Respiratory Health Effects in relation to Crystalline Silica

Screening and Feasibility of Epidemiologic Research

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Executive Summary

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The golden ore in the SA gold mines is embedded in a rock which contains 80-90% of quartz, and consequently the dust that results during the mining process contains high percentage of crystalline silica. It is established that inhalation of crystalline silica can cause, or increase the risk of, respiratory diseases such as silicosis, pulmonary tuberculosis, chronic obstructive lung disease and lung cancer. These diseases are chronic in nature and can develop and progress into a severe disease years after silica dust exposure ceases. It is also recognized that all the above diseases are preventable.

Considerable amount of information on the respiratory disease etiology, the extent and exposure-response relationship has been provided by previous epidemiologic studies of South African gold miners. Newly

implemented epidemiologic studies should aim at disease prevention by researching pre-clinical or early stages of respiratory disease associated with silica dust, and the implementation of measures that results in the prevention of respiratory diseases.

Because of the extensive labour force involved in the gold mining industry, one of the best way to accomplish such research is to implement a large industry-wide cohort study representative of currently employed gold miners. Such a study would involve an extensive study of baseline health effects, including pre-clinical markers of disease, markers of exposure, and measurements of dust exposure, and a prospective follow-up of the subjects for various health outcomes.

The objective of the present study was to establish the feasibility of conducting such a prospective study of respiratory health effect in gold miners. In particular, the objectives were: (1) to establish whether routinely collected lung function and other data on the mines can be utilized for epidemiologic research; (2) to determine which mines could be selected for the prospective study, taking into consideration the wide range of mining conditions (dust levels, silica contents, etc.) and availability of databases; and (3) to develop the cohort study design and instruments for the study.

Because of limited human resources we were able to accomplish only objectives 1 and 3. Nevertheless, the results from the feasibility study provide considerable amount of information that is directly relevant to a design and implementation an industry-wide prospective study. In addition, the information on its own is important for the occupational health in South Africa. As part of the feasibility study we have examined the reliability of lung function measurements

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collected during routine screening on the mines (Section 2). The appropriateness of existing

reference values for epidemiologic research (Section 3). The effect of pulmonary tuberculosis on lung function (Section 4). We have also developed the respiratory questionnaire and radiological reading form (Section 5, Appendix) and are proposing a study design based on the results of the feasibility study.

Section 2: Reliability of lung function measurements collected during routine screening.
Lung function measurements collected from 1994 to 1998 during routine lung function screening programme done by Anglogold Health Services (AHS) were used to establish whether the lung function measurements are reliable and can be utilized for epidemiologic research. The study made the following findings.

(1) The lung function measurements from the AHS lung function screening programme were very reliable for some periods of time and very unreliable at other periods of time. We conclude that routinely collected lung function tests can be potentially used for epidemiologic research provided that reliability of the measurements is regularly checked and quality enforced.
(2) For a large screening programme, the reliability control programme can be implemented on a relatively small sample of miners (around 600-700) who have annual lung function tests done throughout the year. Then, the reliability can be checked on a monthly basis and quality of measurements ensured continuously.

Section 3 - Lung function prediction curves
Using the same set of data from the AHS, we have established that the reference values for lung function obtained from white American or European males are not appropriate for black South African gold miners. We suggest that either an appropriate correction factor is used or reference values established on black South African males be used. We have also established that the

correction factor of 0.88 obtained on US black males and proposed by the American Thoracic Society, and used in many spirometers for ethnic correction in South Africa, is not appropriate for black SA gold miners.

Section 4 - Effect of pulmonary tuberculosis (PTB) on the loss of lung function
In epidemiologic research of the effect of silica dust exposure on the loss of lung function it is necessary to take into account all confounding factors that can affect lung function, e.g. tobacco smoking. The effect of pulmonary tuberculosis on lung function loss has not been well researched although pulmonary tuberculosis is a common lung disease in South African gold miners. In this study we found that the residual loss of lung function after completion of PTB

treatment is very significant and increases with each episode of pulmonary tuberculosis. The effect of PTB on lung function loss is of the same magnitude as the effect of tobacco smoking. Thus, any study of the effect of silica dust exposure on loss of lung function in South African gold miners cannot be valid unless a detailed medical history of pulmonary tuberculosis for each subject is taken into account. Further studies are needed to establish whether the extent of PTB

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involvement during active PTB and residual changes after treatment completion identified on radiographs relate to residual lung function loss.

Section 5 - Outline proposal for an industry-wide prospective study
The industry-side prospective study of respiratory health effects would involve collection of data on the following pivotal measurements on an annual basis: lung function measurement, respiratory symptoms questionnaire, PTB history, radiological reading, and HIV status assessment. The baseline data would include also blood sample, allergy test, etc. Additional tests can be added as the study progresses.

Implementation. The findings of the feasibility study indicate that such a study could be conducted utilizing existing resources for data collection on the mines. To ensure uniform data quality, the staff involved in the data collection (lung function technicians, interviewers, nurses, etc) would be trained at one centre (e.g. MBOD, NCOH). Training of the mining personnel is an important aspect for disease prevention as the development of skills would ultimately result in better quality of the data collected by the mines and will lead to better disease recognition.

Study subjects. To ensure reliability of lung function screening programme, a dynamic cohort of approximately 600-800 miners is required to be tested on an annual basis throughout the year. This cohort would constitute a part of the industry-wide cohort.

Mines involved in the study. Initially only selected mines with established lung function screening programmes will be included in the study. The reliability control programme, staff training and data collection method will be developed for these mines. When this is successfully accomplished, only then the study will be implemented in other mines. Pulmonary tuberculosis record keeping should also be uniformly implemented.

Data collection. The study data collection of the routine measurements would be done using the existing system for the rest of the workforce. On a regular basis (initially monthly) the results will be collected by the Study Centre. The data will be analysed for quality, and feedback provided to the mine medical staff. A close

collaboration between the study centre and the mine medical officers should be beneficial to all parties concerned. For example if the study centre is at NCOH, then resources of the NCOH can be utilized for training and distribution of
information relevant to respiratory disease prevention on the mines (e.g. via the SORDSA Newsletter).

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Application of the screening programme for the cross-sectional assessment of lung function associated with pulmonary tuberculosis

Section 1 - General Introduction

The golden ore in the SA gold mines is embedded in a rock which contains 80-90% of quartz, and consequently the dust that results during the mining process contains high percentage of crystalline silica. It is established that inhalation of crystalline silica can cause, or increase the risk of, respiratory diseases such as silicosis, pulmonary tuberculosis, chronic obstructive lung disease and lung cancer. These diseases are chronic in nature and can develop and progress into a severe disease years after silica dust exposure ceases. It is also recognized that all the above diseases are preventable.

Considerable amount of information on the respiratory disease etiology, the extent and exposure-response relationship has been provided by previous epidemiologic studies of South African gold miners. Newly implemented epidemiologic studies should aim at disease prevention by researching pre-clinical or early stages of respiratory disease associated with silica dust, and the implementation of measures that results in the prevention of respiratory diseases.

Because of the extensive labour force
Because of limited human resources we were able to accomplish only objectives 1 and 3. Nevertheless, the results from the feasibility study provide considerable amount of information that is directly relevant to a design and implementation of an industry-wide prospective study. In addition, the information on its own is important for the occupational health in South Africa. As part of the feasibility study we have examined the reliability of lung function measurements collected during routine screening on the mines (Section 2). The appropriateness of existing reference values for epidemiologic research (Section 3). The effect of pulmonary tuberculosis on lung function (Section 4). We have also developed the respiratory questionnaire and radiological reading form (Section

involved in the gold mining industry, one of the best way to accomplish such research is to implement a large industry-wide cohort study representative of currently employed gold miners. Such a study would involve an extensive study of baseline health effects, including pre-clinical markers of disease, markers of exposure, and measurements of dust exposure, and a prospective follow-up of the subjects for various health outcomes.

The objective of the present study was to establish the feasibility of conducting such a prospective study of respiratory health effect in gold miners. In particular, the objectives were: (1) to establish whether routinely collected lung function and other data on the mines can be utilized for epidemiologic research; (2) to determine which mines could be selected for the prospective study, taking into consideration the wide range of mining conditions (dust levels, silica contents, etc.) and availability of databases; and (3) to develop study design and instruments for the study.

5, Appendix) and are proposing a study design based on the results of the feasibility study. A reader interested in an overview only can read the abstract from each section.

Section 2 - Reliability of a pulmonary function screening programme in the South African gold mines

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Authors: Eva Hnizdo, Gavin Churchyard, Dave Barnes, Rob Dowdeswell

2.1 ABSTRACTS

Objectives - To determine reliability of lung function

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tests performed at a screening programme in a large South African gold mine, and to determine the utility of the reliability coefficient G as a means of monitoring the quality of lung function tests in a mass screening programme.

Method -   The reliability coefficient G, which estimates the amount of random error of measurement, was calculated on 3472 miners who performed two lung function tests within a six month period. The reliability coefficient G, and the within-person changes in forced expiratory volume in one second (FEV1) were used to assess temporal variability in the reliability of the screening programme. The reliability statistics were also estimated by age strata.

Results - Temporal variability in the reliability of the screening programme was observed over a period of 46 months. There was an initial five month period with variable reliability, followed by a 23-month period of increased reliability, followed in turn by a period of decreasing reliability. For the period of increased reliability, the best estimate of the reliability coefficient G was 0.94 for FEV_1, indicating that the random error of measurement represents approximately 6% of the total variation in FEV_1. The reliability coefficient G declined only slightly when the time between two lung function tests was increasing during the period of high reliability, but decreased substantially when the whole 46 months screening period was considered to G=0.85.

Conclusion - The results indicate that it is possible to obtain reliable lung function measurements from a screening programme, but the results of the programme need to be monitored for quality. The reliability coefficient G is a potential   tool for monitoring   the reliability of the screening programme. In a large programme a minimal sample of   400-600 subjects, examined on a yearly basis throughout the year, would provide sufficient data to examine the monthly or quarterly fluctuation in the reliability. Information on potential sources of variation in the lung function tests should be included in the database to allow identification of sources of decreased reliability.

2.2 INTRODUCTION

Screening for lung function impairment in subjects exposed to respiratory hazards should be able to identify those individuals whose lung function falls bellow predicted values, and those who demonstrate accelerated loss of lung function.[1] The reliability with which subjects with "true" respiratory impairment are identified will depend on the accuracy and precision of the lung function measurements. The reliability of the measurements reflect both systematic errors (e.g. procedural differences, instrument variability) and random errors of measurement (e.g. due to temporary bronchoconstriction).[2,3] The amount of variation caused by random error of measurement can be measured by the reliability coefficient G.[4] Other useful applications for the coefficient are to detect temporal variation in the reliability of a screening programme, or to correct for the effect of lung function fluctuation within individual subjects when predicting permanent impairment.[4]

Lung function tests (PFT's) of miners attending the occupational health service of a large South African gold mining company were evaluated. Spirometry is performed routinely on all miners at an initial examination, periodically at three-yearly intervals, and on leaving the industry. Maximal forced expiratory maneuvers are recorded in a computerized database using a Hans Rudolph pneumotachograph (Flowscan, Electromedical Systems Inc). The system software requires and validates calibration with a 3,00 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 maneuvers are obtained according to the standards recommended by the American Thoracic Society (ATS). All testing is done by nursing personnel trained in the techniques of performing spirometry to ATS

The usefulness of workplace monitoring programmes will depend on the reliability of the lung function testing and also on the disease prevention strategies built into the programmes. In the case of gold mining, epidemiologic studies have shown that chronic impairment of lung function and mortality from chronic obstructive lung disease (COPD) are associated with exposure to crystalline silica dust.[5,6,7] Thus, an effective screening programme for lung function impairment based on reliable measurements and scientific evaluation of the data could lead to prevention of COPD at an early stage.

The aim of this study is to evaluate the reliability of the lung function measurements performed at a screening programme in a large South African gold mining company, and evaluate the applicability of the reliability coefficient G for this purpose.

2.3 Material and Methods

2.3.1 Data Source

standards. Height is measured to the nearest centimetre in stocking feet. Data recorded for each test includes date of test, date of birth, height, weight, the highest forced vital capacity (FVC), the highest forced expiratory volume in one second (FEV1) and forced expiratory flow at 25 to 75% of forced vital capacity ($FEV_{25-75\%}$). The programme covers a population of miners which decreased from 71 515 in 1994 to 43 359 in 1997. During a 46-month period (May 1994 to March 1998), 113 120 lung function tests were recorded in the database (14 267 in 1994, 28 402 in 1995, 25 288 in 1996, 32 381 in 1997, and 12 782 in 1998).

2.3.2 Reliability coefficient G - statistical background

The lung function tests [FVC, FEV_1, $FEF_{25-75\%}$, and the ratio of FEV_1/FVC ($FEV_1\%$)] are continuous normally distributed variables with the mean, μ, and the

variance, σ^2. It is well recognized that lung function tests are prone to measurement errors.[2,3] The errors can be broadly categorized as systematic errors of measurement and random errors of measurement. Theoretically, a systematic error could be removed from the data, provided that we have information on its origin (e.g., procedural changes, a technician effect, seasonal variability). A systematic error changes mainly the mean, μ, i.e. it shifts the distribution. By a random error of measurement we understand not only the random error in measurement procedure itself but also, and more importantly, random fluctuation in the measured quantity that reflects the variability in lung function within an individual subject. This fluctuation can be due to factors such as subject's 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, σ^2. When testing the reliability of a lung function measurement, we estimate the size of the random where the correlation coefficient $\rho_{t, t+T}$, available for various values of the time interval T between the two measurements, is related to T and then we can estimate G and λ from a simple linear regression taking the natural logarithm of equation [1], i.e., log $(\rho_{t,t+T}) = g - \lambda T$. The estimated value of $G=\exp(g)$ provides the best estimate of G at time $T=0$. The estimated slope λ provides information on the change in G with increasing time T. This information can be useful for determining the optimal time between periodical lung function tests (PFT's) in a screening programme. The optimal sample size required per year for monthly quality control using the reliability coefficient G was established by calculating the average reliability coefficient G and the coefficient of variation CV for decreasing sample size.

2.3.3 Method of estimation of the reliability coefficient from the screening programme

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.[4] The statistic that measures the relative size of the random error of measurement is the reliability coefficient G.[4,8,9] Appendix A provides statistical details on the coefficient G.

Appendix A shows that the simplest method of estimating the reliability coefficient G is to reexamine lung function in a series of cases over few weeks or months and to calculate the correlation coefficient $\rho_{M_a M_b}$ between the two sets of lung function measurements. The time interval T between two tests should be long enough to include all the potential short term effects involved in the random measurement error, but short enough to avoid systematic changes, e.g., due to age.

To determine whether the reliability coefficient G depends on the time T between two tests can be investigated from the following model[4]

$$\rho_{t, t+T} = G \; \exp(-\lambda T), \qquad (1)$$

We selected all male subjects who had two PFT's done within six months during May 1994 to March 1998. Six months was the shortest period that provided a sufficient number of subjects to evaluate a trend in the reliability coefficient while ensuring that the effect of aging is small. In total 3513 black miners and 97 white miners had two PFT's done within six months. In 75 percent of these, the second examination was an exit examination. Because our objective was to determine the "best" estimate of the within-person variance for the PFT, we excluded observations that were extreme, i.e., outliers. Of the 3513 black miners, we excluded 80 (2.3%) in whom any one of the PFT variables (FVC, FEV_1, FEF) was outside the 99% confidence limits (mean$\pm3.00 \times$ s.d.), and 55 (1.6%) in whom the within-person difference was outside the 99% confidence limits, leaving 3378 black miners in the reliability analysis. Of the 97 white miners, two (2.1%) and one (1.0%) were excluded for the above

reasons, respectively, leaving 94 for analysis. No clinical details were available on the database to establish the reasons for the outliers.

2.3.4   Method of statistical analysis

In the first step of the analysis, we used the analysis of covariance (SAS PROC GLM) to determine whether age, the month of testing, and the time interval T between the two tests had effect on the variation in the within-person difference in FEV_1 (second test-first test). The months of the first and second test were analysed separately and the time interval T was included as a covariate. In the second step, we examined the within-person difference in FEV1 and the reliability coefficient G to identify the period during which the screening programme was most reliable and estimated the random error of measurement using this period only. In the final step, we examined the relationship between the

2.4   Results

Table 2-1 shows the characteristics at the first and second lung function tests, for the 3378 black miners and 94 white miners separately. The mean and variance are shown for the first and second test and for the within-person difference. The average age at the first test was 41.8 years (S.D. 10.1) for black miners and 36.1 years (S.D. 11.1) for white miners. The period between the two tests was 3.73 months for the black and 3.95 months for the white miners. The average within-person differences for the PFT's   were negative and statistically significant. The reliability coefficient G was highest for FEV1.

Although the reliability coefficient was estimated as the correlation coefficient (see Appendix, Eq. 5), we can also calculate G and the size of the random error of measurement from equations [2] and [4] in Appendix A. For example, if we substitute the variances for FEV_1 given in Table 1 for black miners into equation [2], then MaMb = ½ (0.4223 + 0.4318 - 0.0938)=0.3802, and from equation   (4),   G=0.3802/($\sqrt{0.4223}$ ·

reliability coefficient G and time interval T between two tests, i.e., we tested whether the reliability coefficient G changed significantly with time T. Finally, because the screening programme does periodical lung function tests every three years, we examined the minimal sample size required to monitor lung function quality control using the reliability coefficient G. If the sample of subjects have lung function tests done on a yearly basis and are evenly distributed throughout the year, then a monthly trend in the reliability coefficient can be obtained. The minimal sample size was derived by plotting the average reliability coefficient over the 12 month period and the coefficient of variation CV calculated from the monthly reliability coefficients G against a random sample on which these were calculated.

$\sqrt{0.4318}$)=0.8903.   Then the   variance of the observed FEV_1 is $\sigma^2_M = \sigma^2_L + \sigma^2_\delta$, where the variance of the true variable σ^2_L = 0.3803 and the variance of the random error of measurement σ^2_δ =½(0.0938)= 0.0469.

Of the potential systematic effects on the change in lung function that could be investigated, age did not have a significant effect but the month of testing had, and the time interval T was a significant covariable. Figure 2-1 (a) shows the average change in FEV_1 according to the month of the first test, adjusted for age and the interval T. There is a period of larger variability up to September 1994 and a period of large negative changes from September 1996 to June 1997, followed by large positive changes. A similar pattern was observed when the changes were plotted by the month of the second tests. Figure 2-1 (b) shows the reliability coefficient for FEV_1, according to three monthly intervals. The patterns in Figures 2-1 (a) and (b) are similar.

To obtain the "best" estimate of the random error of measurement for the individual

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PFTs, we selected the period when the screening programme was most reliable, i.e., from October 1994 to August 1996. Subjects whose first or second tests were done before September 1994 or after August 1996 were excluded. Table 2-2 shows the reliability statistics for the period October 1994 to August 1996. The value of the reliability coefficient G increased and the within-person differences decreased.

Although age did not show a significant Figures 2-2 (a) and (b) show the relationship between the reliability coefficient G and the time interval T between the two tests, for the most reliable period from October 1994 to August 1996, and for the total screening period from May 1994 to March 1998. The fitted line in Figure 2-2 (a) includes data on 2802 miners who had two tests during the October 1994 to August 1996 period; the maximum time interval T between the two tests was 22 months. However, the number of subjects with two observations of more than 15 months apart was small in this data subset, and the coefficient G became unreliable after T=15. The value of G was consistently above 0.90 up to T=15. For this subset, the estimated value of G at T=0 was 0.93, 95%CI (0.91, 0.99) and the value of the slope λ=-0.001 (p=0.20). In comparison, for the whole screening period there were 16 249 subjects who had two tests done during the May 1994 to March 1998 period; the maximum time interval T between two tests went up to 36 months. Figure 2-2 (b) shows that the reliability coefficient G is much lower; the estimated value of G at T=0 was 0.87, 95% CI (0.86, 0.89), and the value of the slope λ=-0.0014 (p=0.002). The number of For the overall data, there were large and statistically significant within-person differences in the PFT's (see Table 2-1) and the FEV_1 was the most reliable measurement. The time trends in the within-person differences in FEV_1 and the reliability coefficient G (Figure 2-1) show an initial period of five months of increased variability, and a period of

effect on the within-person differences in FEV1, we considered it informative to present the reliability statistics by age categories for the period October 1994 to August 1996; for the black miners only as there were too few white miners to stratify them by age. Table 2-3 shows the mean and variance for the first lung function test and the within-person difference, the probability that the within-person difference equals zero, and the reliability coefficient G for each age category.
subjects was large (ranging from 206 to 790) for all the data points.

Figure 2-3 shows the relationship between the average reliability coefficient G calculated monthly and averaged over 12 month and the coefficient of variation CV for the monthly reliability coefficients G, and the minimal sample size required per year to monitor the lung function reliability on monthly basis. The optimal sample size is 600 to 700 subjects.

2.5   Discussion
The coefficient of reliability G was calculated on 3378 black and 94 white miners who had two lung function tests within six month with the objective to evaluate the reliability of the lung function screening programme. The reliability coefficient G estimates the amount of within-person variability relative to the amount of between-person variability. The trend in the average within-person difference in FEV_1 and in the reliability coefficient G for FEV_1 were used to identify time related changes in the reliability of the screening programme.

large negative differences from September 1996 to May 1997, followed be a period of large positive differences. The reliability coefficient G is consistently above the value of 0.90 during 1995, it starts to declines during 1996, and it declines rapidly during 1997. The decline during 1996 reflects that some of the second tests were done

after September 1996. When subjects with any measurements done from September 1996 were excluded, the reliability coefficient increased and became more consistent for 1996 (see Figures 2-2 (a) and (b) below). During the initial period of four months (May to September 1994), the variability may have been higher due to a learning process. The decrease in reliability from September 1996 probably corresponded with increased retrenchments in the mine.

To obtain the "best" estimates of the random error of measurement, only subjects whose first and second PFT's were done during the period October 1994 to August 1996 were included in the analysis. The within-person differences in lung function shown in Table 2-2 are smaller and the reliability coefficients are higher, except for FVC%.

Reliability statistics stratified by age for the period October 1994 to August 1996 reveal useful information on the data and also show that there is consistency in the data (see Table 2-3). The within-person differences for FEV_1 show that a decline in FEV_1 started from 35-44 years of age, however, none of the within-person differences were statistically significant. This result is consistent with literature where in men, the onset of decline in FEV_1 was observed from 36 years.[11] The amount of decline in FEV_1 per year reported from cross-sectional studies is 20 to 30 ml/yr,[12,13,14] whereas a longitudinal study reported a decline for the 35-44 year category of about 2-3 ml/year [11]. In our data in Table 3, the mean FEV_1 values for cross-sectional age strata show a systematic decline with age starting already from 25 years of age. This decline between the age strata could be also due to a cohort effect.

In a large screening programme when the lung function tests are not done on a yearly basis, as in our programme, the minimal sample size, required to monitor quality control on a monthly basis using the reliability coefficient, is around 600 to 700 subjects, see Figure 2-3. At those sample sizes the value of the monthly reliability coefficient

What value of the reliability coefficient G is required for an effective screening programme capable of identifying accelerated loss of airflow in groups of subjects? Our results indicate that the value of the reliability coefficient G for FEV_1 needs to be at least 0.93. For example, it may be of interest to determine whether a specific group of subjects (e.g. smokers, silicotic subjects) have accelerated loss of airflow. However, even if the coefficient of reliability G is high, around 0.93, a large sample size is required to identify small loss. For example, the observed change in FEV1 for the age category 35-44 yrs is -22.5 ml per 3.78 months (see Table 2-3), which is higher than expected. A minimal sample size required for this difference to be statistically significant is approximately 463 subjects. The literature suggests that at least four years are required to detect reliably the effect of smoking in longitudinal study.[15]

The relationship between the reliability coefficient G and the time interval T between the two tests (Figure 2-2) shows that for the period October 1994 to August 1996, the reliability coefficient for FEV_1 declined little up to time interval T of 15 months, and the best estimate of G at T=0 was 0.93. When the regression was fitted up to T=15 only G at T=0 was 0.95. According to this data, the "best" estimate of the random error of measurement in FEV1 is around 7% of the total variation in the observed FEV_1 measurement. In comparison, when we included the whole screening period from May 1994 to March 1998, and extended T to 36, the reliability coefficient G declined rapidly to about 0.85. Figures 2-2 (a) and (b) confirm the presence of temporary changes in the reliability of the screening programme. stabilise, see the coefficient of variation (CV). If these subjects have lung function tests done on a yearly basis and are evenly distributed throughout the year, then a monthly trend in the reliability coefficient can be estimated.

A previous study which evaluated the reliability coefficient G on lung function tests was

done on a group of South African white miners with a period of one year between two tests.[9] The values of G for FEV1, FVC, $FEF_{25-75\%}$, and $FEV_1\%$ were reported as 0.899, 0.929, 0.836, and 0.786, respectively. The data from this study are comparable to these values (see Table 2-1), and are better when the most reliable period is considered (see Table 2-2).

In conclusion, the temporal pattern in the reliability coefficient G and the within-person differences in the FEV_1 shows periods of decreased and increased reliability in the screening programme. The most reliable period was from October 1994 to August 1996. The decrease in the reliability appears to correlate with an increase in the number of tests due to retrenchments in the mines from September 1996. The random error of measurement constituted around 6-8% of the total variation in the FEV_1. The coefficient G was almost constant up to time of 15 months between two measurements. The coefficient of reliability appears to be a useful tool to monitor the reliability of a screening programme on a continuous basis.

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2.7 Appendix A

To describe the statistical theory for the reliability coefficient,[4,8,9] let us assume that for an individual subject there is a "true" value of a lung function, L. This true value L is observed with a random error δ, resulting in measurement M, where M=L + δ. The observed value M is distributed normally with a mean μ and variance σ_M^2. Assuming that L and δ are normally distributed, then the variance of M is $\sigma_M^2 = \sigma_L^2 + \sigma_\delta^2$. The ratio of the true value variance σ_L^2 to that of the variance σ_M^2 of the observed value is referred to as the reliability coefficient G and can

$$G = \frac{\sigma_L^2}{\sigma_M^2} = \frac{\sigma_M^2 - \sigma_\delta^2}{\sigma_M^2} = 1 - \frac{\sigma_\delta^2}{\sigma_M^2}.$$

be expressed as

(1)

The variance σ_δ^2, required for calculation of G, can be estimated from repeated independent measurements (M_a and M_b) of the same true value L on the same subject over a period of time T (weeks or months). It can be shown that the within-person variance of the difference of the two measurements (σ_{Ma-Mb}^2) is twice the variance of the random error of measurement, $2\sigma_\delta^2$. This follows[10] because

$$\sigma_{Ma-Mb}^2 = \sigma_{Ma}^2 + \sigma_{Mb}^2 - 2\sigma_{MaMb}. \qquad (2)$$

Further, we can assume that $\sigma_{Ma}^2 = \sigma_{Mb}^2 = \sigma_M^2$ and that δ is independent of L. Then the covariance term is the same whether derived from M or L, i.e.:

$$\sigma_{MaMb} = \sigma_{LaLb} = \sigma_L^2.$$

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It follows then that

$$\sigma^2_{Ma\text{-}Mb} = 2\left(\sigma^2_M - \sigma^2_L\right) = 2\,\sigma^2_\delta. \qquad (3)$$

Therefore, $\frac{1}{2}\,\sigma^2_{Ma\text{-}Mb}$ can be substituted for σ^2_δ in the equation (1). A simple alternative is to use the correlation coefficient between M_a and M_b, ρ_{MaMb}, as the reliability coefficient, because

$$(4) \qquad\qquad \rho_{MaMb} = \frac{\sigma_{MaMb}}{\sigma_{Ma}\,\sigma_{Mb}}$$

which simplifies to

$$(5) \qquad\qquad \rho_{MaMb} = \frac{\sigma^2_L}{\sigma^2_M} = G.$$

The simplest method of estimating the reliability coefficient G is from a reexamination of lung function in a series of cases over few weeks or months and calculate the correlation coefficient ρ_{MaMb}. The time interval T between two tests should be long enough to include all the potential short term effects involved in the random measurement error, but short enough to avoid systematic changes, e.g., due to age.

Table 2-1 Characteristics of the subjects who had two lung function tests within six months from May 1994 to March 1998

Characteristic	First measurement		Second measurement		Average within-person difference			
	Mean	Variance	Mean	Variance	Mean	Variance	P-value	G
Black miners (n=3378)								
Age	41.75	101.7	42.00	101.6	3.730			
Weight,kg	67.42	106.7	68.00	108.6	0.588	0.0043	0.0001	
Height,cm	1.697	0.005	1.696	0.004	-0.0016	0.0016	0.0234	
FVC (l)	3.649	0.496	3.638	0.495	-0.0102	0.1360	0.1091	0.862
FEV1 (l)	3.000	0.422	2.978	0.432	-0.0212	0.0938	0.0001	0.890
FEF (l/s)	3.289	1.460	3.234	1.450	-0.0550	0.4136	0.0001	0.857
FEV1%	0.821	0.006	0.817	0.006	-0.0042	0.0020	0.0001	0.820
White miners (n=94)								
Age	36.06	123.3	36.43	124.5	3.947			
Weight,kg	86.33	201.1	86.56	216.4	0.032	10.074	0.922	
Height,cm	1.796	0.004	1.795	0.004	-0.0019	0.0003	0.274	
FVC (l)	4.589	0.799	4.475	0.842	-0.1149	0.1738	0.010	0.894
FEV1 (l)	3.683	0.576	3.587	0.567	-0.0961	0.1030	0.005	0.910
FEF (l/s)	3.750	1.424	3.595	1.186	-0.1546	0.3212	0.010	0.881
FEV1%	0.804	0.005	0.802	0.060	-0.0013	0.0035	0.754	0.818

Table 2-2 Reliability statistics for the period October 1994 to August 1996

Characteristic	First measurement		Second measurement		Average within-person differences			
	Mean	Variance	Mean	Variance	Mean	Variance	P-value	G
Black miners (n=1001)								
Age (yr)	38.09	106.5	38.33	106.9	3.532			
FVC (l)	4.031	0.480	4.035	0.450	0.0037	0.1105	0.724	0.882
FEV1(l)	3.383	0.423	3.375	0.426	-0.0079	0.0615	0.315	0.928
FEF (l/s)	3.856	1.814	3.817	1.784	-0.0387	0.4279	0.062	0.881
FEV1%	0.838	0.006	0.835	0.006	-0.0037	0.0024	0.018	0.793
White miners (n=33)								
Age (yr)	38.88	145.2	39.30	144.0	4.212			
FVC (l)	4.856	1.130	4.868	1.223	0.0116	0.1849	0.879	0.922
FEV1 (l)	3.902	0.736	3.940	0.747	0.0385	0.0926	0.473	0.938
FEF (l/s)	4.004	0.550	4.052	0.498	0.0482	0.3294	0.633	0.920
FEV1%	0.807	0.007	0.814	0.005	0.0064	0.0023	0.447	0.810

Table 2-3 Reliability statistics by age strata, for FEV1, FVC, and FVC%, for period from October 1994 to August 1996

Lung function	Age	N	First PFT		Within-person difference			G
			Mean	Variance	Mean	Variance	P-value	
FEV1	<25	69	3.707	0.270	0.0470	0.0584	0.113	0.898
	25 - 34	352	3.658	0.242	0.0086	0.0665	0.530	0.863
	35- 44	304	3.467	0.312	-0.0225	0.0610	0.113	0.901
	45- 54	184	2.970	0.416	-0.0288	0.0541	0.095	0.933
	55+	92	2.638	0.335	-0.0220	0.0590	0.388	0.911
FVC	<25	69	4.203	0.335	0.0606	0.0734	0.068	0.891
	25 - 34	352	4.264	0.331	0.0227	0.1080	0.196	0.835
	35 - 44	304	4.164	0.411	-0.0224	0.1090	0.238	0.859
	45 - 54	184	3.645	0.477	-0.0084	0.1299	0.753	0.861
	55+	92	3.350	0.351	-0.0011	0.1139	0.975	0.824

Section 3 - Lung function prediction equations derived from healthy South African gold miners

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Authors: Eva Hnizdo, Gavin Churchyard, Rob Dowdeswell

3.1   Abstract

Objectives - To estimate the prediction equations for lung function measurements performed on South African gold miners and to select appropriate normal reference values for the gold mining

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population which consists of around 300 000 miners .

Methods - Data collected from a lung function screening done on a large South African gold mine over four years were used to estimate the prediction equations. The temporal pattern in the reliability of the 113 120 computerized lung function tests was previously determined, and lung function tests from the most reliable period of testing were used for this study. Miners with a previous history of pulmonary tuberculosis or with radiological abnormalities on the miniature chest radiograph were excluded. The prediction equations were estimated cross-sectionally from 15772 lung function tests done on black and 2752 tests done on white miners and compared with published reference equations.

Results - The black miners had lower forced vital

Conclusion - Of the published reference equations, the Knudson's and the European Community of Coal and Steel (ECCS) provided the closest fit with the estimated prediction equations for the white miners. The ECCS equations provided "a lower limit of normal" (i.e. a one-sided 95% lower confidence limit) that was closest to the observed one-sided lower 95% confidence limit based on the Normal distribution for a cross-section of 30-35 years old miners. For the black miners, the reference equations derived from black South African males by Louw et al. fitted best. For the ECCS reference values to be applicable to the black miners we recommend a conversion factor of 0.92 for the predicted FVC and 0.95 for the predicted FEV_1 . None of the equations provided a good fit for the young (20-29 yr) and older (over 55 yrs) age categories. A strong cohort effect for heigh is supported by the fact that men 50 yrs of age are 3.6 cm shorter than 20 yrs olds. Thus the linear regression parameters for age obtained from the cross-sectional data may provide a biased estimate for yearly loss of lung function with age.

capacity (FVC) and forced expiratory volume in one second (FEV_1), but higher the ratio of FEV_1/FVC (FEV_1 %) and forced expiratory flow at 25 to 75% of forced vital capacity ($FEF_{25-75\%}$), compared to white miners. The difference between the two groups in the height adjusted mean values for 40 years old 1.7 m tall men was 220 ml (5.2%) for FVC and 110 ml (3.2%) for FEV_1. The estimated prediction equations (PE) for forced vital capacity (FVC) were as follows: for blacks, -2.901- 0.025×age + 4.655×height; and for whites, -4.407 - 0.036×age + 5.940×height. The PE for FEV_1 were: for blacks, -1.654 - 0.30×age + 3.665×height; and for whites, -2.341 - 0.038×age + 4.314×height. Here, age and height are in years and metres, respectively.

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3.2   INTRODUCTION

Screening for impairment for lung function is an essential element of any occupational health surveillance programme where workers are exposed to respiratory hazards. Primary objectives are to identify those who develop impairment of lung function so that corrective measures can be taken, to assure respiratory fitness for certain categories of work, and for assessing disability for compensation purposes. Fundamental to these objectives is the availability of appropriate reference values.

In the South African gold mining industry about 300,000 miners are at risk of developing respiratory diseases associated with exposure to crystalline silica. Legislation for pulmonary function

screening of all miners has only been introduced in South Africa recently.[1] There is, however, uncertainty as to the most appropriate reference values for assessing black miners. The use of the European Community for Coal and Steel (ECCS) reference values[2] has been suggested for general use in South Africa,[3] but their appropriateness, particularly for blacks, has never been evaluated. The appropriateness of the reference values is potentially important in screening programmes for an early detection of accelerated loss of pulmonary function, the assessment of fitness to work underground and compensation.

The objective of this study was to evaluate how well published equations for lung function[4,5] fit South African gold miners. For this purpose, we used lung function measurements from a large South African gold mining company. In a previous study, we established the reliability of the lung function measurements, and have used the most reliable testing period (average reliability coefficient G 0.93 for FEV_1) for the purpose of this study.[6] Here, we estimate cross-sectionally prediction equations from 15,772 lung function tests done on black and 2752 tests done on white miners.

During the period May 1994 to March 1998, 113 120 spirograms were recorded in the computerized database. In a previous study[6] we examined reliability of the spirograms over time, and for this study used data from the period January 1995 to August 1996 which showed the most reliable measurements. In total 45 053 tests were done during the reliable period,[6] from January 1995 to August 1996. Of these, 36777 (31108 black, 3270 white) were on miners on whom information on history of pulmonary tuberculosis and radiology was available. The remaining subjects were contract workers with incomplete information. From the 31108 tests on black miners, we excluded 3905 subjects with a previous history of pulmonary tuberculosis (TB) and 1485 subjects with radiological changes (due to TB,

3.3   Material and Methods
3.3.1   Spirometry measurements.
Spirometry is performed routinely on all miners at entry into the industry (initial examination), periodically at three-year intervals (periodical examination), and on leaving (exit examination). Maximal forced expiratory maneuvers are recorded using a Hans Rudolph pneumotachograph (Flowscan, Electromedical Systems Inc) by technicians trained in the techniques of performing spirometry to American Thoracic Society (ATS) standards.[7] The system software requires and validates calibration with a 3.00 L syringe and allows keyboard entry of barometric pressure and ambient temperature for the correction to BTPS conditions. A minimum of three acceptable and reproducible forced expiratory maneuvers are obtained according to the ATS standards.[7] Height is measured to the nearest centimetre (without shoes). Data recorded for each test include date of test, date of birth, height, weight, largest forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and forced expiratory flow at 25 to 75% of forced vital capacity ($FEV_{25-75\%}$).

pneumoconiosis, pneumonia, cardiomegaly, pleural changes, etc) (there was an overlap).[1] Of the 26024 remaining tests on black miners, we excluded 273 (1.05%) with lung function or height measurements outside confidence limits (3.5 times the standard deviation). (The 99% confidence limits were too narrow and excluded acceptable observations.) Of the remaining 25751 tests, 1198 were initial, 15572 periodical, 8204 exit and 777 other type of examinations. Of the 3270 tests done on white miners, 2 and 20 were excluded

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[1] All cases of TB were computerized from 1979 to 1998. The yearly radiological screening is done on miniature 100x100 mm chest radiographs, and abnormality were computerized cross-sectionally from 1994 to 1998.

because of a history of TB and radiological changes, respectively, and 39 (1.2%) were excluded because lung functions or height were outside confidence limits (3.5 times standard deviation). Of the remaining 3248 tests, 158 were initial, 2752 periodical, 174 exit, and 59 from other type of examination.

During the preliminary analysis the initial and exit examinations showed slightly decreased values. Since the number of periodical examinations was large, only the periodical examinations were used in the analysis. The initial tests may be lower because of the "learning effect" and the exit examinations may be lower because of a selection process. The periodical examinations are likely to provide a representative sample of the current miners.

3.3.2 Statistical analysis

The lung functions were analysed cross-sectionally. The observed lung function values were standardized to the average height (ht) of the black miners of 1.70 m. To determine the best

The lower limit of normal, i.e, the one-sided lower 95% confidence limit, LL, was calculated as $LL = P_{(age,1.7)} - 1.645 \times SEE$, where $P_{(age,1.7)}$ is the age- and hight-specific predicted value, and SEE is the average standard deviation (s.d.) of the data around the regression line,[4] also called the standard error of the estimate of the regression line. We used the standard deviation around the regression line $S y.x$,[9] obtained as the square root of the mean square error (MSE) from the regression analysis, which is equivalent to SEE.

To compare the proportions of miners that fall below the LL of normal for the various equations, we used a cross-section of subjects in the 30-35 age group. The variation in lung function in this age group is likely to be least affected by adverse health effects due to exposure, and also the observed means for this age group were identical with the reference curves (see Figures 2 and 3,

parameter for body size adjustment we fitted the model[8]

$PF = (b_0 + b_1 \times age + b_2 \times age^2) \times ht^n$.

The best model for body size adjustment for black and white miners was with n=2. Thus, the observed lung function values were hight-adjusted as $PF \times (1.7^2 / ht^2)$. The prediction equations were estimated separately for 15772 and 2752 tests done on black and white miners, respectively, by fitting the following linear regression model[8]

$PF = b_0 + b_1 \times age + b_2 \times height + b_3 \times weight + b_4 \times age \times height + b_5 \times age^2.$ (1)

Only parameters that contributed significantly to the R^2 statistic were retained. The prediction equations were plotted with the observed values, the American Thoracic Society (ATS) reviewed reference equations[4] and the reference equation for South African blacks[5]. Reference equations that fitted closely to the predicted curves are reported.

below). Because we are dealing with an occupational group, the SEE value could be affected by the effect of exposure, especially in the older ages. As the number of subjects in the 30-35 age category was large (4503 blacks and 620 whites), the frequency distribution was close to Normal. The percentage of 30-35 year olds that were below the LL of normal was calculated using the standardized normal deviate, *z*, derived from the observed mean, the LL of normal for each equation, and the observed standard deviation.[10]

The descriptive statistics and the LL of normal were calculated also for percent predicted values. The percent predicted values that corresponded with one-sided 95% confidence limit (mean-1.645 x s.d.) and the 5th percentile were determined by ten year age categories.

3.4   Results

Figure 3-1 shows the age distribution for black and white miners in the study. Table 3-1 shows the observed means for lung function and the estimated prediction equations (regression coefficients and standard errors, s.e.) for blacks and whites. The contribution of age^2 and height x age interaction to the variation explained by the model was small (additional R^2 was 0.0002 and 0.0004, respectively, for FEV_1). This is because most subjects were between 30-50 years of age. Thus for the final prediction equations we included age and height only.

Figure 3-2 shows, plotted against age, the height-standardized observed mean lung functions

Figure 3-4 shows for the cross-section of 30-35 year old black miners, the frequency distribution for height-adjusted FVC, FEV_1, and FEV_1%. Fitted over each observed distribution is the Normal curve for the observed mean and standard deviation, and the Normal curves for the means predicted by the ECCS and Louw's equations and respective published SEE values. The predicted LL of normal for our prediction equation, ECCS and Louw's equations (calculated as Predicted - 1.645 x SEE) are also shown. Table 3-2 shows the corresponding descriptive statistics for the observed data for the 30-35 years olds, LL of normal and the percent of subjects found below the LL of normal for the different equations. Louw *et al.*[5] did not provide reference equation for the FEV_1%.

Table 3-3 shows, for the black miners only, the descriptive statistics for the precent predicted based on our prediction equation, and the percent predicted values corresponding with the one-sided lower 95% confidence interval and with the lower 95th percentile, according to ten years age categories, for the selected reference equations.

3.5   Discussion

The objective of the study was to identify the most suitable published reference equations for the population of South African gold miners. Lung

(FVC, FEV_1, FEV_1%), two-sided 95% individual confidence intervals, predicted curves and the lower limits of normal (Predicted-1.645xSEE), for blacks. Plotted on the graphs are also the best fitting reference equations, and the respective LL of normal (Predicted 1.654xSEE). The reference equations by Louw *et al.*[5] measured by vitalograph fitted best. Predicted values from the ECCS[2] reference equations are too high. ECCS predicted values multiplied by a conversion factor (CF) of 0.92 for FVC and 0.95 for FEV_1 were identical with our predicted curves. Figure 3-3 shows the plots for whites. For whites, the reference equations for ECCS, and Knudson *et al.*,[9] fitted best.

function measurements from a screening programme done on a large gold mine were used. In the preceding study,[6] we established the temporal patterns in the reliability of the lung function tests, and for this study we used the most reliable period. We estimated the best predictive equations for the black and white miners and identified the reference equations that fitted best on visual inspection. Next, we calculated, for a cross-section of 30-35 year old subjects, the percentages that were below the LL of normal for each equation.

The number of subjects included for the estimation was large for most of the age categories, starting from 21 years of age, see Figure 3-1. The body size adjustment was best when the height was exponentiated to the power of two. Only age and height were included in the final regression model, as the other parameters tested [see Eq.1] contributed minimally to the amount of variability explained by the model. Table 3-1 shows the observed means and the predicted value for a male of 40 years of age and 1.7 m tall. The differences in the observed means between the white and black miners was 860 ml (17.3%) for FVC, 630 ml (14.9%) for FEV_1, -180 ml (-6.8%) for $FEF_{25-75\%}$, and -2.38% (-2.9%) for FEV1%. However, after age and height adjustment, the differences for 40 years old and 1.7m tall men decreased to 220 ml (5.2%) for FVC, 110 ml (3.2%) for FEV_1, -160 ml

(-4.3%) for $FEF_{25-75\%}$, and -1.6% (-2.0%) for FEV_1 %,

     The height-standardized means plotted against age and compared to the published reference equation for black and white males are shown in Figures 3-2 and 3-3. For whites, the curves derived from the ECCS and Knudson equations, for FVC and FEV_1, fitted best (Figure 3-3). In comparison to the reference curves, the prediction curves show a steeper decline from about 40 years of age. For FVC, the LL of normal for the ECCS equation was narrower than Knudson's and our's PE, but for FEV1 the limits were similar. The percentage of subjects below the LL of normal, for 30-35 year olds, for the ECCS equation, for whites was 5.4% for FVC, 6.4% for FEV_1 , and 3.1% for FEV_1% (see Table 3-2). For Knudson's equation the percent   rejected for FVC was only 3% indicating that Knudson's LL of normal was too wide. For FEV_1%, the ECCS curve was too low, whereas Knudson's curve fitted well (Figure 3-3). Table 3-2 shows that for 30-35 year old whites, the mean value for FEV1% was 82.5% and the observed one-sided lower 95% confidence interval was 73.0%. The Knudson's LL of normal was identical, whereas ECCS's and our PE were 71.7%.

     For the black miners, the reference equations that fitted best were those derived for black South African males by Louw *et al.*[5] using vitalograph   measurements.   The   study   also measured   the   same   subjects   by   Autolink spirometer, but those values were excessively too high.   The ECCS reference equations   are commonly used in South Africa for all subjects, and an ethnic   conversion factor of 0.88 (as recommended by ATS[4]) is often build into the spirometers. The ECCS curve was almost 500 ml higher at 20 years of age for FVC.   Similar differences applied to the LL of normal. The size of the area below the LL of normal derived for each reference equation, for the observed Normal

     The   above   statistical   considerations assume that the distribution of lung function measurements are normal. Though the observed

respectively.

distribution for the 30-35 year olds, is shown in Figure 3-3 and Table 3-2. For the Louw's equation, the percent rejected was 6.8% for FVC and 3.8% for FEV_1, whereas for the ECCS equation this was 15.2% for FVC, 12.5% for FEV_1 and 3.8% for FEV_1%. The LL of normal obtained from our prediction equations were close to the one-sided   95% confidence intervals for the observed distribution for the 30-35 year old. This result is in agreement with the fact that the predicted curves for FVC and FEV_1, and the LL of normal were parallel with the Louw's reference curves derived on asymptomatic, healthy, non-smokers, i.e,   the regression SEE was not influenced significantly by the older age categories as it was in white miners.

     The percentage rejected for whites by predicted equation was lower than 5% (see Table 3-2). One of the reasons for the differences in decline may be that black miners generally smoke less, and thus their lung function loss with age for "healthy" miners is lower than for the white miners. The observed and predicted values for FEV1% were much higher than the estimates from the ECCS equations, but the decline in FEV1% was steeper in black miners (Figure 3-2). The high FEV_1% could be due to a real effect, or a systematic measurement error resulting in lower FVC. For the observed frequency distribution for FEV_1% for the 30-35 year olds (Figure 3-3), the observed mean was 85.5%. In comparison, the predicted mean from the   ECCS equation was 80.4%. The observed one-sided 95% confidence limit was 75.5%. The lower LL of normal derived from our predicted equation was 74.7% and the one derived from the ECCS equation was 71.7%. The size of the rejection region for each curve is shown in Table 3-2.

frequency distributions for FVC, FEV_1 and FEV_1%, shown in Figure 3-4, appear to be normal, the skewness statistics in Table 3-2 indicate that the

distribution for FVC has a longer tail to the right, the distribution of FEV$_1$ is normal, and for FEV$_1$% it has a longer tail to the left. This pattern is similar for black and white miners.

The usage of 80% predicted as a criteria for "abnormal" is not recommended in adults by the ATS,[4] although some studies have shown that 80% of predicted is close to the fifth percentile.[9] To deal with skewness and variability in the distribution of percent predicted, the 5th percentile is considered a preferable criteria for the LL of normal. Other shortcomings of the usage of fixed value of percent predicted are that shorter, older subjects are more readily classified as "abnormal", whereas taller, younger adult subjects are more likely to be erroneously classified as "normal".[4] In South Africa, it has been suggested that the grading of lung function impairment for compensation purposes is based on percent of predicted derived from the ECCS reference values.[3] The percent predicted categories of impairment for FEV1 and FVC are as follows: normal >=80%, 79-65% for mildly impaired, 64 - 51% for moderately impaired and <51for severely impaired. We examined the percent predicted values corresponding with the 5th percentile and the lower 95% confidence limits, for different reference equations, according to age categories (Table 3-3).

For FVC and FEV1, the lower limit of normal for the percent predicted corresponded

Generally, cross-sectional studies report a linear decline for FEV1 of about 20-30 ml/year from about 25 years of age[7] and our results agree with that. However, longitudinal studies report that the decline in lung function starts later (about 35 years of age) and increases with age.[11] In our reliability study, we observed a similar effect.[6] The discrepancy between the cross-sectional and longitudinal studies may be also due to a cohort effect due to increasing height in the younger age groups. To examine this issue, we related height to age, and found that the estimated decline in height from 20 to 50 years of age was 3.3 cm in whites

with 80% for our prediction equation and Louw's equation, but was lower for ECCS equation (Table 3-3). The percent predicted based on our prediction equation started to decrease below 80% at 50 years of age for FVC and at 40 years of age for FEV1. For FEV$_1$%, the percent predicted started at 89% for the youngest age category, and decreased to around 83% for the oldest age category. There were no important difference between the LL of normal values calculated as the 5th percentile or the 95% confidence limit. The percent predicted values corresponding to the LL of normal depend on how well the reference equation fits the actual data, but even for the best fitting linear curve, the values were age related. If subjects older than 50 years of age have a steeper decline in lung function than the predicted values, then the 80% criteria does not apply for a linear curve. The criteria of 80% of predicted did not apply well to FEV$_1$ % for black miners. If strictly applied, the recommended percent predicted for compensation purposes may lead to the diagnosis of different level of impairment in different age categories and in different race groups. The actual FEV$_1$% of 75% is a more reliable criteria of impairment as it corresponds with the 95% lower confidence limit for both race groups. For a more reliable assessment of the degree of impairment in the over 50 age groups the age[2] parameter should be included in the prediction equations for FEV$_1$ and FVC.

and 3.6 cm in blacks (see Figure 3-5). Since age and height are correlated, and the linear regression model assumptions are that the explanatory variables are independently distributed, the estimated parameters for age and height obtained from our study are likely to be biased and could overestimate the effect of age. Thus, the predicted equations derived from our study are accurate for predicting impairment cross-sectionally, but are likely to be inaccurate for predicting the annual loss of lung function. It has been observed that longitudinal lower limits of normal could add sensitivity when identifying undue loss of lung

function.[12]

When compared to other published studies, the prediction equations for black gold miners agree most closely with those found in other studies of South African black males occupationally exposed to dust (see Table 3-3).[13] Altitude was also observed to be associated with an increase in FEV1 of 173 ml per 1 000 m above sea level.[13] For FVC, the predicted values for 38 years old 171cm tall male are similar to those observed for textile workers[13] and vermiculite miners,[14] and for university workers[15]. Thus the high ratio observed in this study could be due to a real effect.

In summary, for whites, of the reviewed reference equations,[5] the ECCS and Knudson et al. equations fitted best and were very similar. The lower limits of normal derived from the ECCS equations are slightly better for FEV_1 and FVC in terms of rejecting 5% of the subjects. However, for FEV_1%, the Knudson's equation fitted better. For black miners, Louw's reference equations fitted most closely. The ECCS equations did not predict the observed means well and the proportion of subjects that were below the lower limits of normal was too high for FVC (15%) and FEV_1 (13%). The observed FEV_1% values were much higher than the ECCS estimates. When the ECCS reference values were multiplied by 0.92 for FVC and 0.95 for FEV_1, the ECCS curve became almost identical with our predicted curves. We would thus recommend that the ECCS reference values with these conversions be used on black South African miners, rather than the ECCS reference values unadjusted or the ethnic coefficient of 0.88 for FVC and FEV_1 used as recommended by ATS. Because of the strong correlation between height and age, the estimated regression parameters for age and height are likely to be biased, and though the curves are suitable for estimating lung function cross-sectionally, they may not predict the correct yearly loss of lung function.

3.6 REFERENCES

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Table 3-1   The observed means for lung function and the prediction curves and predicted values, for black and white miners

Lung Function	Observed values		Regression Coefficient (s.e.)			R^2(%)	SEE*	Prediction, age 40, ht 1.7 m
	Mean	s.e.	Intercept	Age	Height			
Black miners n=15 772, age 38.7 (s.e.,0.06), height 1.71m (s.e., 0.005)								
FVC (L)	4.10	0.005	-2.901 (0.120)	-0.025 (0.001)	4.655 (0.068)	33.5	0.528	4.02
FEV$_1$ (L)	3.44	0.005	-1.654 (0.109)	-0.030 (0.001)	3.665 (0.061)	35.5	0.477	3.38
FEF (L/s)	3.96	0.010	1.363 (0.274)	-0.056 (0.001)	2.780 (0.154)	14.6	1.200	3.86
FEV$_1$%	84.1	0.055	102.56 (1.511)	-0.237 (0.007)	-5.437 (0.848)	7.24	6.627	83.8
White miners n=2 752, age 36.9 (s.e., 0.06), height 1.80m (s.e., 0.001)								
FVC (L)	4.96	0.016	-4.407 (0.339)	-0.036 (0.001)	5.940 (0.182)	44.1	0.547	4.24
FEV$_1$ (L)	4.04	0.014	-2.341 (0.300)	-0.038 (0.001)	4.314 (0.161)	43.4	0.484	3.49
FEF (L/s)	4.14	0.024	0.824 (0.640)	-0.050 (0.002)	2.866 (0.344)	16.8	1.039	3.70
FEV$_1$%	81.7	0.129	107.68 (3.601)	-0.172 (0.014)	-10.932 (1.94)	5.8	6.555	82.2

* pct=percentile. s.e.=standard error.

Table 3-2   Descriptive statistics for height-standardized lung function for 30-35 years old, and the lower limits of normal and percent rejected for the predicted and selected reference equations

Lung function	Mean	Standard deviation	Skewness	Lower 95% CI	Lower limit of normal and % rejected for the different equations		
Black miners, n=4503, age=32.6 (s.d.1.7), height=1.7					Predicted	Louw	ECCS
FVC (L)	4.21	0.51	0.14	3.37	3.34; 4.6%	3.44; 6.8%	3.68; 15.2%
FEV1 (L)	3.60	0.46	-0.03	2.84	2.81; 4.5%	2.78; 3.8%	3.07; 12.5%
FEV1%	85.6	6.11	-0.74	75.5	74.7; 3.8%	NA	71.7; 1.2%
White miners, n=620, age=32.7 (s.d. 1.7), height=1.8					Predicted	Knudson	ECCS
FVC (L)	4.54	0.53	0.15	3.66	3.53; 2.9%	3.54; 3.0%	3.68; 5.4%
FEV1 (L)	3.74	0.45	-0.01	3.01	2.84; 2.2%	2.98; 4.5%	3.06; 6.4%
FEV1%	82.5	5.8	-0.27	73.0	71.7; 3.1%	73.0; 5.0%	71.7; 3.1%

Table 3-3 The percent predicted corresponding with the 5th percentile and the one-sided 95% confidence limits for different equations

Age	N	Mean	S.D.	Skewness	Predicted equation		Louw's equation		ECCS equation	
					5% pct*	95% CI	5% pct	95% CI	5% pct	95% CI
FVC										
<30	1692	99.2	11.8	0.07	80.6	79.7	78.7	78.0	72.6	72.0
30-39	7430	100.6	12.4	0.17	80.9	80.2	78.9	78.2	73.8	73.0
40-49	4947	100.8	13.7	0.15	79.5	78.3	77.2	76.1	73.4	72.1
50+	1704	99.9	14.6	0.07	76.1	75.8	73.6	73.3	71.7	70.8
FEV1										
<30	1692	99.6	12.3	-0.22	80.4	79.4	82.5	81.7	76.7	75.7
30-39	7430	100.1	13.1	-0.01	78.9	78.5	80.7	80.3	75.2	74.9
40-49	4947	99.9	15.0	-0.17	75.3	75.2	76.3	76.3	71.8	71.7
50+	1704	99.9	16.8	0.23	71.3	72.4	71.2	72.7	68.0	68.9
FEV1%										

<30	1692	100.5	7.0	-0.68	88.5	89.0	NA	NA	94.6	95.0
30-39	7430	99.9	7.3	-0.74	87.3	87.9	NA	NA	92.6	93.3
40-49	4947	99.8	8.5	-0.94	84.9	85.9	NA	NA	89.3	90.6
50+	1704	100.6	9.7	0.97	82.5	84.7	NA	NA	86.3	88.6

Table 3-4   Comparison between studies of occupational groups done on black men in South Africa in higher altitude

First author (ref no)	Mean age,yr Mean ht, cm	Altitude	Males age 38 yr, height 171 cm		Type of sample
			FEV1	FVC	
White (NW)	36.1, 167.3	1 500	4.12 (3.99-4.25)	3.46 (3.36-3.56)	textile workers
Louw (L)	41.1, 169.7	1 700	4.21 (4.14-4.28)	3.44 (3.57-3.51)	bank workers, autolink
Hessel (H)	41.6, 171.4	400	4.13 (-)	3.29 (-)	vermiculite miners
Coetzee (C)	33.1, 169.4	1 700	4.30 (4.25-4.35)	3.55 (3.50-3.60)	asbestos workers
Mokoetle (M)	42.0, 168.7	1 700	4.42 (-)	3.47 (-)	university workers
Fox (F)	34.4, 171.7	1 200	4.20 (4.16-4.24)	3.52 (3.46-3.58)	copper/nickel miners
Our study	38.7, 170.8	1 700	4.12 (4.12-4.12)	3.47 (3.47-3.47)	gold miners

Section 4 - Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment

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Authors: Eva Hnizdo, Tanusha Singh, Gavin Churchyard

4.1 ABSTRACT

Objective - To establish the chronic effect of initial and recurrent treated pulmonary tuberculosis (TB) on lung function impairment.

Material and methods - A cohort of 27660 South African gold miners who had pulmonary function tests done from January 1995 to August 1996 were retrospectively followed for the incidence of pulmonary tuberculosis to 1970. There were 2137 miners who had one episode of TB, 366 who had two, and 96 who had three or more episodes. The average lapsed time from the diagnosis of last episode of TB to lung function test was 4.6 years (range 1 month to 32 years). The incidence of TB and the

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lapsed time were related to lung function at the end of follow-up. Miners without TB or pneumoconiosis were used as a comparison group.

Results - The loss of lung function was highest within six month of TB diagnosis. After 18 months the loss became constant and was considered to be chronic. The chronic loss of FEV_1 after one, two, three or more episodes of TB was 139 ml, 312 ml, and 396 ml on average, respectively. The corresponding losses for FVC were 88 ml, 278 ml, and 337 ml, respectively. The loss of function was similar in HIV+ and HIV- subjects. The percentage of subjects with chronic airflow impairment (%predicted FEV_1<80%) was 18.4% in those with one episode, 27.1% in those with two, and 35.2 % in those with three and more episodes of TB.

Conclusion - TB can cause chronic lung function impairment which increases with the number of episodes of TB. The impairment can lead to the development of chronic obstructive airflow in a large percentage of subjects. Prevention of lung function impairment caused by TB through improved case finding and treatment regiments is important. However, reduction of risk of TB through intervention on risk factors should be a first health and safety priority in the gold mines.

4.2   INTRODUCTION

Several studies have shown that early and partially treated pulmonary tuberculosis can result in airflow obstruction.[1-5] Studies with longer follow-up have shown that a large percentage of cases with treated pulmonary tuberculosis have evidence of permanent airflow obstruction or restrictive impairment.[6-8] There are no published studies in which the effect of recurrent episodes of treated pulmonary tuberculosis on lung function impairment was evaluated.

The South African gold mining industry employs over 300 000 miners. The risk factors for TB in gold miners include silica dust exposure,[9,10] silicosis,[10,11,12] HIV infection,[13] socio-economic factors, and the high risk of TB in the general South African population. 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). With the advent of HIV, the TB rates have been rising consistently and currently these are in excess of 2 000 per 100 000.[14] The mines have active and passive case finding programmes, and the treatment of TB follows to World Health Organization standards. Prior to 1980, miners who developed pulmonary tuberculosis were not allowed to return to underground mining, but with the introduction of a more effective TB treatment in the early 1980s most miners return to underground mining at a certain stage of treatment.

The objective of this study was to estimate the effect of the number of recurrent treated TB episodes, and the time elapsed between the last TB

episode and lung function tests, on lung function impairment in a cohort of 27 660 South African gold miners in whom pulmonary function was assessed cross-sectionally from January 1995 to August 1996, and in whom the incidence of pulmonary tuberculosis was ascertained retrospectively to 1970. Specifically, we evaluated (1) the effect of number of treated TB episodes on lung function loss; (2) the effect of time lapsed from last TB episode to lung function test on lung function loss; (3) the effect of HIV on the loss of lung function due to TB; and (4) the proportion of subjects with chronic airflow impairment (percent predicted FEV1<80%), according to the number of TB The company has an active case finding programme through mass miniature radiograph (MMR) screening and passive case detection. Up to 1993, screening radiographs were taken six monthly, but from 1994 the frequency was reduced to once a year. Patients with radiological changes are referred for further investigation, which includes standard size chest radiographs, sputum microscopy and culture. All patients with suspected TB have three sputum specimens collected for microscopy and culture. All sputum specimens are decontaminated, concentrated and stained with auramine and Ziehl-Neelsen for microscopy, and culture on LÅ Wenstein Jensen slants in the hospital laboratory. Initial identification is done by the local laboratory. From 1994, the Accuprobe ® M. Tuberculosis complex culture identification test (Gen-Probe incorporated, San Diego, USA), a rapid DNA probe test which utilizes the technique of nucleic acid hybridization for the identification of M. Tuberculosis complex species, has been used to distinguish M. Tuberculosis from other mycobacteria. The diagnosis of TB is based on radiological, clinical and bacteriological results using a validated scoring system, in accordance with the standard case definition used by the South African national TB programme [more details needed]. On entry into the employment, the miners are interviewed for a previous history of TB, and this is also computerized.

episodes, in subjects with lapsed time over 18 months.

4.3 Material and Methods

The miners were selected from a large gold mining company, which has kept computerized records of each TB episode on each miner since 1970 and a computerized database of lung function tests performed on all miners from 1994 to 1998.

4.3.1 TB case detection.

4.3.2 HIV testing.

All patients with suspected TB are offered voluntary HIV testing, with pre-and post test counselling. HIV is diagnosed if both the screening (Enzymun-test (R) Anti-HIV 1+2+subtype 0, Boehringer Mannheim Immunodiagnostics) and confirmatory Elisa (IM (R)x system HIV-1/HIV-2 III Plus, Abbott diagnostics) are positive.

4.3.3 Pneumoconiosis detection.

MMR screening for pneumoconiosis is also done. Subjects whose radiographs are identified during the MMR as abnormal are referred for further examination which includes standard chest radiography. Identity of subjects diagnosed as having silicosis category 1/1 and above according to ILO category on standard radiographs has been recorded cross-sectionally on a computerized database since 1994.

4.3.4 Lung function screening.

Lung function screening was introduced in 1994. Miners have lung function examinations on entry into the employment, and thereafter periodically every three years, and on exit from employment. In a reliability study[15], we examined the reliability of lung function testing and cleaned the data for outliers. We established that lung function tests were most reliable from January 1995 to August 1996. We, using data from this period estimated predictive lung function curves for miners without previous TB history or

pneumoconiosis and found these to be comparable to those estimated on non-smoking and non-symptomatic black South African males not exposed to dust.[16] The details of the lung function testing procedure are The cohort of 27660 comprised all miners who had a periodical or exit lung function examination done during the reliable testing period (January 1995 to August 1996). For the cohort, we established retrospectively their TB history by linking the lung function data with the pneumoconiosis status database and the history of TB database. All TB episodes which occurred in a miner prior to a lung function test were related to that lung function test. Only one lung function test per miner was included in the study. For miners who did not have TB, only the first lung function test was used in the analysis. There were 18754 periodic examinations and 8906 exit examinations. In a preliminary analysis, we analysed the two types of examinations separately and established that the results were very similar, and thus the two were combined.

4.3.6   Statistical analysis.

For the descriptive analysis we standardized lung function tests for a height of 1.70 m and tabulated the observed and predicted lung function tests using prediction equations calculated on miners without TB or pneumoconiosis.[16] Multiple regression analysis was used to estimate the effect of the number of episodes of TB and the time lapsed on lung function. In the regression model we used 0/1 dummy variables for one, two and three or more episodes of TB and for the time lapsed categories of 6 months, 7-12 months, 13-18 months, 19-24 months, <3 yrs, <4 yrs, <5 yrs, and 6 or more yrs. To establish that HIV is not a confounding factor, we estimated the effect of TB episodes in subjects who tested negative for HIV and in subjects who tested positive for HIV. A comparison group used throughout the analysis comprised

Table 4-4 shows the age and height adjusted regression coefficients and standard errors for the number of TB episodes (3 and more episodes were combined in one group), and the time elapsed from

described in the reliability study.[15]

4.3.5   Cohort selection.

subjects who did not have a history of TB or pneumoconiosis. The percent of subjects with chronic airflow impairment defined as a percentage of predicted $FEV_1<80\%$ was established using normal distribution statistics[17] in subjects with lapsed time over 18 months.

4.4   RESULTS

Tables 4-1 and 4-2 show the observed and percent predicted mean values for height adjusted FEV_1 and FVC, according to the number of episodes of TB for five year age categories. Subjects who had radiological changes for pneumoconiosis were excluded from these tables. Consistent decrease with each episode of TB is apparent across all age categories.

Table 4-3 shows the, age and height adjusted, regression coefficients β and standard errors (s.e.) for each of the lung function tests (FVC, FEV_1, $FEV_1\%$ and $FEF_{25-75\%}$). The regression coefficients represent the decrement of lung function in litres in subjects with increasing number of TB episodes, in subjects with pneumoconiosis and TB, and in subjects with pneumoconiosis only, in comparison to subjects who did not have TB or pneumoconiosis. For example, the FEV_1 decreased on average by 180 ml in those with one episode of TB, by 362 ml with two episodes, by 462 ml with three episodes, and by 964 ml with four and more episodes. Subjects with pneumoconiosis and a recorded history of TB had a decrease of 384 ml, and subjects with pneumoconiosis only had a decrease of 215 ml.

the diagnosis of the last episode of TB to the lung function test. The coefficients allow us to calculate the loss due to specific number of episodes and time elapsed. For example, the loss of FEV_1 in subjects with

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one episode of TB and a lapsed time of 6 months is $(0.729 + (-1.055))\times1000=-326$ ml, with 12 months it is $(0.729+ (-0.975)\times1000=-247$ ml, with 18 months it is $(0.729+(-0.868)\times1000=-139$ ml, and with 24 months it is $(0.729+ (-0.865))\times1000=-136$ ml. For subjects with three and more episodes, the corresponding losses are -583 ml, -503 ml, -396 ml and -393 ml, respectively. The data show that the loss of lung function is highest in the first six months and continues to decline up to 18 months. After 18 months the loss of FEV_1 stabilized at approximately 139 ml for a person with one episode, 306 ml for a person with two episodes, and 393 ml for a person with three and more episodes.

Table 4-5 shows the age and height adjusted regression coefficients and standard errors for the number of episodes of TB for subjects known to be HIV^- (n=1,038) and for those known to be HIV^+ (n=305). There were no apparent major differences between the two groups.

Figure 4-1 shows the decline in lung function (FVC, FEV_1, $FEF_{25-75\%}$ and $FEV_1\%$) with age for subjects without TB and pneumoconiosis, and for subjects with 1, 2, and 3 and more episodes of TB, estimated cross-sectionally. The plotted prediction curves were estimated individually for each group. In the combined model for FEV_1 presented in Table 4-4, the interaction term for age and 1 episode of TB was statistically significant, indicating that the older subjects with one episode of TB had larger loss of FEV_1 than the younger miners, in comparison to the healthy miners. The effect was not large, however, and thus for simplicity we presented only the model with the main effects. Significant interaction between age and three

There are no published studies in which the effect of recurrent episodes of treated TB on lung function impairment was assessed in a long term follow-up study. The present study evaluates the impact of recurrent treated TB episode on lung function impairment in a retrospective cohort of 27660 South African gold miners. Because of exposure to silica dust the gold miners are at an

episodes of TB was also observed for $FEV_1\%$, suggesting that in older miners the effect of three episodes of TB on obstruction is bigger than in younger miners.

Figure 4-2 shows the percentage of subjects whose percent predicted FEV_1 was below 80%, for miners without TB and pneumoconiosis, and for those with 1, 2, and 3 or more episodes.
To estimate the chronic effect only, we excluded subjects with lapsed time less than 18 months from Figure 4-2 and from the calculations of the percentage below 80%.

4.5   DISCUSSION

Several studies have observed that early and partially treated tuberculosis results in airways obstruction.[1-5] Only few studies with a follow-up longer than 18 months were done. In one study, after 9 to 192 months (5.6 yrs on average) of follow-up from TB diagnosis, 68% of 71 subjects had evidence of airways obstruction.[6] The impairment of airflow was inversely related to the extent of TB determined radiologically and to the amount of sputum produced at the end of follow-up, which also correlated with the extent of the disease.[6] In another study, after ten years of follow-up obstructive changes were most common and correlated with the extent of residual shadowing on the chest radiographs.[7] A third study observed that after 15 years of follow-up, 40 patients with pulmonary tuberculosis who had obstructive impairment on discharge had higher estimated yearly decline in vital capacity than TB patients without obstruction (-54.3 ml/yr versus -27.7 ml/yr), but the decline in FEV_1 was only slightly higher.[8]
increased risk of developing pulmonary TB. Up to the early 1980s miners who developed TB were not allowed to return to underground work, but with introduction of more effective TB treatment and because of the adverse socio-economic impact of unemployment this regulation was discontinued. Because many miners develop several episodes of TB, it is important for prevention of chronic obstructive

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lung disease to establish the impact of recurrent TB episodes on lung function loss in these miners.

The increased number of episodes of TB corresponded with increasing lung function loss (Table 4-3). There appears to be highest loss in the first six months after diagnosis, and after about 18 months the loss stabilizes and becomes chronic. The estimated decrement for FEV_1 in subjects with one episode of TB was 326 ml after six months, 247 ml after one year, 139 ml after year and half, 136 ml after two years, after 18 months the decrement became stable. The estimated chronic losses of FEV_1 in subjects with one, two, three and more episodes were 139 ml, 312 ml, and 396 ml, respectively. The decrement in lung function was similar in TB subjects who tested HIV+ and who tested HIV+ at the time of TB diagnosis (Table 4-5). The effect of pneumoconiosis on lung function loss was similar to that of one episode of TB. It has been observed, however, that many gold miners not reported to have TB and who are diagnosed to have pneumoconiosis, have signs of tuberculosis present on radiographs, this could be due to spontaneous healing.

It is well recognized that pulmonary tuberculosis can cause substantial damage to the lungs. The residual damage in the lungs after tuberculous treatment includes varying degree of fibrous bands, bronchovascular distortion, emphysema and bronchiectasis.[18] Increased sputum production several years after TB treatment that correlated with the initial extent of TB on radiographs was also observed.[6] The present study quantifies the amount of lung function loss caused by initial and recurrent treated TB and specific time lapsed after TB diagnosis, especially the chronic damage due to TB episodes in a gold mining population which is screened and treated for TB according to WHO guidelines. The percentage of subjects with chronic airflow limitation (percent predicted for FEV_1% <80%) 18.4% in those with one episode of TB, 27.1% in those with two episodes of TB, and 35.2% in those with three and more episodes of TB (Figure 4-2).

In conclusion, the study shows that under the current case-finding programme and treatment regimen on the particular South African gold mine, it can be expected that approximately 18% of miners with one episode of TB, 27% of miners with two episodes of TB, and 35% of miners with three and more episodes of TB will develop chronic airflow impairment. The estimated chronic losses of FEV_1 in subjects with one, two, three and more episodes were on average 139 ml, 312 ml, and 396 ml, respectively. The decrement in lung function was similar in TB subjects who tested HIV+ and who tested HIV+ at TB diagnosis.

Prevention of lung function impairment caused by TB through improved case finding and treatment regiments is important. However, reduction of risk of TB through intervention on risk factors should be a first health and safety priority in the gold mines.

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Table 4-1   The mean observed and percent predicted values for FVC, according to the number of episodes of TB

Age Category	Pulmonary Tuberculosis											
	No TB			1 TB Episode			2 TB Episodes			3 TB Episodes		
	N	Obs. (L)	% Pred.	N	Obs. (L)	% Pred.	N	Obs. (L)	% Pred.	N	Obs. (L)	% Pred.
20-24	339	4.32	98.5	1	4.77	109.2						
25-29	2248	4.29	99.7	38	4.10	95.5	2	3.68	85.5			
30-34	5416	4.22	100.1	200	4.06	96.5	13	3.99	94.7	2	3.89	92.5
35-39	5466	4.11	100.1	355	4.01	98.0	38	3.74	91.5	5	2.89	70.5
40-44	4100	3.99	100.4	417	3.86	97.5	75	3.71	93.6	17	3.47	87.6
45-49	2906	3.84	100.7	444	3.72	97.6	104	3.49	91.8	36	3.38	88.8
50-54	1870	3.68	101.1	367	3.54	97.1	64	3.39	93.2	18	3.23	88.6
55-60	1059	3.51	101.3	246	3.40	98.2	58	3.12	89.3	14	3.17	91.4
60>	308	3.34	102.0	69	3.17	96.3	12	3.08	93.8	4	3.27	100.5
Total	23712			2137			366			96		

Table 4-2 The mean observed and percent predicted values for FEV_1, according to the number of episodes of TB

Age Category	Pulmonary Tuberculosis											
	No TB			1 TB Episode			2 TB Episodes			3 TB Episodes		
	N	Obs. (L)	% Pred.	N	Obs. (L)	% Pred.	N	Obs. (L)	% Pred.	N	Obs. (L)	% Pred.
20-24	339	3.79	97.6	1	4.21	109.2						
25-29	2248	3.73	99.6	38	3.59	96.4	2	3.08	82.6			
30-34	5416	3.61	100.1	200	3.43	95.5	13	3.18	88.6	2	3.74	104.3
35-39	5466	3.45	100.2	355	3.31	96.5	38	3.09	90.3	5	2.36	68.5
40-44	4100	3.30	100.7	417	3.12	95.4	75	3.02	92.3	17	2.71	83.0
45-49	2906	3.16	101.8	444	2.95	95.4	104	2.75	89.0	36	2.59	83.9
50-54	1870	2.99	102.3	367	2.77	95.1	64	2.63	90.0	18	2.46	84.0
55-60	1059	2.83	103.3	246	2.60	95.0	58	2.44	88.1	14	2.25	82.2
60>	308	2.65	103.9	69	2.46	95.6	12	2.29	89.4	4	2.38	93.5
Total	23712			2137			366			96		

Table 4-3   Age and height adjusted regression coefficients *B* for lung function tests, for 27660 miners

Parameter	N	FVC		FEV$_1$		FEV$_1$%		FEF$_{25-75\%}$	
		β	S.E.	β	S.E.	β	S.E.	β	S.E.
1 episode of TB	2137	-0.120	0.013 ***	-0.180	0.011 ***	-2.162	0.165 ***	-0.441	0.028 ***
2 episodes of TB	366	-0.328	0.029 ***	-0.362	0.026 ***	-2.721	0.380 ***	-0.709	0.064 ***
3 episodes of TB	79	-0.404	0.062 ***	-0.462	0.056 ***	-3.843	0.810 ***	-0.862	0.135 ***
4+ episodes of TB	17	-0.771	0.133 ***	-0.964	0.120 ***	-10.995	1.742 ***	-1.705	0.291 ***
TB +pneumoconiosis	185	-0.237	0.041 ***	-0.384	0.037 ***	-5.707	0.534 ***	-0.857	0.089 ***
pneumoconiosis only	1164	-0.139	0.017 ***	-0.215	0.015 ***	-2.917	0.223 ***	-0.520	0.037 ***
Total	df=27659 #	R^2=0.3801		R^2=0.4237		R^2=0.1174		R^2=0.2241	

\#   There were 23712 additional miners who did not have TB, who were used as a comparison group in the regression model.
Significance level: <0.05=*, <0.01=**, <0.001=***, n.s.>=0.05.

Table 4-4   Age and height adjusted regression coefficients B for the number of TB episodes and the time elapsed from last TB episode to lung function test for 26311 miners who did not have pneumoconiosis

Parameter	N	FVC		FEV$_1$		FEV$_1$%		FEF$_{25-75\%}$	
		β	S.E.	β	S.E.	β	S.E.	β	S.E.
1 episode of TB	2137	0.578	0.134 ***	0.729	0.120 ***	9.016	1.726 ***	1.221	0.295 ***
2 episodes of TB	366	0.388	0.136 **	0.556	0.122 ***	8.307	1.753 ***	0.957	0.300 **
3+episodes of TB	96	0.329	0.146 *	0.472	0.131 ***	7.211	1.885 ***	0.816	0.322 *
Categorized time elapsed from last TB episode to lung function test									

		FVC			FEV₁			FEV₁%			FEF		
1-6 months	216	-0.883	0.134	***	-1.055	0.121	***	-10.874	1.735	***	-1.765	0.297	***
7-12 months	259	-0.791	0.137	***	-0.975	0.123	***	-10.963	1.766	***	-1.698	0.302	***
13-18 months	198	-0.666	0.138	***	-0.868	0.124	***	-10.827	1.778	***	-1.628	0.304	***
19-24 months	179	-0.636	0.138	***	-0.865	0.124	***	-11.396	1.784	***	-1.644	0.305	***
25-36 months	291	-0.653	0.136	***	-0.882	0.123	***	-11.405	1.761	***	-1.631	0.301	***
37-48 months	268	-0.688	0.137	***	-0.898	0.123	***	-11.092	1.765	***	-1.699	0.302	***
49-60 months	216	-0.733	0.139	***	-0.886	0.125	***	-9.669	1.790	***	-1.529	0.306	***
61-375 months	972	-0.665	0.135	***	-0.895	0.121	***	-11.597	1.741	***	-1.671	0.298	***
Total	df=26309 #	R^2=0.3711			R^2=0.4075			R^2=0.1011			R^2=0.2012		

\#   There were 23710 miners who did not have TB, who were used as a comparison group in the regression model.

Significance level: **<0.05=*, <0.01=**, <0.001=***, n.s.>=0.05.**

Table 4-5   Age and height adjusted regression coefficients B for the number of TB episodes and 25055 subjects   known to be HIV⁺ or HIV⁻

Parameter	N	FVC		FEV₁		FEV₁%		FEF₂₅₋₇₅%	
		β	S.E.	β	S.E.	β	S.E.	β	S.E.
HIV⁻									

1 episode of TB	747	-0.172	0.020	***	-0.233	0.018	***	-2.439	0.260	***	-0.523	0.045	***
2 episodes of TB	218	-0.332	0.037	***	-0.377	0.033	***	-3.066	0.475	***	-0.769	0.082	***
3+ episodes of TB	73	-0.485	0.064	***	-0.529	0.057	***	-4.084	0.814	***	-0.918	0.301	***
HIV⁺												
1 episode of TB	234	-0.162	0.036	***	-0.210	0.032	***	-1.586	0.457	***	-0.382	0.079	***
2 episodes of TB	55	-0.433	0.073	***	-0.479	0.066	***	-3.273	0.939	***	-0.863	0.163	***
3+ episodes of TB	16	-0.500	0.136	***	-0.564	0.122	***	-4.520	1.739	**	-0.974	0.301	**
Total	df=25053 #	R^2=0.3511			R^2=0.3784			R^2=0.1095			R^2=0.2447		

\# There were 23712 miners who did not have TB, who were used as a comparison group in the regression model.
Significance level:<0.05=*, <0.01=**, <0.001=***, n.s.=>=0.05.

Section - 5 Feasibility of Epidemiological Research
The feasibility of epidemiological research on respiratory diseases associated with silica dust in goldminers

_____

5.1   Introduction

Any newly implemented epidemiologic study of respiratory health effects should aim at disease prevention by researching   pre-clinical or early stages of respiratory disease associated with silica dust, and the implementation of measures that results in the prevention of respiratory diseases.

Because of the extensive labour force involved in the gold mining industry, one of the best way to accomplish such research is to implement a large industry-wide cohort study representative of currently employed gold miners. Such a study of respiratory health effects would involve an extensive study of baseline health effects, including pre-clinical markers of disease, markers of exposure, and measurements of dust exposure, and a prospective follow-up of the subjects for various health outcomes. The study would be able to determine the development of the silica dust related disease and methods of prevention of the disease at early stages.

5.2   Results of the feasibility study relevant to the study design

Using the same set of data from the AHS, we have established that the reference values for lung function obtained from white American or European males are not appropriate for black South African gold miners. The study suggest that the best correction factor is 0.92 for FVC and 0.95 for FEV_1. We suggest that either an appropriate correction factor is used or reference values established on black South African males be used. We have also established that the correction factor of 0.88 obtained on US black males and proposed by the American Thoracic Society, and used in many spirometers for ethnic correction in South Africa, is

Reliability of lung function measurements collected during routine screening (Section 2).
Lung function measurements collected from 1994 to 1998 during routine lung function screening programme done by Anglogold Health Services (AHS) were used to establish whether the lung function measurements are reliable and can be utilized for epidemiologic research. The study made the following findings.

(1) The lung function measurements from the AHS lung function screening programme were very reliable for some periods of time and very unreliable at other periods of time. We conclude that routinely collected lung function tests can be potentially used for epidemiologic research provided that reliability of the measurements is regularly checked and quality enforced.   (2) For a large screening programme, the reliability control programme can be implemented on a relatively small sample of miners (around 600-700) who have annual lung function tests done throughout the year. Then, the reliability can be checked on a monthly basis and quality of measurements ensured continuously.

Lung function prediction curves (Section 3) not appropriate for black SA gold miners.

Effect of pulmonary tuberculosis (PTB) on the loss of lung function (Section 4)
In epidemiologic research of the effect of silica dust exposure on the loss of lung function it is necessary to take into account all confounding factors that can affect lung function, e.g. tobacco smoking. The effect of pulmonary tuberculosis on lung function loss has not been well researched although pulmonary tuberculosis is a common lung disease in South African gold miners. In this study we found that the residual loss of lung function after

completion of PTB treatment is very significant and increases with each episode of pulmonary tuberculosis. The effect of PTB on lung function loss is of the same magnitude as the effect of tobacco smoking. Thus, any study the effect of silica dust exposure on loss of lung function in South African gold miners cannot be valid unless a detailed medical history of pulmonary tuberculosis for each subject is taken into account. Further studies are needed to establish whether the extent of PTB involvement during active PTB and residual changes after treatment completion identified on radiographs relate to residual lung function loss. The study also established that a large study is required to obtain reliable estimates of the effect of PTB on the loss of lung function. This part of the feasibility study included 2137 subjects with one episode of TB, 366 subjects with 2 episodes and 96 subjects with 3 or more episodes, and in total 27 659 subjects were included in the study.

5.3 Outline proposal for an industry-wide prospective study

The industry-side prospective study of respiratory health effects would involve collection of data on the following pivotal measurements on an annual basis:

lung function measurement

5.3.2 Study subjects - To ensure reliability of lung function screening programme, a dynamic cohort of approximately 600-800 miners is required to be tested on an annual basis throughout the year. This cohort would constitute a part of the industry-wide cohort. However, to obtain better estimates of the effects a minimum of 1000 miners per mine should be included in the study. The cohort will be age stratified, ensuring a proportional sample from each age strata.

5.3.3 Mines involved in the study - Initially only selected mines with established lung function screening programmes will be included in the study. The reliability control programme, staff training and

respiratory symptoms questionnaire
PTB history
radiological reading
HIV status assessment.

The baseline data would include also blood sample, allergy test, etc.

Additional tests can be added as the study progresses.

Continuous analysis of the data to ensure good quality of the data and regular feedback to the mines on data quality control and on disease incidence.

5.3.1 Implementation - The findings of the feasibility study indicate that such a study could be conducted utilizing existing resources for data collection on the mines. To ensure uniform data quality, the staff involved in the data collection (lung function technicians, interviewers, nurses, etc.) would be trained at one centre (e.g. MBOD, NCOH). Training of the mining staff in data collection is an important aspect for disease prevention, as the development of skills would ultimately result in better quality of the data collected by the mines and will lead to better disease recognition.

data collection method will be developed for these mines. When this is successfully accomplished only then the study will be implemented in other mines. Pulmonary tuberculosis record keeping should also be uniformly implemented.

5.3.4 Data collection - The data collection for the routine measurements would be done using the existing system for the rest of the workforce. On a regular basis (initially monthly) the results will be collected at the Study Centre. The data will be analysed for quality and feedback provided to the mine medical staff. A close collaboration between the study centre and the mine medical officers should be beneficial to all parties concerned. For

example if the study centre is at NCOH, then resources of the NCOH can be utilized for training and distribution of information relevant to respiratory disease prevention on the mines (e.g. via the SORDSA Newsletter).

5.4 Appendix B

PROJECT: Respiratory health parameters in gold miners

Respiratory questionnaire

Surname: _____

First name(s): _____

Home Address: _____

_____

Teba district: _____   Teba code: _____

Standard of education: _____

Company Number Industry Number
Identity Number
Passport Number

Sex [M=1 F=2]

                        Day   Month   Year

Date of birth

Place of birth: _____

Race: A=Asian, B=Black, C=Coloured, W=White :...

Interviewer : (name)_____

                        Day   Month   Year

Date of interview

I am going to ask you some questions, mainly about your chest. I should like you to answer YES or NO whenever possible.

Cough

1a.   Do you usually have a cough on most days?
         (Count a cough with first smoke or on first
         going out doors? Exclude clearing of throat).   1. Yes _____   2. No _____

        If yes
1b.   Do you usually cough as much as 4 to 6 times
         a day?   1. Yes ____   2. No ____

1c. Do you usually cough like this on 4 or more days
of the week?   1. Yes ___   2. No ___

1d. Do you usually cough like this on most days for
3 consecutive months during the year?   1. Yes ___   2. No ___

1e. For how long have you had this cough?   _____ Yrs, Mnths

Phlegm

2a. Do you usually bring up phlegm from your chest?
(Count phlegm with the first smoke or on first going
out doors. Exclude phlegm from the nose. Count
swallowed phlegm).   1. Yes ___   2. No ___

If yes
2b. Do you bring up phlegm as much as twice a day?   1. Yes ___   2. No ___

2c. Do you usually do this 4 or more days of the week?   1. Yes ___   2. No ___

2d. Do you usually bring up phlegm during the rest of
the day or at night?   1. Yes ___   2. No ___

If yes
2e. Do you bring up phlegm like this on most days for
3 consecutive months during the year?   1. Yes ___   2. No ___

2f. For how long have you had this phlegm?   _____ Yrs, _____Mnths

Breathlessness

**If the subject is disabled from walking by any condition other than heart or lung   disease,
omit question 3 and enter 1 here.**

3a. Are you troubled by shortness of breath when
hurrying on level ground or walking up a slight
hill?   1. Yes ___   2. No ___

3b.   Are you troubled by shortness of breath when
working underground?   1. Yes ___   2. No ___

If yes
3c.   Do you get short of breath walking with other
people of your own age on level ground?   1. Yes ___   2. No ___

If yes
3d.   Do you have to stop for breath when walking at
your own pace on level ground?   1. Yes ___   2. No ___

Wheezing

4a.   Does your chest ever sound wheezing or whistling?   1. Yes ___   2. No ___

If yes
4b.   Does this happen when you have a cold?   1. Yes ___   2. No ___

4c.   Do you get this more then 3 times a week?   1. Yes ___   2. No ___

4d.   Have you ever had attacks of shortness of breath
with wheezing?   1. Yes ___   2. No ___

If yes
4e.   Is/was your breathing normal between attacks?   1. Yes ___   2. No ___

Chest illnesses

5a.   During the past three years have you had any chest
illness which has kept you away from work for
as much as a week?   1. Yes ___   2. No ___
If yes
5b.   Did you bring up more phlegm than usual in any
of these illnesses?   1. Yes ___   2. No ___

If yes
5c.   Have you had more than one illness like this in
the past three years?   1. Yes ___   2. No ___

Past illness

6a.   Have you ever had any chest operations?   1. Yes ___   2. No ___

If yes
6b.   Please specify_____

6c.   Have you ever had any chest injuries?   1. Yes ___   2. No ___
         If yes
         Please specify_____

Have you ever been told by a doctor that you have :

7a.   Heart trouble   1. Yes ___   2. No ___

7b.   Bronchitis   1. Yes ___   2. No ___

7c.   Asthma   1. Yes ___   2. No ___

7d.   Pleurisy   1. Yes ___   2. No ___

7e.   Pneumonia   1. Yes ___   2. No ___

7f.   Hay fever   1. Yes ___   2. No ___
7g.   Other chest trouble   1. Yes ___   2. No ___

If yes
7h.   Please specify _____

Pulmonary tuberculosis

8a.   Have you ever had pulmonary tuberculosis?   1. Yes ___   2. No ___

If yes

8b.   Was it confirmed by a doctor?   1. Yes ___   2. No ___

8c.   What age did you first have pulmonary tuberculosis?   _____ Years

8d.   How many times have you had it?   _____ Times

8e.   Do you still have it?   1. Yes ___   2. No ___

Medication

9a.   Do you take any medication?   1. Yes ___   2. No ___

If yes

9b.   For what condition/disease?
Please specify_____

Childhood illnesses

As a child, were you ever treated by a doctor for any of these:

10a.   Bronchitis   1. Yes ___   2. No ___

10b.   Asthma   1. Yes ___   2. No ___

10c.   Pneumonia   1. Yes ___   2. No ___

10d.   Hay fever   1. Yes ___   2. No ___

10e.   Other respiratory conditions   1. Yes ___   2. No ___

Tobacco smoking

11a.   Have you ever smoked?
(Yes means more than 20 packs of tobacco in your
life or more than 1 cigarette a day for a year).   1. Yes ___   2. No ___

11b.   Do you smoke now?
Yes= Present smoker, No= Ex-smoker   1. Yes ___   2. No ___

If No to 11a and 11b go to question 14.

Present smoker

12a.   What do you smoke?
(1= commercial cigarettes, 2= hand rolled, 3= pipe)   1 ___   2 ___   3 ___

12b.   How old were you when you started smoking?   _____ Years

12c.   How much do you smoke per day at present (number
of, 1= commercial cigarettes, 2= hand rolled,
3= grams of pipe)   1=___ 2=___ 3=___

Ex-smoker

13a.   What did you smoke? (1=commercial cigarettes,
2= hand rolled, 3= pipe)   1 ___   2 ___   3 ___

13b.   How old were you when you started smoking?   _____ Years

13c.   How old were you when you stopped smoking?   _____ Years

13d.   In the past on average, how much did you smoke?
(number of, 1=commercial cigarettes,
2= hand rolled, 3= grams of pipe per day)   1=___ 2=___ 3=___

Alcohol consumption

14. How many of the following do you usually drink?

Daily Weekly Weekend

14a. Cartons of beer/home-brew ___ ___ ___

14b. Cans of beer ___ ___ ___

14c. Glasses of wine ___ ___ ___

14d. Tots/shots of hard liquor
(eg. brandy, whisky, etc.) ___ ___ ___

Dagga consumption

The following information will be kept strictly confidential, and used for research purposes only. It is important that you answer the following questions as truthfully as possible.

15a. Do you smoke dagga? 1. Yes ___ 2. No ___

15b. Have you smoked dagga within the last year? 1. Yes ___ 2. No ___

If yes
15c. How many times per month do you smoke dagga? _____ Times

15d. Do you smoke dagga during the week? 1. Yes ___ 2. No ___

15e. Do you smoke dagga over the weekend? 1. Yes ___ 2. No ___

5.4.2 Chest X-ray Sheet

PROJECT: Respiratory health parameters in gold miners

Radiological Assessment

FACILITY
WORKER'S Industry Number   TYPE OF READING   IDENTIFICATION

1A. DATE OF X-RAY

MONTH   DAY   YR

1B. FILM QUALITY   If Not Grade 1
Give Reason:

1C. IS FILM COMPLETELY
        NEGATIVE?