per 100,000 men per year [13, 14]. Until recently, TB was the second largest cause of mortality amongst mine workers [15], but deaths from TB now exceed deaths from mine accidents. The increase in case rates among South African gold miners corresponded with the early stages of the South African HIV epidemic, which is one of the worst in the world [16]. With such an extreme epidemic there is now pressing need to improve TB control in miners.

1.2   Active case-finding among South African gold miners

The mining industry has used mass miniature radiography (MMR) to screen for pneumoconioses and mycobacterial diseases for decades. In a gold mining company in the Free State region for the period 1990 -1996, the rate of new pulmonary TB detected by the radiological screening programme (RSP) did not increase significantly (623 to 702 per 100,000 population), whereas the rate of self presentation with symptoms increased significantly from 185 to 732 / 100,000 (p < 0.001) (Figure 1). The proportion of TB cases detected by the RSP declined from 77% in 1990 to 49% in 1996 (p<0.001) [13]. The majority of patients (78%) with new pulmonary TB detected by the RSP were bacteriologically confirmed. The significant decline in the proportion of TB cases detected by the RSP was associated with HIV-infection and reducing the frequency of the RSP from biannually to annually in April 1994. The impact of HIV-infection on case detection may be due to a more rapid progression from TB infection to disease. Reducing the frequency of the RSP may have contributed to the reduced effectiveness of the RSP.

Pulmonary TB cases detected through active case finding are more likely to have negative sputum smears [13, 17] and a lower mortality while on TB treatment [18].

1.3   Study rationale and justification

Although radiological screening has been used for decades the effectiveness of the RSP has never formally been evaluated. Both 6-monthly and annual radiological screening were used in different companies and no data were available as to which approach was the more effective, particularly with an emerging HIV epidemic in the workforce.

2   AIM AND OBJECTIVES

The aim of this study was to determine the effectiveness of 6-monthly compared to annual radiological screening in terms of:

1. TB incidence
2. The proportion of TB cases detected by the RSP
3. The proportion of smear negative / culture positive cases of all culture positive cases.
4. Severity of radiological disease at diagnosis and completion of treatment.
5. Mortality during the first 2 months of treatment

3 METHODS

3.1 Study design

This was a randomised controlled trial. Study participants were individually randomised into one of two arms comparing 6-monthly (intervention arm) with annual screening (control arm) over a period of two years.

3.2 Study site and population

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. The study population comprised all underground and surface workers in employment groups 3 – 8 ("unskilled" workers).

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 15,000 in 2001.

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 (OHC) provides annual radiological screening for occupational diseases.

3.3 Information systems

The mining company and health service where the study was conducted have unusually good information systems that enabled access to high quality demographic, occupational and health records. All mine employees are issued with unique identification numbers (industry, company and hospital numbers) that facilitate access to individual employment and health records. Employees keep their company number for the duration of their mining career.

3.3.1 Company employee database

The demographics, payroll and occupational records of employees are kept on a mainframe database. The date of birth, date of first employment, serial job description according to time period, date and reason for termination of employment, area of origin and ethnic group were obtained from the company's payroll database using the company number.

3.3.2 Occupational health database

Mine employees are required by law to have a medical certificate of fitness to do risk work, i.e., dust-exposed work. All miners undergo an annual medical examination, on return from leave, at the occupational health centre to determine fitness to do risk work. Any miner who has not attended the OHC for a medical examination 15 months since the previous examination is prohibited from returning to work until he has obtained a new certificate of fitness to continue working. Radiological screening for mycobacterial disease and silicosis forms part of the annual medical examination. Each mini radiograph is reviewed by a single reader for new abnormalities suggestive of mycobacterial disease and the presence of silicosis fulfilling criteria for compensation (moderate to advanced). The results of these annual medical examinations are captured onto a medical information system.

3.3.3 Medical information system

Employees are issued with a hospital number at the time of first admission to hospital or visit to a clinic or outpatients department. In addition to patient demographics, the date of admission, discharge or clinic / outpatient visit, admission diagnosis and results of laboratory investigations were entered into the medical information system from 1987. The hospital number was used to access results of laboratory investigations. The results of sputum microscopy, mycobacterial culture, organism identification and drug susceptibility testing were obtained from the medical information system. Only authorised heath care professionals have access to results from the medical information system.

3.3.4 Hospital TB database

From 1975 information from each episode of TB was captured onto separate TB case notes. A separate TB database with detailed clinical records for all cases of TB was kept from 1990. Data were entered retrospectively to 1986. An earlier TB database, but with less detail, was also available from 1984. Cases of TB were identified from the TB database.

3.3.5 Research TB database

All TB episodes recorded on the hospital TB database from the 1st January 1998 to the 31st January 2002 were reviewed retrospectively by the study manager. Existing data were verified. Any missing data were completed after reviewing out-patient medical records, hospital folders, and computerised results of laboratory investigations. The verified data for each TB episode were recorded onto a separate data capture form and double entered into a separate database.

3.4 Mycobacteriology

Miners with suspected mycobacterial disease are investigated using a standard protocol with 3 sputum specimens taken over 2 days. Slides are

made from concentrated sputum and stained with auramine for fluorescent microscopy. Positive slides 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. Smear and culture results are reported using standard quantitative grades. 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 National Health Laboratories for drug susceptibility testing of *M tuberculosis* strains.

3.5 HIV tests

HIV testing, with pre- and post-test counselling, is offered to all patients with suspected TB. The uptake of HIV testing among patients with suspected mycobacterial disease was greater than 80%. HIV test results are kept confidential to the health service. In accordance with WHO recommendations, HIV-infection is 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) are positive.

3.6 Radiological screening

Individuals in the control and intervention arms were scheduled to have three annual screening radiographs over a two year period. Individuals in the intervention arm, in addition to the three annual screening radiographs, were scheduled to have two "intervention" screening, interposed between the annual chest radiographs (Figure 2). Intervention screening chest radiographs were done after work, using a mobile X-ray unit located at a Primary Health Care Centre at a mineshaft closest to their workplace. All intervention radiographs were registered on the occupational health database and read at the Occupational Health Centre (OHC). Trained radiographers, based at the OHC, read both the annual and intervention screening miniature radiographs using a viewing screen and large magnifying glass. The readers were not blinded to which arm the individual belongs as the screening chest radiographs were compared with previous films to look for new and changing radiological abnormalities, and it would have been impractical to mask all radiographs. Radiological abnormalities were classified as normal or abnormal. Abnormal radiographs were classified as new or unchanged. Individuals whose screening chest radiographs had changes suggestive of TB, were referred to the Outpatient Department for further investigations according to a standardised protocol.

3.7 Radiological extent of TB disease

A standard sized chest radiograph is 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 are stored in the radiology department. Standard size chest radiographs on a sequential sample of patients presenting with a new episode of pulmonary TB,

were graded for extent of radiological TB disease at diagnosis and end of TB treatment. The radiological extent of disease was determined by dividing the lung on each side into three equal zones and allocating a score according to the total number of zones involved. Two readers, blinded to study arm and method of detection, scored the chest radiographs. Where results were discordant, a result was obtained by consensus.

3.8   Case definitions

3.8.1   Pulmonary TB

Definite: sputum culture positive for *M. tuberculosis* with >5 colonies OR two or more sputum specimens smear positive for acid-fast bacilli (AFB).
Probable: any of i) single smear positive for AFB, ii) sputum culture positive for an unidentified mycobacterium, iii) both smear and culture negative, AND (in all cases) both a chest radiograph suggestive of TB AND improvement of radiographic appearances on TB treatment.
Possible: all other individuals who were treated for pulmonary TB

3.8.2   Extra-pulmonary TB

For the purposes of this study, we only included individuals with forms of extra-pulmonary TB that are detectable by chest radiography (i.e., pleural, pericardial or miliary shadowing on the chest radiograph).
Definite: relevant specimen culture positive for *M. tuberculosis* with >5 colonies

Probable: Pleural: any of exudative effusion (>30g/l), granulomata or AFB on pleural biopsy. Pericardial: echo demonstration of effusion. Miliary: recent development of classical miliary appearance on chest radiograph.
AND (in all cases) improvement of radiological appearance on TB treatment
Possible: All other cases treated for pleural, pericardial or miliary TB.

3.8.3   Smear positive pulmonary TB

Pulmonary TB cases were classified as smear positive if they met the case definition for definite or presumed pulmonary TB and were smear positive on at least one smear, as prescribed by WHO [19].

3.8.4   Method of detection

The method of TB case detection was classified as:
i) *Radiological screening pick-up* if TB was diagnosed following investigations for new or changing radiological lesions on the screening chest radiograph.
ii) *Self-presentation* if TB was diagnosed in a patient who spontaneously presented to the health service with symptoms suggestive of TB.

iii) *Other* included patients who were being followed up at the TB clinic following TB treatment and were diagnosed with recurrent TB; were transferred in with a diagnosis of TB from another clinic; were hostel room mates of an index patient and were diagnosed as a result of contract tracing; were detected during routine TB screening (symptoms, chest radiograph and sputum smears and culture) prior to initiation of TB preventive therapy; were an incidental pick up during a hospital admission, e.g., for trauma, or if the method of detection was unknown.

3.8.5   Treatment category

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

3.8.6   Site of disease

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

3.9   Data management

3.9.1   Randomisation

The company numbers of all miners in employment on the 15th October 1998 was obtained from the human resource database. A computer programme (Microsoft Excel, Office 1997) was used to individually randomise employees, using their company numbers, to the intervention or control arms.

The following inclusion and exclusion criteria were used to identify individuals eligible for the analysis:

Inclusion criteria
- ? An annual (baseline) screening radiograph taken between 15th September 1998 and 15th November 1999
- ? Company employees
- ? Job category 3 - 8

Exclusion criteria
- ? Contractors and other non employees
- ? Non job group 3 – 8 employees
- ? Any individual who was in the study for less than 30 days
- ? Any individual who was on TB treatment for the entire study period

3.9.2 Study period of observation

Study start date
Miners entered the study on the date of baseline annual screening radiograph between the 15th September 1998 and 15th November 1999. One month's leeway was given either side of the exact dates (15th October 1998 and 15th October 1999). This date defined the start of the observation period for each individual (study start date).

Study end date
The end of the study period (study end date) was determined by one of the following:
   (1) An annual screening radiograph taken between 548 days (1.5 years) and 914 days (2.5 years) following the start date. If more than one screening radiograph was taken during this period, the date of the screening radiograph closest to 730 days (2 years) following the start date was chosen.
   (2) Date of termination of employment, transferred out, lost to follow up, first TB episode or death during the study period, if date based on (1) not identified.
   (3) A date 914 days (2.5 years) following the start date if (1) and (2) do not identify a date.
   (4) If any of these dates were after the 31st January 2002 the study end date was taken as the 31st January 2002.

3.9.3 Study TB episodes

Any TB episode recorded on the research TB database that occurred between the study start date and the study end date +90 days was included in the analysis. There is often some delay between an individual presenting with symptoms suggestive of TB, or being found to have an abnormal screening radiograph, and the start of TB treatment, while investigations for TB are carried out. We therefore extended the observation period by 90 days in order to detect any TB cases who were under investigation for TB on the study end date. If the study end date +90 days was after the 31st January 2002 the observation period to detect TB cases was censored at 31st January 2002.

Any TB episode identified as a result of the baseline annual screening radiograph (the radiograph taken on the study start date) was excluded from analysis. Any such episode is referred to as a "baseline screening episode" of TB. If an individual had more than one TB episode during the study period, only the first episode was used in the analysis.

3.9.4 Time at risk

In order to determine the incidence rate of TB, the time at risk for each individual was defined by the study start and end date. Individuals with a

baseline screening episode of TB entered time at risk following completion of TB treatment.

3.10 Data analysis

Data were analysed with STATA 6.0 software (STATA Corporation, Texas, USA).

3.10.1 Main (intention to treat) analysis

The main analysis was based on an intention to treat, that is individuals randomised to the 6-monthly screening arm, regardless of whether they received the appropriate number of radiographs, were assumed to have received the intervention.

Difference in proportions was analysed using a chi-squared test or Fisher's exact test where appropriate. Poisson regression was used to calculate univariate and adjusted TB incidence rate ratios (per 100 person years) and 95% confidence intervals (CI) for different variables. Overall significance, tests for trends for ordinal variables with more than two categories and tests for effect modification were determined using the likelihood ratio test.

3.10.2 Per protocol analysis

A per protocol analysis was also carried out, restricted to individuals who were not lost to follow-up during the study period, comparing TB rates for those individuals with at least two research radiographs during the study period versus the rest.

3.10.3 Mortality while on TB treatment

The number of deaths, person years and mortality rates (per 100 person years) were summarized by intervention arm, age group, occupational group, HIV status and prior TB history. Mortality rate ratios, 95% CI and associated p-values are also summarized. The data were analysed using Cox regression.

The analysis was based on all individuals with at least one TB episode during follow-up, and the outcome was defined as death within the first two months of TB treatment or death at any time following a TB diagnosis. Individuals were censored at the time of death or for those not known to have died at a date two months after the start of TB treatment or the study end date.

3.10.4 Radiological extent of disease

Extent of radiological disease, at diagnosis and end of TB treatment, was analysed according to zones scores categorized into 3 groups (0-1, 2-3 or 4-6). Differences in zone scores between study arms was assessed using the chi-square test or Fisher's exact test, where appropriate.

4   RESULTS

A total of 22634 miners were randomised to the intervention or control arms. The workforce had declined to 15189 miners at the time the last intervention radiograph was done (20th April 2001). During the study period 20140 intervention-screening radiographs were scheduled to be taken six-months after the previous annual screening radiograph, of which 17659 (87.7%) were done. Of the 2481 intervention radiographs not done, the majority (58.9%) were due to termination of employment (999) or miners being on leave (462). Only 3.6% (406/22634) of miners scheduled to have an intervention radiograph refused participation.

Of those individuals randomised 2.7% (622/22634) were excluded from analysis (Table I), leaving 10997 and 11015 miners in the intervention and control arms respectively. Cohort characteristics are presented in Table II. Almost a third of miners were lost to follow up, largely due to retrenchments. Approximately two thirds of miners in each study arm had two annual screening radiographs during the study period. The two groups were similar with respect to median age, occupational group, duration of follow up and proportion lost to follow up and reason for loss to follow up.

A total of 1302 had at least one episode of TB during the study period, with similar proportions occurring in the control 632 (5.7%) and intervention 670 (6.1%) arms, and 42 individuals had a second TB episode during the study period. There was no significant difference, between the intervention and control arms, in the proportion of first episodes of TB stratified by HIV status, method of detection, year of occurrence, prior history of TB, occupational group or site of disease (Table III). The certainty of case definitions (definite, probable or possible) among pulmonary TB cases was greater in the intervention arm compared to the control arm (p=0.01).

Excluding TB cases where the method of detection was other, the proportion of TB cases detected by the RSP was similar in the control and intervention arms (28% and 29% respectively, p=0.67) and remained so when the analysis was restricted to cases of pulmonary TB, with or with out extrapulmonary TB. It was also similar when stratified by HIV status (Table IV).

The proportion of sputum culture positive pulmonary TB cases, detected by the RSP or self presentation, that were smear negative did not differ significantly between the control or intervention arms (16% and 14% respectively, p=0.56), and remained so when the analysis was stratified by HIV status (Table V).

The prevalence of TB detected through the RSP was not significantly different between the control and intervention arms at the time of the final annual radiological screen (0.91% [65/7111] and 0.65% [46/7075] respectively, p=0.07). TB incidence and incidence rate ratios are presented in Table VI. TB incidence was similar in the control and intervention arms in the intention to

treat (2.72 and 2.90 per 100 person years respectively, P=0.3) and per protocol (2.11 and 2.06 per 100 person years respectively, 0.73) analyses respectively.

The fatality rate during the first two months of TB treatment was significantly lower in the intervention arm compared to the control arm (10.1 and 22.5 per 100 person years respectively, unadjusted hazard ratio 0.45 [0.22 − 0.92], p=0.024) (Table VII). A greater fatality rate was also associated with self presentation versus detection by the RSP (p=0.004) and HIV infected versus HIV uninfected (p<0.001). The mortality rate, from TB diagnosis to end of follow up, was significantly reduced by 27% in the intervention arm compared to the control arm (Control arm: 19.0 per 100 person years and Intervention arm: 14 per 100 person years, unadjusted hazard ratio 0.73 [95% CI 0.55 − 0.97], p=0.03).

TB cases in the intervention arm, compared to the control arm, had less extensive radiological disease (based on zone score) at diagnosis (p=0.05), but not at the end of TB treatment (p=0.7) (Table VIII).

5   DISCUSSION

This large individually randomised study comparing radiological screening once a year to twice a year has failed to demonstrate a difference in the proportion of cases detected by the RSP and in the proportion of sputum culture positive, smear negative pulmonary TB cases between the two arms. However, there was a modest reduction in the TB case fatality rate within the first two months of TB treatment.

These results are opposite to the anticipated outcome. The possible reasons for this are discussed followed by recommendations for TB active case-finding.

This study was undertaken during an advancing HIV epidemic, both in terms of increasing numbers of HIV infected individuals and stage of HIV disease. As HIV infection is associated with more rapid progression of TB disease, the effectiveness of increased frequency of radiological screening may have been undermined.

In principle, community-wide active case-finding should lead to a reduced prevalence of active TB and as a consequence reduced TB transmission and in time reduced TB incidence. Intensification of the RSP should initially lead to an increase followed by a decline in numbers of TB cases detected by the RSP as undiagnosed "chronic" TB cases that are asymptomatic or minimally symptomatic are diagnosed and treated. A two year intervention may have been inadequate to document a significant reduction in TB prevalence.

As the intervention was restricted to the mining workforce, TB transmission from the surrounding communities would remain unaltered and if this accounts for a significant proportion of TB resulting from recently acquired infection, intensification of active case-finding in the mining workforce would not lead to a reduced TB incidence among miners.

Gold miners are a highly screened population. In addition to the annual radiological screening programme there is screening of hostel room contacts and miners have ready access to a high quality health service. The long standing radiological screening programme has probably reduced and maintained the prevalence of radiologically detectable active TB at a relatively low level. This may explain why increasing the frequency of the RSP did not increase the proportion of cases detected by the RSP.

The routine "annual" RSP was not optimally implemented, as not all employees actually underwent "annual" screening within the 24-month study period. This resulted in incomplete implementation of the intervention radiographs, which were interposed between the annual radiographs.

Results from a recently completed study, in the same workforce, demonstrate that the sensitivity of radiological screening to detect pulmonary TB is relatively poor (27.7%) although it is comparable to screening with symptoms (29.8%) [17]. Research on TB epidemiology and control combined with mathematical modelling of the likely dynamics of the HIV and TB epidemics in the study population, suggest that it may be possible to reduce TB incidence in a workforce with high HIV prevalence [20]. Interventions that are community-wide and aim to reduce the prevalence of infectious TB and / or latent TB infection in the community will have the greatest impact. The mathematical modelling

suggests that without active case-finding in the South African gold mining industry TB case rates would be 240% higher than the current rate. If the sensitivity of an active case-finding programme is 70% and screening is increased from once to twice a year the projected decline in TB incidence after 1, 5 and 10 years would be 19%, 32% and 34% respectively. If active case-finding is increased to four times per year the projected decline in TB incidence would be 38%, 47% and 51% respectively. Therefore, increasing the frequency of a screening tool with a relatively low sensitivity, such as radiological screening, is likely to have a limited impact on reducing TB prevalence. If we wish to intensify active case finding it may be more appropriate to use a method with a higher sensitivity, such as sputum culture.

Cause of death during the first two months of TB treatment in this study was unknown. However, death from TB in HIV infected and uninfected miners, while on TB treatment, generally occurs within the first two months of TB treatment [18]. It is hypothesised that active case-finding may reduce TB mortality through earlier diagnosis of TB in both HIV infected and uninfected individuals. The significantly lower mortality during the first two months of TB treatment among individuals in the intervention arm compared to the control arm is consistent with this hypothesis. HIV infected individuals have a more than five fold greater risk of dying in the first two months of treatment, possibly from TB or opportunistic infections, particularly in individuals with advanced immunesuppression. The smaller difference in mortality between the two arms with long term follow up is probably due to similar rates of HIV disease progression and death from opportunistic infection among HIV infected individuals in the two groups that would be unaffected by radiological screening.

An individually randomised study design was chosen because at the time the study was planned, a cluster randomised study was not feasible. An individualised study design limits the ability to determine the impact of increased case-finding on reducing TB incidence, as any reduced transmission from individuals in the intervention arm would be experienced equally by individuals in both intervention and control arms.

Although increasing the frequency of the RSP did not lead to a decrease in TB prevalence in this study, a sizable proportion of TB cases (± 30%) were detected by the RSP in both the intervention and control arms, which is likely to reduce transmission through earlier detection and treatment. The importance of active TB case-finding in TB control has been acknowledged by the World Health Organisation [21]. A Consortium to Respond Effectively to the Aids / TB Epidemic (CREATE), funded by the Bill and Melinda Gates foundation, will be evaluating novel community-wide interventions with the aim of improving TB control in communities with a high burden of TB and HIV. Active case-finding will be formally evaluated in cluster randomised studies that will enable the impact of active case-finding on TB incidence to be evaluated. The results of these studies will inform international policy on optimal TB control strategies.

6   CONCLUSION AND RECOMMENDATIONS

Although the proportion of TB cases detected by the radiological screening programme has decreased over the past decade in parallel with the increasing HIV epidemic, a sizeable proportion of TB continues to be detected by the RSP. We would encourage health services to continue to implement the RSP and strive to meet their objectives of an annual screening radiograph. Companies doing 6-monthly radiological screening should continue to do so and those using annual radiological screening should consider the cost benefit of deaths averted by doing 6-monthly radiological screening. Intensification of the active case-finding programme by the addition of symptom screening to the RSP would improve the proportion of TB cases detected, but would also increase the number of TB suspects requiring further investigations. The cost benefit of this approach has not been evaluated.   Ideally the active case-finding programme should be intensified using a direct approach such as sputum cultures. This approach has not been formally evaluated and would prove logistically difficult and may be expensive. Health care staff should be adequately trained to promptly and appropriately investigate patients presenting to the health service with signs and symptoms suggestive of TB. Although national and WHO guidelines do not recommend routine sputum cultures for patients with suspected TB who have never previously been treated for TB, a strong case can be made for including sputum cultures as a standard of care in the mining industry. A recent study in the same workforce demonstrated that a large proportion of the prevalent undiagnosed TB cases present in the workforce at the time of screening were smear negative, culture positive [17]. The omission of sputum cultures when investigating patients detected through active case-finding may result in the under diagnosis of active TB.

In conclusion, active TB case finding, in addition to a strong DOTS based programme, should remain an integral part of the industry's TB control programme. HIV prevention and care programmes should be expanded. HIV infected individuals without active TB should be offered TB preventive therapy regardless of prior TB history. The role of highly active antiretroviral therapy (HAART) in TB control remains to be determined. HAART, which is essential to reduce the morbidity and mortality of HIV associated TB, that is targeted at only individuals with advanced immunosuppresion, may paradoxically worsen TB control [20]. As the industry begins with implementing HAART TB surveillance should be strengthened.

Table I. Reason for exclusion from the study

	Control (N=11317)	Intervention (N=11317)	Overall
No valid study start date	275	287	562
In study <30 days	13	14	27
On TB treatment throughout study period	14	19	33
Total	302	320	622

Table II. Cohort characteristics, by intervention arm

		Control	Intervention
Total (N, %)		11015 (100)	10997 (100)
Age (in years)	Median (min, max)	39 (17-67)	39 (18-64)
Occupation group (N, %)	Underground Surface	9606 (89) 1191 (11)	9622 (89) 1192 (11)
Follow-up (Days)	Median (min, max)	743 (39-914)	743 (32-913)
Number of annual radiographs [1] (N, %)	0 1 2 =3	1118 (10) 2669 (24) 6387 (58) 841 (8)	1086 (10) 2456 (23) 6130 (56) 1235 (11)
Number of intervention radiographs (N, %)	0 1 2 =3	11014 (99.99) 1 (0.01)	854 (8) 3944 (36) 5904 (54) 295 (2)
Lost to follow-up (N, %)	Yes No	3012 (27) 8003 (73)	3025 (28) 7972 (72)
Reason for loss to follow-up (N, %)	Died Retrenched Other	269 (8.9) 2663 (88.3) 80 (2,7)	248 (8.2) 2704 (89.4) 73 (2.4)

[1] excluding baseline annual radiograph

Table III. Description of first TB episode occurring during the study period, by intervention arm

		Control N / (%)	Intervention N / (%)	p-value
Total		632 (100)	670 (100)	
Prior history of TB	No	465 (74)	523 (78)	0.06
	Yes	167 (26)	147 (22)	
Year of TB episode	1998/1999	215 (34)	215 (32)	0.63
	2000	290 (46)	325 (49)	
	2001/2002	127 (20)	130 (19)	
HIV status [1]	Negative	170 (27)	188 (32)	0.63
	Positive	379 (60)	391 (68)	
Method of detection	RSP	179 (28)	197 (29)	0.67
	Self-presentation	453 (72)	473 (71)	
Occupation group [2]	Underground	568 (92)	590 (90)	0.17
	Surface	51 (8)	69 (10)	
Site of disease	PTB alone	533 (84)	562 (84)	0.74
	ETB alone	62 (10)	73 (11)	
	PTB+ETB	37 (6)	35 (5)	
PTB [3,4]	Definite	375 (66)	439 (74)	0.01
	Probable	90 (16)	68 (11)	
	Possible	105 (18)	90 (15)	
ETB alone [4]	Definite	22 (22)	27 (25)	0.43
	Probable	26 (26)	35 (32)	
	Possible	51 (52)	46 (43)	

RSP = radiological screening programme, PTB = pulmonary TB, ETB = extrapulmonary TB. [1] HIV status unknown in 83 (13%) and 91 (14%) in the control and intervention arm respectively, [2] Missing data on 13 & 11 miners from the control and intervention arms respectively, [3] PTB with or without ETB, [4] See text for definitions.

Table IV. Proportion of TB cases detected by the radiological screening programme [1]

	N	Method of detection	Control	Intervention	p-value
Overall			N / (%)	N / (%)	
All cases	1302	RSP Self	179 (28) 453 (72)	197 (29) 473 (71)	0.67
PTB (+/- ETB) ~ definite, probable or possible	1167	RSP Self	170 (30) 400 (70)	180 (30) 417 (70)	0.90
PTB (+/- ETB) ~ definite or probable	972	RSP Self	153 (33) 312 (67)	163 (32) 344 (68)	0.80
PTB alone ~ definite, probable or possible	1095	RSP Self	165 (31) 368 (69)	177 (31) 385 (69)	0.85
HIV positives					
All cases	770	RSP Self	69 (18) 310 (82)	71 (18) 320 (82)	0.99
PTB (+/- ETB) ~ definite or probable	561	RSP Self	60 (18) 271 (82)	57 (20) 233 (80)	0.47
HIV negatives					
All cases	358	RSP Self	72 (42) 98 (58)	84 (45) 104 (55)	0.66
PTB (+/- ETB) ~ definite or probable	283	RSP Self	62 (46) 73 (54)	68 (46) 80 (54)	1.00

[1] Number of TB cases detected by the RSP over the combined total of TB cases detected by the RSP and those who self presented with symptoms. RSP = radiological screening programme, Self = self presentation with symptoms, PTB = pulmonary TB, ETB = extrapulmonary TB

Table V. Proportion of culture positive cases that were smear negative [1]

	N	Smear status	Control N (%)	Intervention N (%)	p-value
Overall					
PTB (+/- ETB) ~ definite, probable or possible	736	Positive Negative	291 (84) 55 (16)	334 (86) 56 (14)	0.56
PTB (+/- ETB) ~ definite or probable	731	Positive Negative	290 (84) 54 (16)	334 (86) 53 (14)	0.44
HIV positives					
PTB (+/- ETB) ~ definite, probable or possible	434	Positive Negative	167 (80) 41 (20)	195 (86) 31 (14)	0.09
HIV negatives					
PTB (+/- ETB) ~ definite, probable or possible	213	Positive Negative	89 (89) 11 (11)	97 (86) 16 (14)	0.49

[1] Restricted to pulmonary TB cases detected by the radiological screening programme or self-presentation, PTB = pulmonary TB, ETB = extrapulmonary TB, N = number

Table VI. TB incidence and incidence rate ratios

Type of analysis		N / pyears[1]	Rate[1]	IRR (95% CI)	p-value
Intention to treat [2]					
Overall		1302/462	2.82		
Intervention arm	Control	632/231	2.72	1	
	Intervention	670/231	2.90	1.06 (0.95, 1.19)	0.3
Per protocol [2]					
Overall		765/364	2.10		
Intervention arm	Control	518/244	2.11	1	
	Intervention	247/120	2.06	0.97 (0.84, 1.13)	0.73

[1] per 100 person years, [2] See text for methodology, IRR = incidence rate ratio, N = number, IRR = incidence rate ratio, CI = confidence interval

Table VII. Unadjusted analysis of risk factors for death during the first two months of TB treatment

Variable	Description	N/ /per yrs	Rate[1]	Hazard ratio (95% CI)	p-value
Overall mortality rate		34/210.9	16.1		
Treatment group (n=1300)	Control	23/102.1	22.5	1	0.024
	Intervention	11/108.7	10.1	0.45 (0.22, 0.92)	
Method of detection (n=1300)	RSP	3/61.0	4.90	1	0.004
	Self-presentation	31/149.9	20.7	4.21 (1.29, 13.77)	
Age group (years) (n=1300)	?34	7/41.2	17.0	1	0.08
	35-39	10/41.5	24.0	1.42 (0.54, 3.74)	
	40-44	12/57.3	21.0	1.23 (0.49, 3.13)	
	?45	5/70.8	7.0	0.42 (0.13, 1.31)	
Occupation (n=1276)	Underground	19/188.4	10.1	1	0.23
	Surface	4/19.4	20.6	2.05 (0.70, 6.02)	
Previous TB (n=1300)	No	27/160.2	16.8	1	0.63
	Yes	7/50.6	13.8	0.82 (0.36, 1.88)	
HIV status (n=1126)	Positive	2/58.2	25.0	1	<0.001
	Negative	31/124.1	3.40	7.29 (1.74, 30.45)	

[1] per 100 person years, N = number, per yrs = person years, CI = confidence interval, RSP = radiological screening programme

Table VIII. Extent of radiological pulmonary TB disease [1]

Extent of disease	Description	Control	Intervention	p-value
At diagnosis	0-1 2-3 4-6	28 (33) 23 (27) 33 (39)	28 (26) 47 (44) 31 (29)	0.05
At end of TB treatment	0-1 2-3 4-6	26 (37) 30 (42) 15 (21)	26 (31) 41 (49) 16 (19)	0.7

[1] Extent of disease based on Zone score and restricted to pulmonary TB cases detected by radiological screening programme or self-presentation with symptoms.
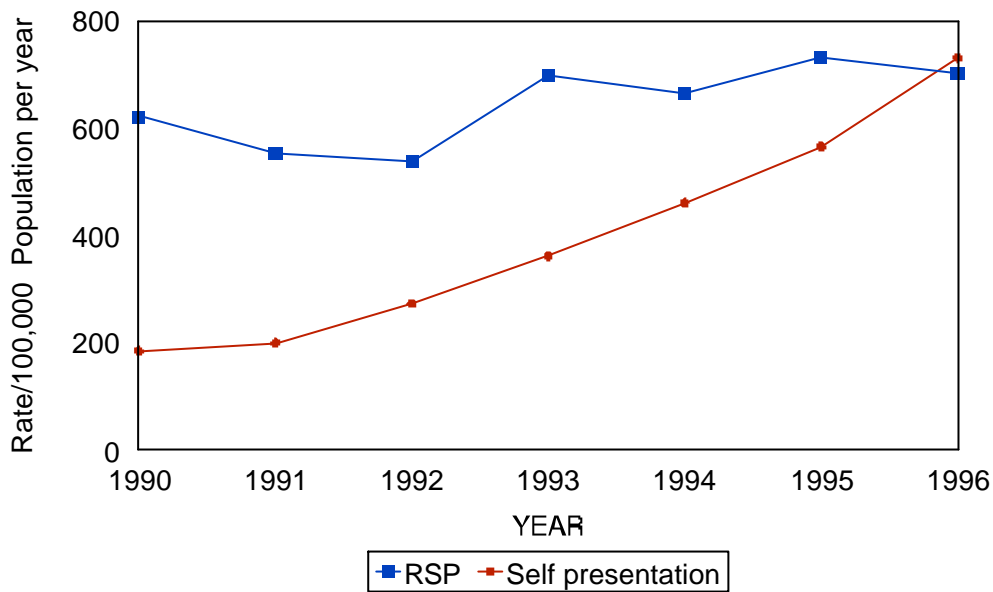
Figure 1. TB incidence rate of miners who self presented with symptoms or were detected by the radiological screening programme (RSP) [13]
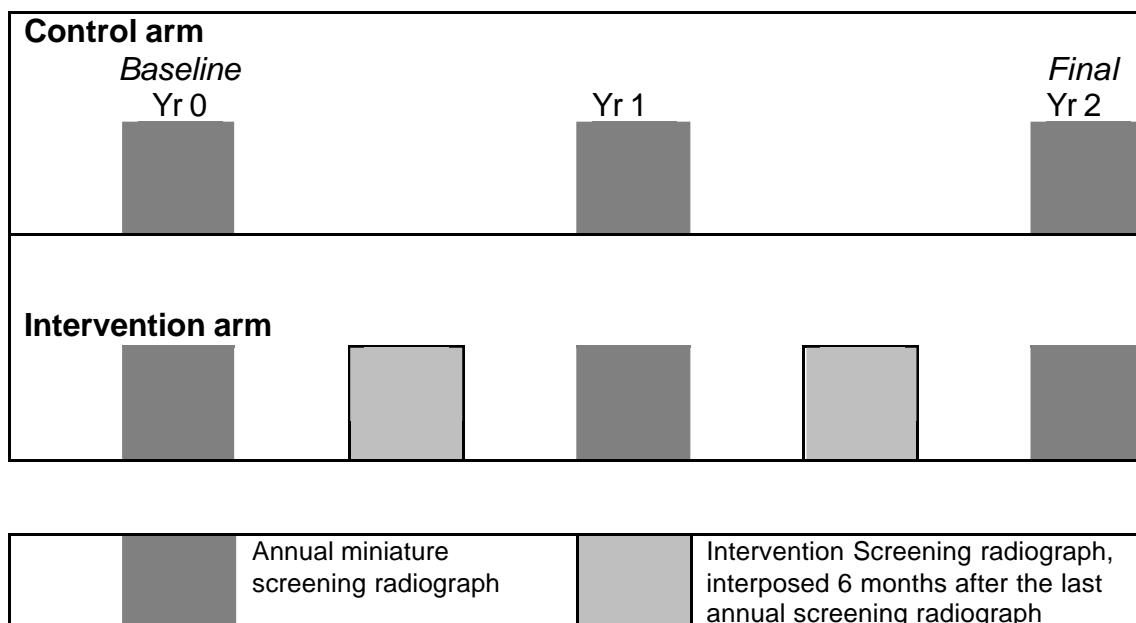

	Annual miniature screening radiograph		Intervention Screening radiograph, interposed 6 months after the last annual screening radiograph

Figure 2. Radiological screening in the control and intervention arm

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