ILLUMINATING A NEGLECTED POPULATION: EPIDEMIOLOGICAL AND CLINICAL FEATURES OF SILICOSIS AND TUBERCULOSIS AMONG FORMER GOLD MINERS FROM LESOTHO

By

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This dissertation is submitted to the School of Public Health, University of Cape Town in the fulfilment of the requirements for the Masters of Philosophy (MPhil) Degree in Occupational Health.

I, Botembetume Maboso, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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DEDICATION

Dr Tony Davies, Emeritus Professor, University of Witwatersrand - stated in 2012 that “The search to overcome tuberculosis in South African mining industry has always been on ways of interrupting this relentless cycle of new labour, short contracts, recruit more, examine them, and so on. And all the time, the real problem was not the people who came back to the mine, but the people who did not. And we have no knowledge of what happens to them.” To all of you mineworkers, throughout Africa, who did not go back to the mine, and we do not know what happened to you, I dedicate this dissertation.

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ABSTRACT

Background

Silicosis, tuberculosis (TB), and human immunodeficiency virus (HIV) infection, singularly and together, are all global health concerns. Southern Africa, with its high HIV and TB prevalence and incidence, is the most affected region by these conditions. The large South African mining industry, especially gold mining, is known as the amplifier of this triple epidemic of silicosis, TB and HIV. Furthermore, ex-mineworkers from South African mines have a higher mortality rate than active mineworkers and the general population. They carry a heavy burden of silicosis, TB, HIV and other pulmonary diseases, which strongly contribute to this higher mortality.

Lesotho is a tiny country with about 2.3 million inhabitants of which about 95,000 are ex-gold miners from South African industry. Over 40% of Basotho ex-gold miners attending invited examinations have silicosis, more than 50% of them have been treated at least once for TB, and 60% have lung lesions on chest x-ray (CXR) suggestive of TB. In this country, many silicosis cases have been treated repeatedly for TB, and some have been documented as MDR-TB on the basis of plain CXR alone, even when bacteriologic tests gave negative results.

Objectives

To address the problem of TB, in general and the high morbidity and mortality among ex-gold miners, in particular, we designed three separate studies with the following objectives: (1) To illustrate the challenges in diagnosing active TB in this setting, specifically in distinguishing pulmonary TB (past and current) from silicosis; (2) to assess the performance of the screening CXR and symptoms of cough and fever in the diagnosis of active TB disease using Xpert MTB/RIF sputum test as the reference standard; and (3) to identify predictors of silicosis, tuberculosis, and associated hypoxaemia to better understand the predictive effects of comorbidity, the determinants of severity, and health care implications.

Methods

Three separate but inter-related sub-studies (two cross-sectional and one case series) were conducted from a single database of men who worked in South Africa gold mines for at least 12 months and visited Mafeteng Occupational Health Service Centre from January 2017 to November 2018. We analysed the medical history information, CXR, and Xpert MTB/RIF sputum test results for all attendees. For sub-study 1, four cases were discussed. For sub-study 2, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), of CXR and symptoms, in the diagnosis of TB, were computed. For sub-study 3, multiple logistic regression modelling of various variables against silicosis, active TB and hypoxaemia as dependent variables in separate models was carried out.

Findings

The first study of four cases demonstrated that ex-gold miners from the South African mines present with complex lung disease, with poor agreement between radiological findings and clinical presentations, poor agreement between radiographs suggestive of TB and Xpert MTB/RIF sputum results, and overlap of clinical and radiological presentations of silicosis and TB.

The second study composed of 2572 ex-gold miners and revealed CXR sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPVs) of 0.93 (95% CI: 0.87-0.99), 0.41 (95% CI:0.39-0.99), 0.05 (95% CI:0.04-0.06), and 0.99 (95% CI:0.98-1), respectively. Symptoms, on their own, could only identify about half of the active TB cases (i.e., a sensitivity of 0.45, 95% CI:0.34-0.56). Computing of either an abnormal CXR or symptoms of cough or fever slightly increased the sensitivity (0.96, 95% CI: 0.92-1) while it substantially decreased specificity (0.33, 95% CI: 0.31-0.35).

The third study composed of 2678 ex-gold miners and found high odds of silicosis among ex-gold miners who had longer lengths of service (OR: 2.21, 95% CI: 1.68-2.74), higher level of dust exposure (OR: 1.57, 95% CI: 1.28-1.86), a history of past TB (OR: 2.66, 95% CI: 2.21-3.11), shortness of breath (OR: 1.47, 95% CI: 1.14-1.80), and decreased lung function. HIV-infected ex-gold miners had significantly lower odds of silicosis than their colleagues who were HIV-negative (OR: 0.62, 95% CI: 0.50-0.73). There were high odds of active TB among ex-gold miners who had silicosis (OR: 2.30, 95% CI: 1.56-3.08) and those who were HIV-positive (OR: 1.57, 95% CI: 1.04-2.10). Furthermore, there were high

odds of hypoxaemia among those with a history of past-TB (OR: 1.48, 95% CI: 1.17- 1.79) and those with silicosis (OR: 2.41, 95% CI: 1.92-2.90), while the odds of hypoxaemia were significantly lower among HIV-infected ex-gold miners.

Conclusions

These studies demonstrate that mining work, and prominently exposure to silica dust, continue to cause morbidity in ex-gold miners, years after exposure has ceased, imposing a health cost on the poor ex-miner and the health system of their countries. They highlight the permanency of the situation caused by silica exposure; reveal the gap in the compensation system, either through the government (i.e., ODMWA, CCOD) or non-government channels (i.e., Tshiamiso Trust, Q(h)ubeka Trust), by demonstrating that silica-induced and aggravated conditions impose persistent/lifelong health costs to ex-gold miners that exceed current compensation. Consequently, they highlight the needs for the compensation system and law enforcement agencies to consider providing for and extending support for mining-induced medical needs (i.e., long-term management of chronic lung diseases, ambulatory or long-term oxygen therapy) to ex-gold miners, including those outside of South Africa borders.

There is a need for training of healthcare providers in the labour sending communities in the diagnosis and management of mining-induced medical problems (silicosis, TB, silicotuberculosis, COPD, etc.). Clinicians and policy makers need to consider adjusting the new TB management policy to the predictive values of symptoms and the CXR in diagnosing active TB in this population. In addition to action to provide access to diagnosis, care and compensation, we need further research into the combined lung disease burden, and special health service and social security needs of this long neglected population.

CHAPTER 1: INTRODUCTION

Background

Silicosis, tuberculosis (TB) and infection with human immunodeficiency virus (HIV), singularly and together are all global health concerns [WHO, 2021; UNAIDS, 2021; Fedotov, 1997]. Worldwide, TB is the leading cause of death from a single infectious agent [WHO, 2021]. Southern Africa is one of the regions highly affected by this triple epidemic. The WHO African Region and Lesotho, with annual TB incidence rates of 222 and 650 per 100 000, were, respectively, the most affected region and country in 2020 [WHO, 2021]. The large South African mining industry, and particularly gold mining, is known as an amplifier of this triple epidemic in this part of the world [Basu et al., 2009].

Statement of the Problem

Gold miners are exposed to significant concentrations of respirable crystalline silica Exposure to this substance may cause multiple ill health conditions, including but not limited to silicosis. Long-term exposure to RCS with or without radiological silicosis heightens susceptibility to TB, even after exposure to silica dust ends [Hnizdo et al. 1998; teWaterNaude et al., 2006; Ehrlich et al., 2021].

Silicosis and silica dust-associated TB remain occupational health issues in low and middle-income countries [Rees and Murray, 2007]. Infection with HIV and silicosis have synergistic effects on TB risk [Corbett et al., 2000]. The prevalence of silicosis among older or long-service gold miners, active or former, in South Africa and in ex-miner populations living across its borders is very high and ranges from 20% to 50% [teWaterNaude et al., 2006; Trapido et al., 1998; Steen et al., 1997; Girdler-Brown et al., 2008; Maboso et al., 2020; Q(h)ubeka Trust, 2021; Meel, 2002]. Correspondingly, TB incidence among these populations remains extremely high [The World Bank, 2017].

Data Source and Study Area

The Tuberculosis in the Mining Sector (TIMS) programme in Lesotho

The TIMS programme emerged from the need for a regional coordinated response to the epidemic of TB and related illness among mineworkers, ex-mineworkers and their families and communities. The programme was sponsored by the Global Fund to Fight TB, HIV and Malaria [TIMS, 2019]. The main purpose of the TIMS programme was to screen current and former miners, their families, and community members for TB, and to link them to treatment as needed. A secondary purpose was to screen mineworkers for lung disease that qualifies as compensable under South Africa's Occupational Diseases in Mines and Work Act (ODMWA) [Republic of South Africa, 1973] and to assist mineworkers with these diseases to apply for compensation in South Africa. To achieve this, TIMS established 11 occupational health service centres (OHSCs) in eight southern African countries. Lesotho was one of these countries and had two OHSCs.

Study location

This study was conducted in Lesotho (Figure 1). Formerly known as Basutoland, this country is the product of colonial history in which Sotho-speaking people under King Moshoeshoe I sought British colonial protection in the 19th century, after encroachment by Boer trekkers [Guy and Thabane, 1998].

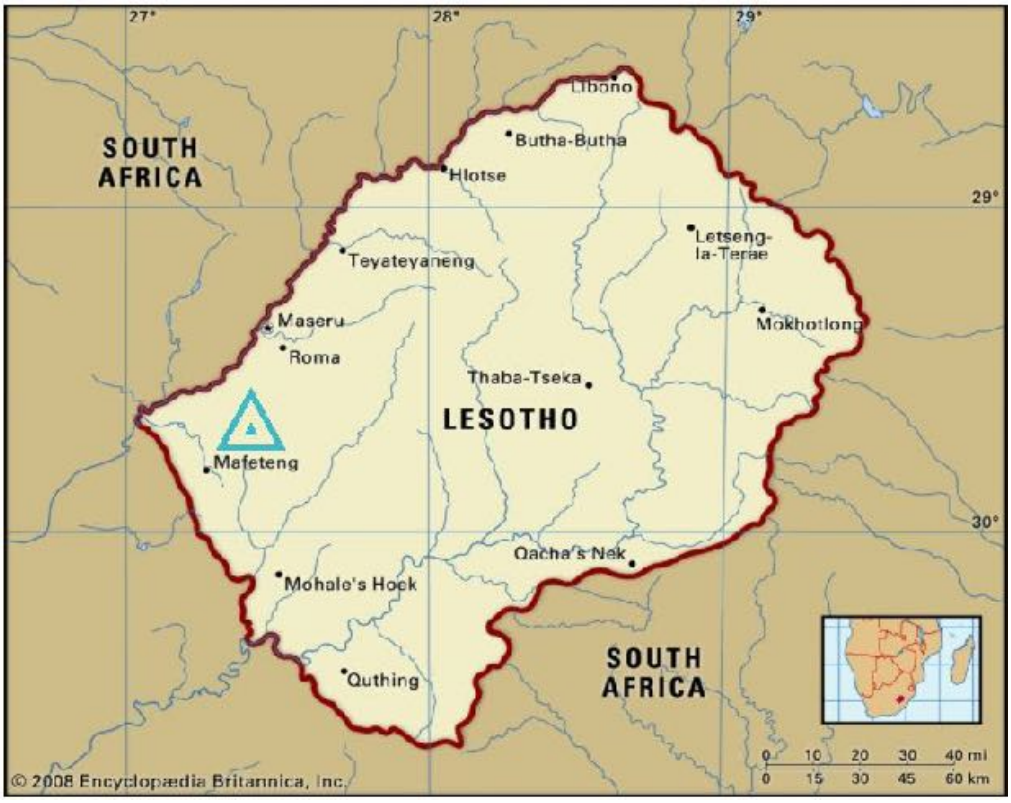

Figure 1. Lesotho Map including study site at Mafeteng

Landlocked within a mountainous area of South Africa, Basutoland was renamed the Kingdom of Lesotho upon independence from Great Britain in 1966 and is a parliamentary constitutional monarchy, currently headed by King Letsie III. Lesotho's narrow economic base consists of textile manufacturing, agriculture, diamond mining, remittances from Basotho migrants working in South Africa, and regional customs revenue. About three-quarters of the population are engaged in animal herding and subsistence agriculture (Figure 2) [The Heritage Foundation, 2022]. Lesotho has supplied the South African gold mines with migrant workers for 120 years, making up 25% of the workforce in 1970s [Ehrlich et al., 2023].

As noted, the country had the world's highest annual TB incidence in 2020, with an HIV prevalence of 23.6%. We estimated in 2020 that there are 95000 living former gold miners in Lesotho [Maboso and Ehrlich, 2020].

Figure 2. Animal herding in the rural life of Lesotho.

STRUCTURE OF THE DISSERTATION

A single database was used to conduct three separate sub-studies, which are inter-related and complement each other. Consequently, the first three chapters and the section on strengths and limitations are common to the three sub-studies.

The work is structured into seven chapters, each with its own reference list. Chapter 1, Introduction, includes background and statement of the problem, thesis objectives, description of the data source, and study area (e.g. TB in the Mining Sector in Southern Africa program in Lesotho, study location). Chapter 2 is the literature review. Chapter 3, General research methods, describes the methods common to all sub-studies. Each chapter comprises a sub-study (i.e., 4 to 6) with its own justification, objectives, specific methods; results or case description, depending on its nature; discussion, recommendations and conclusion. The last chapter is a wrap-up of the full dissertation, including considerations and recommendations applicable across the sub-studies, and the limitations and strengths of the overall research.

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CHAPTER 2: LITERATURE REVIEW

Introduction

This chapter gives an overview of knowledge and gaps relevant to the current dissertation, including the value of the CXR and symptoms in the diagnosis of TB, the difficulties in the separation of silicosis and pulmonary TB in silica exposed gold miners, and the risk factors for silicosis, TB and hypoxaemia.

The difficulties in the separation of silicosis and pulmonary TB in silica dust exposed gold miners

Exposure to silica dust with or without radiological silicosis increases the susceptibility to TB [Ehrlich et al., 2021] making TB much more prevalent among gold miners than the general population [Cowie, 1994, Hanifa et al., 2009]. Additionally, silicosis is especially common in long-service miners. In a recent examination series , 42.5 % of Basotho ex-miners had silicosis, 6.8% active TB and 53.4% a history of past TB treatment. Sixty percent had radiologic features read as either silicosis, tuberculosis or combined disease, i.e. silicotuberculosis [Maboso et al. 2020]. Furthermore, 50% of cases of active TB were asymptomatic. Over 30% of the sample was HIV infected. Depending on degree of immunosuppression, radiological presentation of active pulmonary TB may be atypical in the presence of HIV infection, with false negative bacteriological tests [San and Muhamad, 2001].

Radiological distinction of silicosis and TB can be difficult even for experts [Solomon and Rees, 2010; Franzblau et al., 2018]. Clinical distinction may also be difficult for a number of reasons. Chronic simple silicosis, which is the most common form of this disease among active and ex-miners, may express few symptoms. However, when advanced or complicated, which is common in ex-gold miners, the disease presents non-specific symptoms and signs that may also be present in those with pulmonary TB and any other inflammatory condition of the lungs [Taylor and Alexander, 1938; Lee, 1948].

According to the South African guidelines for TB management, TB treatment should be started for a patient who has either bacteriologically confirmed TB (e.g. positive Xpert MTB/RIF, or acid fast bacilli (AFB) on smear or culture), or in the presence of clinical signs such as cough, weight loss, night sweats and/or fever, and/or radiological evidence with or without bacteriological confirmation (empirical treatment) [Republic of South Africa, 2017].

This may be an appropriate approach for the general population. However, in a population with a high prevalence of silicosis and TB (past and current) such as the ex-gold-miner population [Maboso et al. 2020], this case definition is likely to mislead clinicians.

The most important sources of difficulty, evoked above, are TB fibrotic nodules masses and other features of lung fibrosis/destruction due to TB, which obscure silicosis. Miliary TB could be another source. For example, the presence of cavitation in the lungs on CXR usually suggests active TB, but not necessarily so, as an ischaemic necrosis may occur in the central part of a silicotic fibrotic lesion, leaving an excavated area [Lee, 1948].

However, there are clues which may guide the distinction. Simple silicosis, being bilateral, leaves the trachea in the midline. Even PMF may leave the trachea intact. When the trachea is deviated toward one side, it is suggestive of a previous tuberculous fibrosis/ contraction on one side, more commonly the right.

Clinically, active TB disease in adults in the presence of silicosis should be suspected in the presence of the following: cough becoming increasingly productive, haemoptysis, chest pain, loss of weight, limited chest expansion on one side, elevated temperature and radiological changes, including coalescing shadows, especially if unilateral or increasing in extent, enlarged hilar or mediastinal glands bilaterally, cavitation, or rarely displaced trachea in severe disease. It has been stated that obvious pulmonary architectural distortion, manifested by broncho-vascular-bundle and mediastinal distortion, and volume loss, as well as evidence of parenchymal or nodal calcification, should offer little difficulty in recognition of TB [Solomon and Rees, 2010].

Nonetheless, clinicians should keep in mind that minor changes of TB in gold miners are regularly superimposed on the radiographic appearance of silicosis; and the more advanced the silicosis, the greater the TB risk [Solomon and Rees, 2010]. Subtle radiographic change may be the initial manifestation of TB and should be sought, particularly in the absence of sputum identification of TB bacilli. Nodules in unexpected sites, for example, the supra-clavicular region, variable profusions and opacities which are not uniformly distributed in both lungs, should raise suspicion of TB. A miliary or peribronchiolar nodular superimposition on the silicotic nodular changes is another subtle TB presentation and it is easily missed [Solomon and Rees, 2010]. In these cases, it is

difficult to diagnose TB with a single CXR. It often requires previous CXR images to look for changes over time. Furthermore, although the TB may be active, the likelihood of a negative smear TB may be elevated among gold miners [Solomon and Rees, 2010]. Tubercle bacilli invade the respiratory tract via the bronchial pathway. In this case, the pathologic lesions remain in contact with the airways. Recovery and identification of the Koch's bacillus are dependent on this airway contact. However, when TB manifests as an interstitial-compartment abnormality such as in miliary pulmonary TB, localised and isolated, interstitial granuloma, or profuse nodular interstitial TB asmay be the case in ilicotic subjects, recovery of the organism may not be possible [Solomon and Rees, 2010]. The situation is further complicated by the HIV epidemic among ex- and active miners in southern Africa [Maboso et al., 2020; Park et al., 2009] as HIV infected subjects have an increased prevalence of smear-negative pulmonary TB [Campos et al., 2016]. This poses a serious problem as silicosis and HIV combine multiplicatively to increase the risk of TB [Corbett et al., 2000].

Misdiagnosis of TB among South African miners is a public health concern. Over 50% of active pulmonary TB cases of miners have been shown to go undiagnosed [Field et al. 2011]. Thus, given the mortality and morbidity associated with TB, it is essential to be rigorous when assessing the CXR of silica-exposed workers to ensure that radiologic diagnosis of TB is not missed.

It is a wise approach to lower the diagnostic threshold and increase the suspicion index when it comes to the decision of initiating TB treatment in active gold miners who are HIV-positive, with mild radiological silicosis and no history of past TB treatment. However, can we say the same for a population of ex-gold miners with a high prevalence of silicosis, and a high prevalence of past- and current TB such as Basotho formerly employed in South African gold mines [Maboso et al. 2020]?

The reasons for the uniqueness of this population are many, and emphasise the questionability of a approach derived from non-silica exposure settings in the diagnostic definition and empirical TB treatment initiation in ex-gold miners. The reasons include that TB is a recurrent disease among gold miners [Charalambous et al. 2008, Maboso et al. 2020] and, even when successfully treated, TB often leaves chronic pulmonary changes seen on CXR in up to 80% of cases [Roy and Ellis, 2010]. These residual lesions may mimic active TB disease on radiological grounds, especially when there is no reference to

previous chest images. Therefore, the a promoted low threshold approach toward TB treatment may lead to an unnecessary over-treatment of ex-gold miners for TB, which is not without consequences of high costs and side effects.

The value of cough, fever and chest radiograph (CXR) in the diagnosis of active TB disease among former gold miners.

The CXR is an essential and cost-saving tool for screening active pulmonary TB. It is also beneficial in detecting old healed TB [Mor et al. 2012, den Boon et al. 2006]. The known TB related symptoms have low sensitivity, and specificity [den Boon et al. 2006],(both of which increase when combined with CXR [Lewis et al. 2009].) According to some national guidelines for TB management [Republic of South Africa, 2017], TB treatment initiation is recommended in the presence of clinical signs such as cough, weight loss, night sweats and/or fever, and radiological changes suggestive of TB with or without bacteriological confirmation. However, a higher prevalence of chronic cough, for instance, should be expected in ex-gold miners due to silica-dust related bronchitis, post-TB lung abnormalities or emphysema [Barnes et al., 2019], which could mimic clinical TB. Further, ex-gold miners with chronic cough may find it difficult to report a “change”, regarding it as “normal” [Maboso et al., 2023], which would further reduce the sensitivity and specificity of cough in identifying active TB in this population. Nonetheless, none of the work that investigated the value of the CXR was done in an ex-gold miner population. There are a few publications on South African gold miners, although none of them reported on the levels of exposure to silica dust nor the prevalence of silicosis [Day et al., 2006; Lewis et al., 2009].

Strong evidence of the association between prevalence and specificity exists. Specificity of a test decreases on average by 0.02 units for every 1 percentage point increase in prevalence [Leeflang et al. 2013]. Evaluation of CXR values on the screening for pulmonary TB in African general populations have shown a sensitivity and specificity of 80% to 97%, and 63% to 99%, respectively [Mor et al., 2012; den Boon et al. 2006, van Cleeff et al. 2005].

In summary, ex-gold miners from the South African mines are different from the general population not only because TB is highly prevalent and recurrent [Charalambous et al., 2008; Maboso et al., 2020], but also because of the high prevalence of HIV and silicosis [Maboso et al., 2020].

Risk factors associated with silicosis, TB and hypoxaemia

Morbidity related to silicosis, HIV and TB is higher in ex-mineworkers [Bloch et al., 2018] than active mineworkers for a number of reasons. Many mineworkers leave the workplace due to ill-health. Ex-mineworkers generally lose access to company medical services when they leave the mines. Silicosis and silica-related lung function impairment are progressive conditions. Accumulated lung dust load, especially in conjunction with HIV, maintains the high susceptibility to TB [Ehrlich et al. 2021]. Finally, there is weak post-employment surveillance of ex-mineworkers in remote rural areas [Ehrlich et al. 2022] and in low resource neighbouring countries with lack of adequate skills to manage mining-induced lung diseases in the communities. Although there is a large general literature on the factors associated with these conditions, most of the studies in southern Africa have focused on active mineworkers. There is a need to understand the factors associated with these conditions in the forgotten population of ex-mineworkers.

Active tuberculosis

TB incidence among mineworkers in southern Africa has been reported to be extremely high [The World Bank. TIMS 2017]. Girdler-Brown and colleagues reported a high prevalence of current TB disease (6.2%) and history of past TB (26%) in a sample of men formerly employed in South African gold mines [Girdler-Brown et al., 2008]. A second study, 25 years later, of Basotho men formerly employed in the South African gold mines found the same high burden of tuberculosis: current TB 6.8%, history of past TB 54% [Maboso et al., 2020].

Age, silicosis status, HIV infection, history of previous TB, premorbid focal radiological scarring and a dusty job in the mine have all been found to be predictors of active TB in gold mineworkers [Park et al., 2009].

Silicosis

Being a black mineworker, duration of mining service, age at the time of diagnosis, mean intensity of exposure to dust and cumulative dust exposure are known predictors of silicosis in the gold mining workforce [teWaterNaude et al., 2006, Murray et al., 1996, Knight et al., 2020].

The mining industry through its oscillating migration phenomenon, has also played a role in the expansion of the HIV epidemic in this region [Rees et al., 2010; Corno and de

Walque, 2012]. The prevalence of HIV among South African gold mineworkers, active or former, in South Africa and across the borders is very high and ranges from 22% to 31% [Corbett et al., 2004; Baltazar et al., 2015; Maboso et al., 2020]. Therefore, an important question is whether or not HIV infection affects the occurrence and progression of silicosis. Although there are some lines of biological plausibility, there are, thus far no data to support this hypothesis.

Chronic oxygen desaturation

Hypoxaemia (i.e., low concentration of oxygen in the blood) is associated with chronic lung function impairment and chronic lung disease, contributes to reduced quality of life, and is a predictor of mortality [Kim et al., 2008; Paciocco et al. 2001].

Chronic exposure to respirable crystalline silica with or without silicosis is independently associated with airflow obstruction [Hnizdo, 1992; Ehrlich et al. 2010]. It has further been shown that TB can cause protracted impairment of lung function, which increases incrementally with the number of episodes of TB [Hnizdo et al., 2000, Ehrlich et al., 2010].

A range of pulmonary function tests are available to assess the severity of disease in chronic lung disease. However, in a low resource country such as Lesotho where only one health facility can perform arterial blood gas (ABG) analysis, and spirometry can be performed in only three health facilities, pulse oximetry remains the most accessible tool for this purpose.

Information on chronic oxygen desaturation in gold miners with occupational lung disease is scarce. Oxygen desaturation is associated with increased mortality [Kim et al. 2008, Paciocco et al,. 2001]. Hypoxemia at rest and with exercise is associated with silicosis [Donroe et al. 2008]. We earlier found that 27% of Basotho ex-gold miners from South African industry had an oxygen saturation (SpO2) below 95% and that 3% had a SpO2 below 91% in room air [Maboso et al., 2020].

Understanding factors associated with hypoxaemia in this setting would contribute to clinical and health system interventions to improve the quality of life and reduce mortality of mineworkers affected by chronic lung disease.

Thesis objectives

Objective 1: Making use of a series of illustrative cases to indicate the difficulties that arise in making this distinction between silicosis and TB, particularly in low resource settings.

Objective 2: To assess the predictive value of the symptoms of fever and cough and plain chest radiography (CXR) in the diagnosis of active TB disease among ex-gold miners.

Objective 3: To examine factors associated with silicosis, active TB, and hypoxaemia in ex-gold miners to better understand occupational aetiology, the effects of comorbidity, determinants of severity, and health care implications.

For each of these objectives, a separate study was undertaken.

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CHAPTER 3: GENERAL RESEARCH METHODS

This chapter describes the methods relevant to all the three sub-studies.

Population

The study population consisted of ex-miners from the South African gold mines living in Lesotho.

Study design

Case series and two cross-sectional designs.

Sampling

Data collected as part of routine clinical operation in one of the TIMS OHSCs, Mafeteng-OHSC, were analysed. The dissertation author, Masters candidate BM served as medical officer in this clinic. In Lesotho, there were two TIMS OHSCs, one in Maseru, the capital city, and another one in the district of Mafeteng. Invitations to mineworkers (active and former) to attend screening were extended throughout Lesotho by means of public gatherings, media (radio stations), word of mouth, outreach campaigns, and civil society organisations. The sample was thus self-selected rather than a random sample.

During the study period, Mafeteng OHSC serviced 3 166 subjects, including active and ex-mineworkers, family and community members. To be included in this analysis, subjects had to be an ex-mineworker who had attended Mafeteng-OHSC between January 2017 and November 2018, and have worked underground for a minimum duration of 12 months in a South Africa gold mine. A total of 2 678 (84.6%) subjects met the inclusion criteria and were thus included in the analysis.

Measurement: variables and quality control

Gold miners (ex or active) were invited to visit the OHSC, and were aware of the possibility of compensation as well as detection and treatment of TB. The screening included anamnesis, physical examination, CXR, Xpert MTB/RIF sputum test (Cepheid, California, USA) on sputum, spirometry, and pulse oximetry at rest for all attendees. The sputum induction technique was applied to obtain sputum samples from those who could not produce it spontaneously.

CXRs were read by BM who had attended training courses on the reading of CXRs for detection of pneumoconiosis based on International Labour Organization (ILO) guidelines, and on spirometry, at the Medical Bureau for Occupational Diseases (MBOD) and the National Institute of Occupational Health (NIOH), Johannesburg, South Africa. A random sample of 300 CXRs were read independently by two specialist occupational physicians familiar with the ILO classification of pneumoconioses. One reader reported an 80-90%, the other 90% agreement with the clinic reading. Furthermore, external assessors (a team of occupational medicine specialists engaged by the Global Fund), who were quality assessing the OHSC's delivery quarterly, rated the quality of the data produced as high. Table 1 provides the details of the variables used in this dissertation.

The Xpert MTB/RIF test was performed by qualified lab technicians,at the Mafeteng District Hospital laboratory.

Table 1. Variables included in the analysis

Variable	Means of measurement/collection	Quality control/ comment	Sub-study that relates to variable
Age (years)	Calculated from the birth date on ID document to date of visit to OHSC.		• Case report • Predictors of disease
Length of mine service (years)	Estimated from first and last year of service.	A one-week validation check of clinical files found 83% (2223) with a confirmatory record of service.	• Case report • Predictors of disease
Occupation (high dust, low dust)	Longest job occupied. High dust: rock drill operator, winch operator, stope team, loader operator, construction worker, blasting assistant, etc.). Low dust: belt attendant, chair lift attendant, loco operator, general worker, etc.	0.2% (5) missing.	• Case report • Predictors of disease
Smoking history (ever, never)	Recorded by medical practitioner. Ever: had ever smoked for a period of six months or more. Never: never smoked or had smoked for a period of less than 6 months.	1.1% (29) missing.	• Case report • Predictors of disease
Silicosis (ILO >= 1/1, with or without TB)	Chest X-ray classified by a medical practitioner with training on the ILO classification of pneumoconioses, after treatment of attendee for any active TB.	A random sample of 300 chest x-rays was read independently by two specialist occupational physicians familiar with the ILO classification. One reported a 80-90%, the other, 90% agreement with the clinic reading.	• Case report • The value of symptoms and CXR in the diagnosis of TB • Predictors of disease
Silicotuberculosis	Silicosis as above plus TB, active and/or radiological, including parenchymal, pleural or mediastinal abnormality suggestive of inactive or active TB.	As for silicosis.	• Case report • Predictors of disease
HIV status	HIV test offered to all not on antiretroviral therapy. HIV positive: positive status already known (as shown in participant's medical booklet), or diagnosed positive at the OHSC (Uni-GoldTM rapid test, Trinity Biotech). HIV negative: tested negative at OHSC or elsewhere within the previous 12 months as shown in the medical booklet.	0.6% (16) missing.	• Case report • The value of symptoms and CXR in the diagnosis of TB • Predictors of disease

History of past TB treatment	Self reported.	Where possible, verified on Lesotho medical booklet, mine exit medical certificate, MBOD certificate or TB DOT card.	• Case report • The value of symptoms and CXR in the diagnosis of TB • Predictors of disease
Radiological changes suggestive of TB	Read by medical practitioner. Parenchymal, pleural or mediastinal abnormality suggestive of inactive or active TB.	As for silicosis.	• Case report • The value of symptoms and CXR in the diagnosis of TB • Predictors of disease
Current active TB	TB diagnosed at the OHSC on positive GeneXpert (Cepheid, USA) with or without clinical and/or radiological features of TB, or TB diagnosed elsewhere and on TB treatment at time of attendance.	GeneXpert testing routinely done on all attendees' sputum regardless of presumptive TB status, excluding those already on TB treatment or within 12 months of treatment completion. Sputum was obtained on 96% of attendees, with use in a minority of sputum induction or return with next day sputum where necessary.	• Case report • The value of symptoms and CXR in the diagnosis of TB • Predictors of disease
Cough (> 2 weeks)	Recorded by medical practitioner.	0.4% (11) missing.	• Case report • The value of symptoms and CXR in the diagnosis of TB • Predictors of disease
Shortness of breath (any)	Self-reported	0.6% (16) missing.	• Case report • Predictors of disease
Shortness of breath at rest	Assessed clinically by medical practitioner.	-	• Case report • Predictors of disease
Peripheral capillary oxygen saturation (SpO2) (%)	Measured on multi-parameter patient monitor (Aquarius G91025, Aquarius Electronics, London, UK).	11.9% (319) missing.	• Case report • Predictors of disease

BMI (kg/m2)	Height and weight measured on a Charder scale (HM 20IM). BMI = weight (kg)/height (m2). Overweight/obese: BMI>=25 Kg/m2, underweight: BMI<18.5 Kg/m2, Normal weight: BMI between 18.5 to 24.9 Kg/m2.		• Predictors of disease
FEV1, FVC, FEV1/FVC, all as percentage of predicted	Measured on Easy on-Pc Spirometer (ndd Medizintechnik AG, Zurich, Switzerland). Predicted value 0.9 x ECCS (European Community of Coal and Steel) reference value.	ATS criteria were applied. Spirometer calibrated with 3 liter syringe each day before starting testing; with changes in temperature and humidity; and after every 6th subject. Annual calibration Stanyer Electroserve (Pinetown, South Africa). Only results that met validity	• Case report • Predictors of disease
Reported death	Miners and family members were advised to report any major health issue concerning the miner (e.g. death, hospitalisation) to the OHSC. The death of miners was added to their records.	Only death cases that were reported to the OHSC were included in the analysis.	• Predictors of disease

The variable listed in Table 1 above were included in relevant analyses of sub-studies 2 (the value of symptoms of cough and fever and CXR on the diagnosis of TB) and 3 (predictors of disease). Except for the variables BMI, FEV1, FVC, FEV1/FVC and age which were grouped as ordinal the remaining variables were binary.

Ethics approval

Risks and benefits

Gold miners who have worked in the South African mines are a potentially vulnerable group by virtue of their migrant labour status, their base in impoverished rural areas, exposure to hazardous employment, and high disease burden. The need for this research arose from these vulnerabilities.

This was a study of secondary data on ex-miners collected as part of a regional screening programme for TB and compensatable lung disease. Individual identifiers and clinical

information were confidential to the researchers. No personal identifiers appear in reports or published research. Ex-miners examined under the TIMS programme were referred clinically and/or submitted to the MBOD at the time. The research was retrospective and did not affect any of these processes or benefits.

Informed consent and permission

TIMS was not a research programme. Participation was on the basis of voluntary attendance following an invitation campaign in Lesotho under the auspices of the Lesotho Ministry of Health supported by the Wits Health Consortium. The clinical records are held by the Ministry of Health. Permission to analyse and publish the data was provided by the Wits Health Consortium-TIMS project and full ethical clearance exemption was obtained from the Human Research Ethics Committee of Lesotho (ID: 142-2018), and the UCT-Human Research Committee (HERC REF 699/2020) (attached as appendix 1 to 3) on the basis that this analysis was based on review of anonymous clinical data.

CHAPTER 4: DIFFICULTIES IN THE SEPARATION OF SILICOSIS AND PULMONARY TUBERCULOSIS IN SILICA EXPOSED GOLD MINERS – A REPORT OF FOUR CASES

INTRODUCTION

Background

Since the early twentieth century, knowledge has accumulated about silicosis and pulmonary TB as distinct diseases in gold miners [Schepers, 1964, Mintz, 2009, Madl et al. 2008]. However, despite progress in technology and the multiple diagnostic tools and treatment options for TB that have been developed, the challenge of distinguishing and therefore efficiently managing these two conditions remains the same [Taylor and Alexander, 1938; Solomon and Rees, 2010].

While computed tomography (CT) scanning is able to identify features of silicosis not visible on plain chest x-ray (CXR) and might have a role to play in distinguishing old/ healed TB from active TB and TB from silicosis, this technology is generally not available in low resource settings [Skoura et al. 2015]. The focus of this study was therefore on plain CXRs. The objective was to present a case series illustrating the diagnostic and health service problems of distinguishing TB and silicosis clinically and radiologically in former gold miners from the South African mines.

The objective of this sub-study was to present a case series illustrating the diagnostic and health service problems of distinguishing TB and silicosis (i.e., clinically and radiologically) and to make recommendations for more accurate discrimination between silicosis and TB, particularly in low resource settings.

MATERIALS AND METHODS

Study design

This was a case series

Population

In this case report of four cases, cases were selected from former employees of South African gold mines living in Lesotho, a country with a population of about 2.2 million bordering on South Africa [World Bank, 2022]. Data collected at an Occupational Health Service Centre (OHSC) in the town of Mafeteng as part of the TB in the Mining Sector in Southern Africa (TIMS) programme [TIMS, 2019] were analysed. Author BM served as the medical officer at this clinic. Invitations to mineworkers who had worked in the South African mining industry, to attend screening were extended throughout Lesotho by means of public gatherings, public media, word of mouth, and via civil society organisations. The miners were invited to visit one of the two service centers in Lesotho and were aware of the possibility of compensation as well as diagnosis and referral for treatment of TB. The screening protocol included history, physical examination, chest X-ray (CXR), sputum Xpert MTB/RIF test (Cepheid, California, USA) spirometry, as appropriate, and pulse oximetry (Aquarius G91025, Aquarius Electronics, London, UK) at rest.

The Centre at which miners were examined was programme specific. It was therefore unable to investigate complex cases to a precise diagnosis through computed tomography (CT) and/or bronchoscopy, for example. Its primary role was screening for TB, with referral to district hospitals where necessary. A secondary objective was screening for compensable disease, notably silicosis and silicotuberculosis. For all those with a suspected occupational disease listed in the Occupational Disease in Mines and Works Act (ODMWA), a claim was submitted to the MBOD in Johannesburg.

Selection of the four cases was purposive to illustrate the main issues discussed. For each case, the medical assessment is described, including occupational history, past and current medical history, physical examination, radiological and laboratory findings. Only spirometric values as a percent of predicted were available for analysis. Those suspected of having active TB disease did not undergo spirometry, for reasons of infection control. The CXRs were initially read by BM, with quality control by two occupational medicine specialists attached to the TIMS programme. CXRs and case histories were reviewed by three occupational medicine specialists and a radiologist with extensive experience in

reading CXRs of gold miners (the “panel”). As the Centre did not have pulmonology facilities, and no formal responses were received from district hospitals regarding referrals to them, each case report is based on the primary assessment, taking the CXR and occupational and medical history into account.

In this report, silicotuberculosis is defined as a combination of silicosis and TB, whether the latter was active or old healed (inactive) disease or both. Silicosis was defined as abnormalities on CXR that are consistent with the ILO classification profusion 1/1 or above and/or with progressive massive fibrosis (PMF) [ILO, 2011]. Radiological TB is defined as any abnormality suggestive of active or old healed TB.

Permission to analyse and publish the data was provided by the Wits Health Consortium-TIMS project and ethical clearance was obtained from the Human Research Ethics Committee of Lesotho (ID: 142-2018), and the UCT-Human Research Committee (HERC REF 699/2020) on the basis that the study involved the analysis of anonymized secondary clinical data collected for service purposes.

CASE DESCRIPTIONS

Case 1

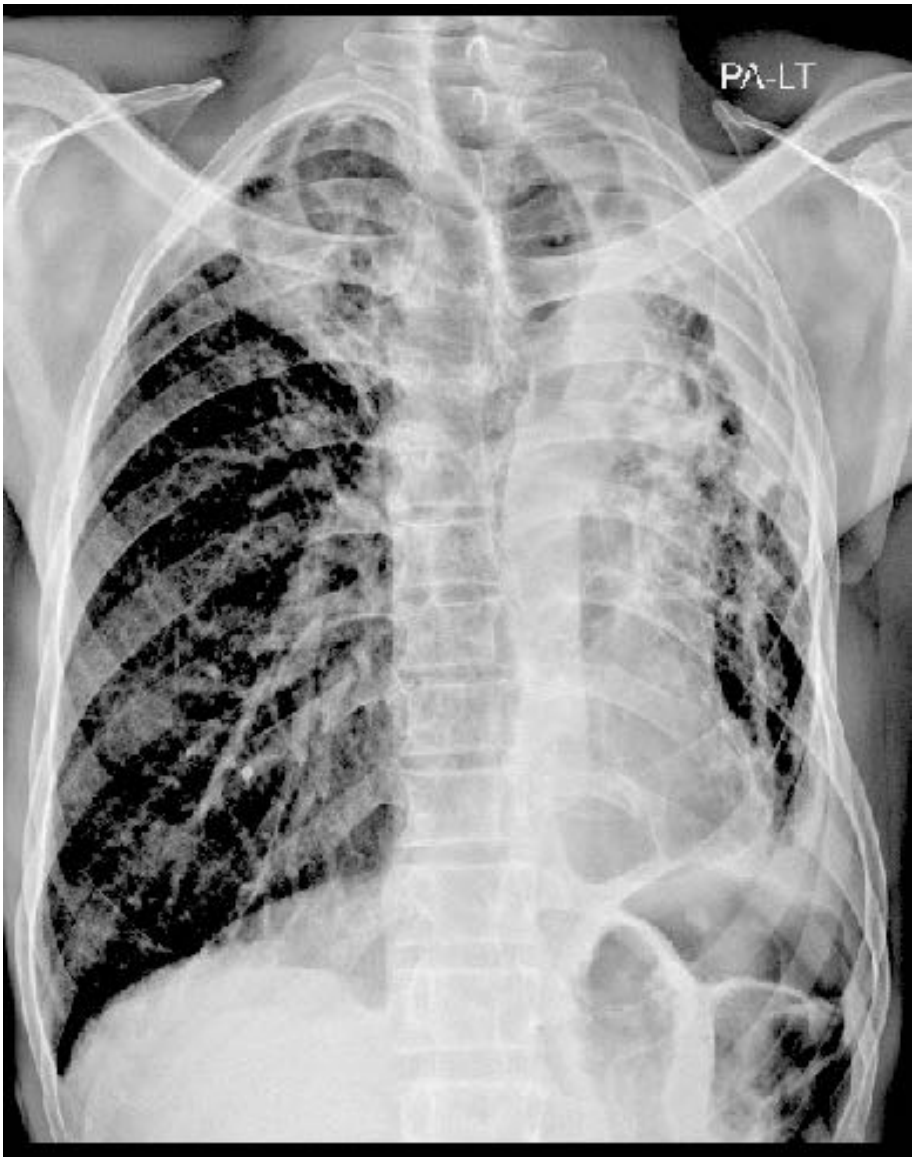
This was a 61 year-old man, former smoker, HIV positive on antiretroviral therapy, who had worked in gold mines from 1978 to 1999 (21 years) as a rock drill operator. When he visited the OHSC in 2017, he had already been treated four times for pulmonary TB, and was undergoing a fifth course of treatment. This current treatment was initiated on the basis of CXR findings and chronic productive cough (recorded in his medical booklet), as the Xpert MTB/RIF sputum test was negative. At his visit, he had no physical complaints, did not look physically ill, and was afebrile, but had a slightly reduced oxygen saturation of 94% in room air (normal value >95%).

The attendee's medical booklet had previous TB treatments documented, which indicated that the first TB episode was bacteriologically proven with a positive acid-fast bacilli (AFB) sputum smear test. The only evidence of the second and third TB treatments was his TB directly observed treatment (DOT) cards, which did not document whether the decision to treat was on bacteriological grounds. The fourth and fifth treatments were based on persistent cough with a non-improved x-ray, as recorded in the medical booklet.

The CXR taken on the day of the visit to the OHSC (Figure 5) showed extensive fibrosis of the left lung with volume loss and compensatory hyperinflation of the right lung. Extensive pleural thickening of the left hemithorax was present, as were cystic changes, areas of calcification, and features suggestive of bronchiectasis. The right lung showed uniform opacities of about 2-3 mm diameter in the upper part of the middle zone (ILO profusion 1/1 q/q).

The panel assessed this CXR image as silicotuberculosis. Although the panel could not recognise any signs of active TB, it noted that it was not possible to exclude active TB on radiological grounds alone. Given that the attendee was already undergoing TB treatment and that monitoring of treatment was not in the scope of the Mafeteng OHSC, the patient was referred back to his treating facility.

Figure 3. CXR (taken in 2017) of a 61-year-old ex-gold miner with 21 years of underground mining, a history of four episodes of past TB treatment and undergoing a fifth TB treatment course .


PA-LT

Case 2

This was a 67 year old man, former smoker, HIV negative, who had worked in gold mines from 1976 to 2011 (35 years) as a winch operator. He had been treated for pulmonary TB in 2008. In January 2018, when he visited the service center, he was on TB treatment initiated a week earlier based (reportedly) on a history of persistent productive cough and abnormal CXR. Xpert MTB/RIF sputum test at the time of diagnosis was negative. At his visit, he reported a chronic productive cough with progressive shortness of breath. He did not appear physically ill and was apyrexial, although with an abnormal oxygen saturation of 93% in room air.

In October 2019, the same individual visited the Centre again for follow up. Symptoms persisted and physical examination findings were unchanged. His CXR images are shown in Figure 4.

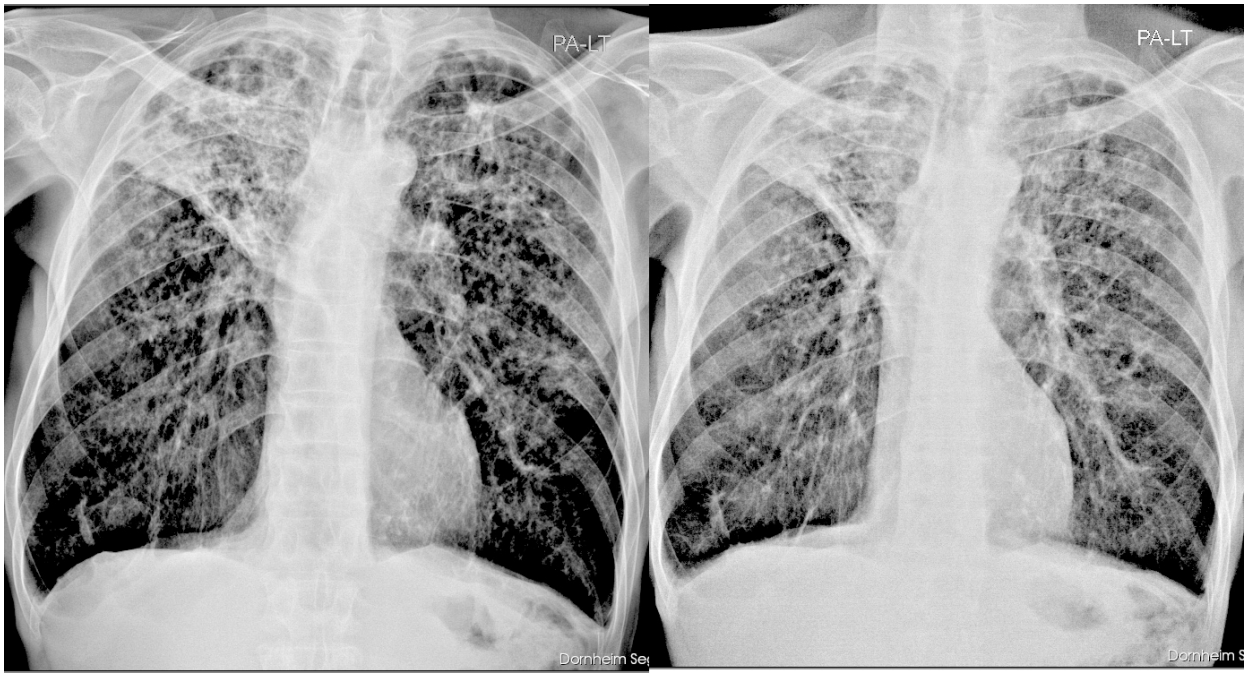


Figure 4. CXRs, of a 67-year-old ex-gold miner with 35 years of underground mining, obtained in January 2018 (on the right) and in October 2019 (on the left) at Mafeteng OHSC.

Both CXRs showed bilateral, multiple nodules of q size, mostly in the upper and middle zones, with extensive bilateral fibrotic changes. Cystic and peribronchiolar changes, pleural thickening and diffuse loss of bronchiovascular markings were also identifiable. Cavities were noted in the upper zones bilaterally in Figure 4 (i.e., right), which after 12 months of treatment, Figure 4 (i.e., left) are less evident, taken as a positive response to TB treatment. Although lung hyperinflation was noted in both CXRs, spirometry, performed

(only) at the second visit, was normal. The panel's assessment was silicotuberculosis, including both old healed and active TB.

Case 3

This was a 73 year old man, former smoker, HIV negative, who had worked in a gold mine as a general underground miner from 1992 to 2000 (8 years). When he visited Mafeteng service Centre in 2017, he had no medical complaint and denied any cough or shortness of breath, and gave no history of TB. Physical examination revealed no abnormality of note, with oxygen saturation normal (97%) in room air. His sputum Xpert MTB/RIF test was negative.

Surprisingly, in view of his lack of symptoms, his CXR (Figure 5) showed marked volume loss of the left lung with extensive pleural thickening with calcification. This was read as consistent with old healed TB, with other causes not definitively excluded. Uniform rounded opacities, read as ILO 2/2 q/r were noted in the right upper and mid zones. The panel assessment was silicotuberculosis.

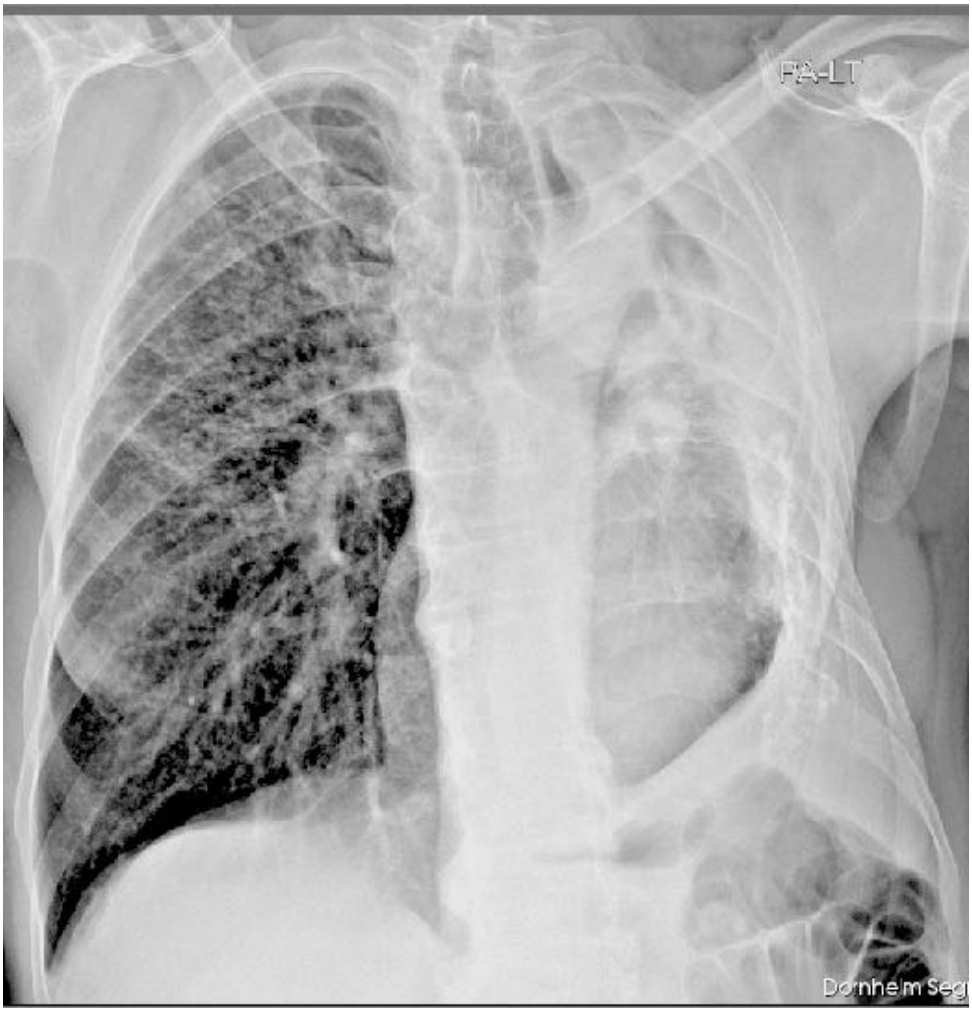


Figure 5. CXR, of a 73-year-old ex-gold miner with 8 years of underground mining, obtained in 2017 at Mafeteng OHSC.

Case 4

This was a 67 year old man, former smoker, HIV negative, who had worked in underground gold mines from 1968 to 2008 (40 years) as a rock drill operator, a winch operator and a loader operator. When he visited the Mafeteng Centre in 2017, he complained of acute exacerbation of a chronic productive cough and longstanding progressive shortness of breath. Other recent symptoms were chest pain, blood-stained sputum, decreased appetite and intermittent fever. He was on treatment for obstructive lung disease, which he described as “asthma”, initiated four months earlier. He had a history of past pulmonary TB treatment in 1996 and 2002.

Physical examination revealed an ill-looking patient with reduced oxygen saturation (88%) in room air. He was tachypnoeic, at 24 cycles per minute. The patient also had orthopnea and a regular tachycardia (115 beats/minute) hepatomegaly with raised jugular venous pressure, and bilateral pitting pedal oedema. Xpert MTB/RIF sputum tests performed on two different occasions were negative.

CXR, shown in Figure 6, revealed areas of confluent opacification in the upper zones bilaterally, cystic change, an enlarged heart silhouette and a rightward deviation of the trachea. Based on the many years of silica dust exposure and clinical and CXR features, the original Centre diagnosis was silicotuberculosis with cor pulmonale. The patient was referred as an emergency to the district hospital for high-level care, but died two days later. The panel’s assessment was that the radiological abnormalities were not consistent with silicosis, either in respect of opacities or of progressive massive fibrosis (PMF). Accordingly, their radiological assessment was TB only (i.e. without silicosis).

Subsequently, it transpired that the ex-miner had already received compensation for second degree occupational lung disease under ODMWA, which is the maximum degree for compensation under the legislation.

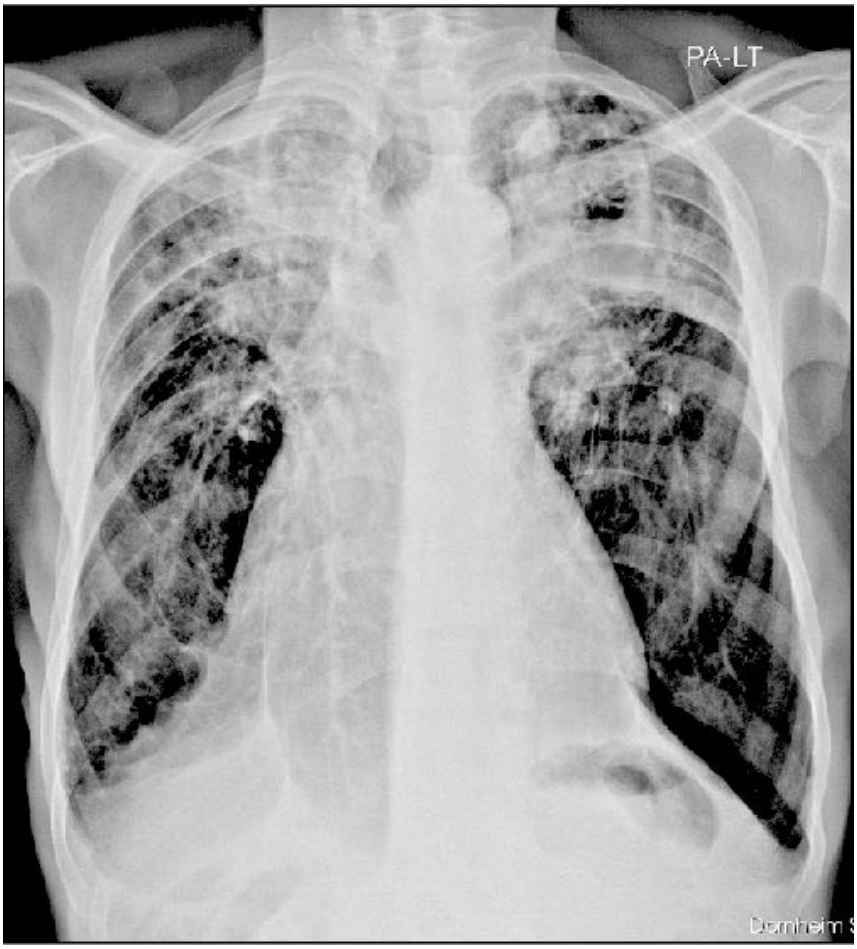


Figure 6. CXR, of a 67-year-old ex-gold miner with 40 years of underground mining, obtained in 2017 at Mafeteng OHSC.

DISCUSSION

More than 84 years ago, Taylor and Alexander [Taylor and Alexander, 1938] reported the diagnostic problem arising from radiological overlap between silicosis and TB. The difficulty in radiologically distinguishing TB from silicosis is therefore longstanding [Skoura et al., 2015]. There are features in the literature that guide the distinction [Lee, 1948]. Trachea in the midline, nodules of uniform size and distribution and regular shape favour silicosis. Consolidation, adenopathy, cystic disease/cavitation, asymmetric nodules of various size and shape, clustering of nodules, irregular masses, parenchymal distortion and pleural effusion favour TB. Features such as emphysema, massive fibrosis and calcified adenopathy may accompany either disease.

Features which might further distinguish active TB disease from old healed TB include adenopathy, cavitation “soft infiltrates”, patchy consolidation, diffuse military pattern and pleural effusion. CXR changes of recent origins should also be a maker of possible active TB. However, given the wide-ranging radiological manifestations of silicosis, old/healed TB and active TB disease, these three conditions may display considerable overlap [ILO, 2011]. TB may mimic silicosis, particularly when nodular, massive or miliary, or alternatively, mask silicosis. Both silicosis and silicotuberculosis (for example, fibrosis, focal modularity, volume loss) may progress in the absence of active TB [Roy and Ellis, 2010].

Given the high prevalence of silicosis and past TB among South African ex-gold miners [Maboso et al., 2020], clinicians involved with the diagnosis of occupational lung disease in miners need to reduce the area of diagnostic uncertainty and settle on appropriate management and treatment protocols, typically in low resource settings. Clinical and health service issues arising from each of the cases are considered below.

Case 1: Recurrent TB; HIV

Recurrent TB is common in this population [Maboso et al., 2020], as indicated by cases 1,2 and 4. There are a number of reasons for this. Gold miners with silica-dust loaded lungs have impaired innate lung immune responses [Konency et al., 2019], rendering them particularly susceptible to TB. The high susceptibility to TB following silica dust exposure and silicosis is further complicated by the HIV epidemic among former and active miners in southern Africa [Maboso et al., 2022; Park et al., 2009]. Silicosis and HIV combine multiplicatively to increase the risk of TB, such that the relative risk of TB on HIV infected silicotic miner is 15 times that of a miner with neither condition [Corbett et al. ,2000]. HIV-infected individuals may develop paucibacillar TB owing to their weakened cell-mediated immune system reducing the sensitivity of bacteriological tests [Montales et al., 2015].

Chronic lung damage caused by silicosis and TB renders the lung susceptible to TB recurrence [Taylor and Alexander, 1938]. Hence, reactivation of dormant bacilli is possible at any time [Ravimohan et al., 2018]. In addition, as long as ex-miners live in high TB-burden communities, reinfection will occur [Corbett et al., 2000].

Given that medical examiners consequently have to maintain a low threshold for investigation for TB in ex-miners, it is understandable that empirical treatment is common. However, the fact that, in case 1, the ex-miner had been treated empirically on four occasions, suggests that there is risk of over-treatment of TB in this population. Since distinguishing nodular TB from silicosis may pose difficulties, particularly where CT is unavailable, an analagous situation pertains to the diagnosis of silicosis. Underdiagnosis is more likely where an occupational history is not taken and/or the examiner is unfamiliar with the disease. Overdiagnosis of silicosis is also a possibility. Where active TB is diagnosed, practice in the region is to delay the diagnosis of silicosis until TB treatment is complete to determine the extent of clearing.

Case 2: Active TB superimposed on chronic silicotuberculosis

Although its sensitivity is higher than the conventional sputum smear test for acid fast bacilli, Xpert MTB/RIF test sensitivity does not match that of culture [Panday et al., 2017, Kendal et al., 2019]. Hence, negative results, especially in an ex-gold miner with cough, and highly suggestive CXR findings do not confidently exclude active disease. As with the patient described in case 1, the clinician is faced with the problem of excluding active TB, given a negative Xpert TIB/RIF test, non-specific respiratory symptoms, and a CXR showing extensive abnormalities consistent with silicosis and old healed TB. In this case, the presence of cavities was specific enough finding to create a presumption in favour of superimposed active TB, with the receding cavities serving as evidence for the appropriateness of empirical treatment. The diagnostic difficulty is greater where the initial CXR is consistent with silicotuberculosis but lacks findings suggestive of active TB. In the absence of radiological clearing and symptom improvement, the likelihood of unnecessary treatment would have to be considered. As mentioned earlier, given that silicotuberculosis may progress over time, radiological worsening itself does not necessarily indicate active TB. Further, cavities suggestive of active TB need to be distinguished from the particular pattern of post TB fibrosis, as “fibrocystic”.

Progression of chronic silicotuberculosis other than due to newly confirmed active disease, is a phenomenon that has been poorly studied. One reason in the South African mining context is that combined disease disqualifies miners from continuing in to work in high risk areas, which, in most cases, results in them leaving the industry. Given the lack of surveillance and follow-up of ex-miners, silicotuberculosis tends to disappear from epidemiological view.

Case 3: No symptoms, negative Xpert MTB/RIF test, no history of TB treatment, but with silicotuberculosis on CXR

Some asymptomatic ex-gold miners present with severe lung damage, a combination which is difficult to explain. Habituation to chronic low grade symptoms such as dyspnoea and cough, to the extent that the miner does not regard them as abnormal, is one possibility.

The absence of a TB history presents a similar puzzle. Given the high susceptibility of ex-gold miners to TB, and the negative sputum test, it has become practice to call this “old” “healed”, “inactive” or “prior” TB. Different explanations present themselves for the absence of a TB history. It is possible that some ex-miners cannot recall their TB treatment. Alternatively, the TB course might have been that of “low grade” or “indolent” TB, which did not elicit TB testing. There may be insufficient bacilli present to be identified with laboratory testing, particularly where molecular tests such as Xpert are not available. Finally, the organism might be a non-tuberculous mycobacterium (NTM), which cannot be diagnosed by Xpert MTB/RIF given the high specificity of this test for TB [Kendall et al. ,2019]. However, it remains surprising that a TB or NTM infection that causes the extensive lung destruction seen in this case would go unnoticed or remain asymptomatic.

Case 4: Massive fibrosis, previous TB and cor pulmonale

After consideration based on CXR reading of pneumoconiosis (no clearly identifiable nodules attributable to silicosis as per the ILO Classification and with featuresas suggestive of TB), the panel attributed all the changes seen with the patient described in case 4 to TB.

The possibility of effacement of the nodular appearance of silicosis by confluence of the nodules and contraction of the upper zone as part of the development of progressive massive fibrosis (PMF) is impossible to exclude. Confluence or “massive” fibrosis has long presented difficulty in distinguishing complicated silicosis from TB radiologically. In the article from the pre-TB treatment era cited earlier, the view attributed to Gardner, an authority in the pre-treatment era, was that TB was a necessary factor in the development of PMF [Taylor and Alexander, 1938]. However, the authors present a classification of silicosis alone in which advanced disease (the “third stage”) includes various features of PMF, including coalescence of fibrotic nodules or areas, massive fibrosis resembling consolidation, pleural thickening and emphysema [Taylor and Alexander, 1938]. This accords with the modern consensus that PMF is a complication of silicosis without TB as a necessary co-factor.

This case suggests, as seen with the patient described in case 3, that the identification of separate disease processes in heavily fibrosed lungs may be impossible, clinically and that, despite lacking specific radiological features of silicosis, silicotuberculosis cannot be excluded, especially in an individual with an exposure history as long as 40 years. This

would inform, particularly, the adjudication of eligibility for workers' compensation in such cases.

Recommendations

Striking a balance between underdiagnosis and overdiagnosis of TB

Underdiagnosis of active TB among southern African miners has been a public health concern. In one report, over 50% of miners who had active TB diagnosed at autopsy were undiagnosed in life [Field et al., 2011; Murray et al., 2000]. Given the high mortality and morbidity associated with TB, and transmission of the disease within communities, it is essential that medical examiners be rigorous when assessing the chest radiograph of silica-exposed workers to ensure that diagnosis of TB is not missed [Solomon and Rees, 2010]. Since subtle radiographic changes may be the initial manifestation of TB, clinicians should lower the diagnostic threshold for suspecting TB. In these cases, it may be difficult to diagnose TB with a single CXR [Lewis et al., 2009]. Previous chest radiograph images are needed to look for changes over time.

However, as described earlier, this population is also characterised by a high prevalence of post-TB lung sequelae [Roy and Ellis, 2010]. This may result in overdiagnosis of microbiologically negative TB and, hence, over-treatment. Accordingly, one should keep in mind that, in ex-gold miners with lung lesions due to silicosis and/or old-healed TB lesions, radiographic changes over time are not always due to superimposed active TB. An occupational history should be taken in all adults in Lesotho presenting with lung disease, and silicosis considered in all former gold miners with abnormal CXRs.

Clinicians should seek bacteriological confirmation of TB before initiating TB treatment, although empiric treatment is justified in circumscribed circumstances, such as persistent TB suggestive symptoms and CXR abnormalities [WHO, 2006]. More generally, compensation and screening programmes for former gold miners should offer testing of sputum for TB to all such miners whether symptomatic or not. Apart from diagnosis of silicosis and TB treatment decisions, the identification of old-healed TB remains important in this ex-goldminer population where silicosis, in combination with TB, whether old-healed or active, is a second degree compensable disease [ODMWA, 1983].

For purposes of comparison of serial chest images, systematic digital record keeping of CXRs, TB tests and treatment of miners, starting while in service, is needed. These

records should be accessible to all healthcare providers who attend to former miners. There is also a need for occupational lung disease training for medical examiners in labour sending areas in occupational lung disease, with emphasis on pneumoconiosis and TB.

CXR classification of silicotuberculosis

In the early version of what is now the ILO International Classification of Radiographs of Pneumoconioses there was an additional symbol for active TB ("tba"), which was dropped from later revisions [ILO, 2011]. Beyond TB, the current reader has a number of symbol options for elaborating the reading of silicotuberculosis, including cavity (cv), pleural effusion (ef), marked distortion of an intrathoracic structure (di), bullae (bu), significant apical pleural thickening (at) and emphysema (em).

However, a judgement about active disease is not called for, while important TB descriptors such as extent of disease, massive fibrosis, and bronchiectasis are absent. There is currently considerable interest in "post-TB lung" as a chronic condition requiring follow up and, in some circumstances, treatment. For these reasons, whether they are using the ILO Classification or not, readers should attempt to describe TB in greater detail than provided for by the Classification. The current "Comment" section could be used for this purpose, although that requires ignoring the instruction that it should be used for non dust-related disease.

CXR reading courses, combining silicosis and TB, whether active or old, are needed for doctors serving mining or ex-mining populations where silicotuberculosis is common. This would require chest imaging teaching sets, exemplifying silicosis, TB and combined disease across the range from subtle to florid, as well as training in the progression of such features over time, or regression with TB treatment. Such sets could serve as informal standard films for readers as an adjunct to the ILO Classification of pneumoconiosis.

Health care costs support beyond current workers' compensation system

Gold-mining related diseases, such as silicosis, COPD and TB, are either progressive or leave long-term sequelae that may significantly affect the lives of ex-gold miners years after they leave the mine. The example given here is Case 4. This ex-gold miner had a history of past TB treatment on two occasions, and had received maximum compensation under the ODMWA. His current medical evaluation took place only because of the TIMS

programme, seven years after workers' compensation certification. Jobless, with no financial capacity, in a country with very poorly resourced medical care, he would not be able to meet the costs of health care such as diagnostic investigations, and treatment, such as long-term oxygen therapy. While Section 36 of ODMWA makes provision for medical expenses for compensable disease to be paid by the mine owner (and/or the Commissioner) for both employed and former miners, this provision has, to our knowledge ,never been instituted.

Research on silicotuberculosis

Despite progress in technology such as molecular diagnostics and advances in chest imaging, including computer aided detection, the challenge of distinguishing TB from silicosis remains as it was nearly a century back. In 1938, Taylor and Alexander [Taylor and Alexander, 1938] reported that the United States, Canada, Great Britain, Germany, Italy, Australia and South Africa had the greatest number of published studies on silicosis. South Africa remains the only one of these countries where silicotuberculosis continues to impose such a heavy burden on the population. Advanced mining technology in the industrialised part of the world has substantially reduced silica-exposure, while the TB burden has declined to low levels. Consequently, there is low incidence of silicosis and silicotuberculosis.

South Africa has been joined by other countries such as India [Nandi et al., 2021] and China [Tse et al., 2007] with large numbers employed in mining, quarrying and stone-work in a high TB burden setting, with resultant silicotuberculosis. These countries should take the lead in encouraging and funding studies that would help meet the challenges of distinguishing silicosis from TB and devising optimal screening and treatment protocols. South Africa, with its miner autopsy system, for example, is well placed to conduct clinico-pathological correlation studies [Ehrlich et al., 2021]. Collaboration among affected countries and sharing of experiences in diagnosing and managing combined disease should also be pursued.

Strengths and limitations

To our knowledge, this is one of the first studies to examine the difficulty of distinguishing TB and silicosis among migrant ex-gold miners a relatively long time after exposure to dust has ceased. A major limitation was that the evaluation was limited to CXR, as the Centre where the ex-miners were examined did not have access to pulmonology expertise or CT scanning. A lesser limitation was the lack of access to Mycobacterium TB culture, the gold standard for active disease, since Xpert (MTB/RIF) was used in all cases. However, in a comparable setting, Xpert has been shown to have a specificity and sensitivity against culture of greater than 90% [Kendall et al. 2019]. Since these limitations reflect the situation facing many health care providers in areas where ex-miners live, the considerations and recommendations arising from these cases are of practical relevance.

CONCLUSION

We have demonstrated, using the four cases from Lesotho that ex-gold miners from the South African mines may present with complex lung disease with poor agreement between radiological findings and clinical presentation, poor agreement between radiographs suggestive of TB and Xpert MTB/RIF sputum results, and overlap of clinical and radiological presentation of silicosis and TB.

While CT may help distinguish old-healed TB from an active TB lesion and from silicosis, its limited accessibility and high cost make it impractical in this setting. The lesions observed in the lungs of ex-gold miners are permanent and progressive in most, if not all, of those affected. As these ex-miners continue living in high TB burden communities, and given their impaired lung defences due to silicosis and silica loading [Pasula et al., 2009] and their high prevalence of latent TB infection (89%) [Hanifa et al., 2009], TB re-infection, reactivation and recurrence [Maboso et al., 2020; Ehlich et al., 2012] impose a lifelong population burden [Tse et al., 2007]. To this burden must be added missed diagnosis of silicosis in which all the abnormal findings are attributed to TB, with consequent loss of the opportunity for proper assessment of prognosis and opportunity for compensation.

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CHAPTER 5: THE VALUE OF THE CHEST RADIOGRAPH (CXR) AND THE SYMPTOMS OF COUGH AND FEVER IN THE SCREENING AND DIAGNOSIS OF ACTIVE TUBERCULOSIS AMONG FORMER GOLD MINERS.

INTRODUCTION

Background

The plain chest x-ray (CXR) is recommended as an essential and cost-saving tool for screening active pulmonary tuberculosis (PTB) [Assefa et al., 2019; van Clef et al., 2005; More et al., 2012]. It is also beneficial in detecting old healed TB lesions [Mileche-Obimbo et al., 2022]. According to World Health Organisation (WHO) guidelines for TB management [WHO, 2007], TB treatment initiation is recommended in the presence of clinical signs and symptoms and radiological changes suggestive of TB with or without bacteriological confirmation.

Evaluation of CXR as a screening tool for pulmonary TB relative to TB culture in African general populations has shown sensitivity and specificity in the ranges of 80% to 97% and 63% to 99% respectively [Assefa et al., 2019; van Clef et al., 2005; More et al., 2012]. However, there are a number of reasons why the value of CXR in the screening and diagnosis of active TB amongst ex-gold miners might differ from that of active gold miners and the general population.

The proportion of subjects affected by TB (past, active and recurrent) is high in this population resulting in a large burden of symptomatic and radiological post-TB sequelae [Mor et al., 2012; Charalambous et al., 2008; Maboso et al., 2020; Q(h)ubeka Trust, 2021]. HIV is common, with infected individuals more likely to present with smear-negative TB and a radiological pattern different from that of typical adult post-primary TB [Dembele et al., 2008]. Finally, the high burden of silicosis in this population [Maboso et al., 2020; Q(h)ubeka Trust, 2021] creates diagnostic difficulty in distinguishing silicosis from pulmonary TB [Maboso et al., 2023; Solomon et al., 2000]. Therefore, possibly affect the performance of CXR in this group.

Study objective

The objective of this study was to measure the performance of CXR as well as symptoms against GeneXpert in the diagnosis of active TB amongst ex-gold miners in Lesotho. The Kingdom of Lesotho is a small low income country with the world's highest TB incidence rate [WHO, 2022] and second highest HIV prevalence [UNAIDS, 2022]. A substantial number of its inhabitants are ex-gold miners from South African gold mines [Maboso and Ehrlich, 2020]. Of all adolescent and adult primary healthcare encounters in Lesotho, 48% present with lung lesions on CXR, while two percent have silicosis [Seung et al., 2012]. The country has only one laboratory that can process TB cultures and fewer than twenty health facilities that can bacteriologically diagnose pulmonary TB. This setting therefore provides a challenging context for the use of screening tools.

RESEARCH METHODS - PARTICULARS OF THIS SUB-STUDY

Study design

Cross-sectional study of screening and diagnostic test accuracy.

Measurement : variables and quality control

In pursuit of improving point of site testing efficiency, (i.e. accessibility, short turnaround), the present study analyses the value of CXR and symptoms of cough and fever in the screening and diagnosis of TB using Xpert MTB/RIF sputum test as the diagnostic standard. Xpert MTB/RIF sputum test sensitivity and specificity for identification of active TB have been reported to be very high, close to culture [Kabir et al., 2021, Panday et al., 2017; Maclean et al., 2019; Sedky et al., 2018; Shapiro et al., 2021].

Of the 2678 who met the initial inclusion criteria as stated earlier, 106 (4%) were either on TB treatment when they visited the OHSC or they had a positive GeneXpert test within the past twelve months, hence, they were excluded from this sub-study's analyses. A total of 2572 (96%) were included in the analyses.

Statistical analysis

Data were computerised using Numbers software (version 6.2.1, Apple Inc., 2008-2019). Statistical analysis was performed using Wizard Pro 1.9.38 (wizardmac.com). The analysis output was sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), against the Xpert MTB/RIF test for active TB as the reference standard. The sensitivity and specificity of this test for identification of active TB have been reported to be very high, close to those of culture. 16-18 These performance metrics were calculated for the following investigations : (1) CXR, (2) fever and/or cough (3) CXR reading and/or symptoms of cough and/or fever and (4) CXR and symptoms of cough and/or fever. These metrics were also computed by HIV status, silicosis status and history of past TB.

RESULTS

Sample characteristics

A total of 2572 participants were included. Characteristics of this population, including the prevalence of silicosis, HIV, lung function impairment and TB have been published elsewhere [Maboso et al., 2020] and are summarised in the Table 2.

Table 2. Characteristics of the sample.

	Absolute number	Proportion
Median age (range) in years	62 (28-98)	-
Median length of service in the mining (range) in years	28 (1-52)	-
Prevalence of untreated active TB in this sample	76/2572	2.95%
Prevalence of silicosis	1079/2572	41.9%
Proportion of ex-gold miner with TB on CXR	1536/2572	59.7%
Prevalence of HIV	776/2572	30.1%

Tables 3 below summarises the findings.

Table 3. The performance of CXR and symptoms of cough and fever in screening for TB among ex-gold miners.

	Xpert +	Xpert -	Total (%)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
CXR performance (N=2572)							
CXR+	70	1466	1536 (59.7)	0.93 (0.87-0.99)	0.41 (0.39-0.42)	0.05 (0.04-0.06)	0.99 (0.98-1)
CXR-	5	1031	1036 (40.3)				
Total	75	2497	2572				
The performance of symptoms of cough and/or fever (N=2572)							
Symtoms +	34	716	750 (29.2)	0.45 (0.34-0.56)	0.71 (0.69-0.73)	0.05 (0.03-0.07)	0.98 (0.97-0.99)
Symptoms -	42	1780	1822 (70.8)				
Total	76	2496	2572				
The fever							
Fever +	2	16	18 (0.8)	0.03 (0.01-0.07)	0.99 (0.99-1)	0.11 (0.04-0.26)	0.99 (0.99-1)
Fever -	60	2084	2144 (99.2)				
Total	62	2100	2162				
The CXR and/or symptoms of cough and/ or fever							
CXR- Symptom(s) +	73	1681	1754 (68.2)	0.96 (0.92-1)	0.33 (0.31-0.35)	0.04 (0.03-0.05)	0.99 (0.98-1)
CXR- Symptom(s) -	3	815	818 (31.8)				
Total	76	2496	2572				
The CXR and symptoms of cough and/ or fever							
CXR- Symptom(s) +	31	501	532 (20.7)	0.41 (0.30-0.52)	0.80 (0.78-0.82)	0.06 (0.04-0.08)	0.98 (0.97-0.99)
CXR- Symptom(s) -	45	1995	2040 (79.3)				
Total	76	2496	2572				

CI, confidence interval; PPV, positive predictive value; NPV negative predictive value.

In this group of ex-goldminers, the CXR was highly sensitive in detecting (93%) and ruling out active-TB (NPV=99%). However, specificity was poor (41%) and PPV very low (5%). Thus, 95% of the CXRs read as positive would not be bacteriologically confirmed as having active-TB.

Using only symptoms (cough and/or fever) as the screening test, sensitivity was much lower than for CXR alone (45%). Specificity was moderate (71%), but considerably higher than for CXR. There was no change in the predictive values compared to CXR, with an NPV of 98% and a PPV of 5%.

Only 18 (0.8%) of those examined had fever. The specificity was very high (99%), but with a low PPV (11%). Sensitivity was extremely low (3%), but NPV remained very high (99%)

Requiring a positive CXR or symptoms of cough and/or fever made no statistical difference to sensitivity (96%) or NPV (99%). However, it significantly reduced the specificity from 4%1 to 33%, with no overlap in the 95% confidence intervals (CI). The PPV remained very low.

Requiring both the CXR and one or both symptoms greatly reduced sensitivity compared to CXR alone (from 93% to 41%), with no effect on NPV. Specificity was significantly increased (from 41% to 80%), but again with almost no effect on the low PPV.

Table 2 below shows the numbers by CXR reading and performance metrics per modifiers (e.g. history of past -TB, silicosis, HIV) against GeneXpert outcome.

There was no difference in the performance of CXR between HIV positive and HIV negative ex-gold miners.

Ex-miners with a history of prior-TB had a lower specificity (27%) than those without a TB history (59%). Those with silicosis also had a lower specificity (3%) than those without silicosis (70%). However, CXR sensitivity remained the same in all these subgroups.

DISCUSSION

Nearly two-third of TB sufferers retain radiologic abnormalities after completion of TB treatment [Mileche-Obimbo et al., 2022], which may be difficult to distinguish from active TB on radiological grounds [Maboso et al., 2023; Roy and Ellis, 2010]. The lesions observed in the lungs of ex-gold miners are permanent and progressive in most [Ehrlich et al., 2021; Nandi et al., 2021]. Therefore, as long as these ex-miners continue living in high TB burden communities [WHO, 2022], given their impaired lung defences due to silica dust lung loading, silicosis [Konency et al., 2019; Pasula et al., 2009] and HIV, and the high prevalence of latent TB infection (89%) [Hanifa et al., 2009], new TB infection and recurrence will remain a lifelong threat. Consequently, the proportion of those with radiological TB would be expected to increase over time. Hence regular screening is valuable for a number of purposes - monitoring of progression of silicosis and post-TB lung lesions and timely detection of active TB disease.

We found that the sensitivity of CXR as a screening tool for active TB in SA ex-gold miners (93%) falls in the upper range of that reported in general, i.e. non-occupational, populations (80-97%) [Assefa art al., 2019; van Clef et al., 2005; More et al., 2012]. By contrast, its specificity was considerably below the range found elsewhere (41% versus 63 - 99%). Taken with a prevalence of Xpert positive TB of approximately 3%, only 5% (the PPV) of those identified as radiological TB have sputum confirmed active disease. This low specificity compared to that of other studies [Assefa art al., 2019; van Clef et al., 2005; More et al., 2012] is most likely attributable to the high prevalence of silicosis and post TB sequelae in our population [Maboso et al., 2020; Q(h)ubeka Trust, 2021], both of which confound the radiological reading of active TB [Maboso et al., 2023; Solomon et al., 2000].

The sensitivity and specificity of symptom screening in this population are lower than that in the general population [Assefa et al., 2019]. However, a higher prevalence of chronic cough would be expected in ex-gold miners due to dust related bronchitis, post TB lung abnormalities or emphysema [Barnes et al., 2019], which are common confounders. Further, ex-gold miners with chronic cough may find it difficult to report a “change”, regarding it as “normal” [Maboso et al., 2023], which would further reduce the sensitivity of cough in identifying active TB.

The fact that more than half of these ex-gold miners have been treated at least once for PTB and present with a CXR suggestive of TB, e.g. due to silicosis (42%),

silicotuberculosis, and/or old healed TB lesions (60%), and a chronic cough [Maboso et al., 2020], compare to only 18% of previous TB history [Binegdie et al., 2022] and 3% CXR suggestive of TB in the general population [Mor et al., 2012] implies that our findings have important implications on TB screening, diagnosis and treatment of active TB in silica exposed individuals living in high TB burden countries such as Lesotho and South Africa.
We found no difference in performance of CXR between HIV positive and HIV negative ex-gold miners. Other evidence supports a higher CXR sensitivity amongst HIV negative individuals [Assefa et al., 2019]. Typically, HIV infection modifies the normal post primary TB lung presentation [Lyon et al., 2023]. The high degree of lung comorbidity in this population might obscure these HIV related differences. It is also likely that ex-miners with low CD4 counts were too sick to attend the examination.

CXR having a significantly lower specificity amongst ex-gold miners who had a history of past TB compared to those with no prior TB history, as found in this study, corroborates previously published data [Mileche-Obimbo et al., 2022], according to which more than half of subjects treated for TB retain chronic sequelae, which are difficult or impossible to distinguish radiologically from active TB [Roy and Ellis, 2010].

The fact that over two-third of ex-gold miners with silicosis had had TB, and would likely retain TB sequelae [Mileche-Obimbo et al., 2022] on top of silicotic lesions, implies that most cases of silicosis in this population were complex, e.g. advanced silicosis, silicotuberculosis, known to be difficult to distinguish radiologically from TB [Maboso et al., 2023; Solomon et al., 2000], explain the extremely poor specificity of CXR amongst ex-gold miners who had silicosis than their counterpart without this condition.

A major strength of this study was having CXR readings and Xpert results available on all participants, i.e., irrespective of presumptive TB status, in a primary setting. This is unusual in screening programmes which typically have triage protocols restricting CXR investigation to a subset, i.e.,. symptomatic participants.

Having the CXRs read by the medical officer in charge of the OHSC rather than by a radiologist might be seen as a limitation. However, previous studies have demonstrated that CXR reading for TB screening by medical officers has a higher sensitivity and an equal specificity to that of expert radiologists or pulmonologists [Hoog et al., 2011]. This

methods also offers a test of screening performance in the typical low resource setting where most individuals with TB are likely to present [WHO, 2022].

Our TB reading did not attempt to distinguish between likely active TB and past TB changes. One might argue that this would have increased sensitivity and reduced specificity relative to studies where such a distinction was made. However, trying such a discrimination would be highly speculative in our population with high rates of confounders, since radiologically distinguishing past TB from active TB lesions, or silicosis has never been accurate even to experts [Maboso et al., 2023; Roy and Ellis, 2020]. In addition, similar studies without radiologically discriminating active from past TB lesions found similar sensitivity as us, but with a higher specificity, in the general, non-mining population [Assefa et al., 2019; van Cleeff et al., 2005].

In order to avoid unnecessary TB treatment and other consequences of false-positive TB [Houben et al., 2019] in this population, clinicians should seek bacteriological confirmation before initiating TB treatment and limit empirical treatment. This can only be possible if governments and international partners (e.g., the WHO, Partners in Health) find ways to increase the capacity of bacteriological TB diagnostic facilities in such low resource settings. By doing so, it should be noted that despite its widespread availability, the poor sensitivity of acid fast bacilli smear stains [Agrawal et al., 2016] makes it inadequate as a TB diagnostic test in this population, especially given the increased likelihood of paucibacillary TB [Struckler et al., 2013].

The low specificity of CXR found in this study is a consequence of the burden of mining induced silicosis and TB in the Southern Africa region. Therefore, strengthening regional collaboration in tackling silicosis and TB is needed. Such a collaboration should ensure, for instance, that compensation and screening programmes for ex-gold miners offer GenXpert testing of sputum for TB to all such miners, whether symptomatic or not. Medical practitioners providing health services to ex-miners in labour sending areas should receive adequate training in the recognition of silicosis and related TB.

More broadly, investment in systematic digital record keeping of CXRs, TB tests and treatment of miners, including while in service, is needed. This should be the subject of a collaborative arrangement between the mining industry, the SA government and compensation agencies or Trusts. An example in the compensation arena is the

Compensation Claims Management System (CCMS) (www.recordables.com/workers-comp-claims-management-software/), which provides comprehensive reporting, tracking and analysis through a TrackComp application. The database has to cover all ex-miners in SA and neighbouring countries, and a system of digital access developed for local healthcare providers attending to these miners, in order for them to be able to compare CXR images from previous ones and access the other past records (e.g. history, TB test results).

Countries with lack of skills in occupational medicine in general and mining-related disease in particular, such as Lesotho [Ehrlich et al., 2021], might think of computer-aided diagnosis (CAD) of TB, or telemedicine with expert reading of CXR as potential solutions to addressing the burden of TB amongst these ex-gold miners. However, although the ability to distinguish active from inactive TB by CAD has not yet been tested in a population with high background of confounders such as TB and silicosis, it is unlikely to be helpful. Since not only because its specificity (23%) tested in the general population [Codlin et al., 2021] is lower than that of the human reader in ex-gold miners as found in our study (41%), but also it performance decreases further amongst subjects with a history of previous TB [Kagujje et al., 2022]. Furthermore, the CAD reading algorithm uses expert reading [Codlin et al., 2021]. Therefore, using telemedicine experts would result in a lower sensitivity than medical officer's reading although with similar specificity, as elaborated earlier [Hoog et al., 2011]. Consequently, whilst CAD could be useful in identifying negative CXRs [Muyoyeta et al., 2014], none of these two technologies would remedy this problem given the high rate of previous TB in this population [Maboso et al., 2020; Q(h)ubeka et al., 2021]. Therefore, training of community healthcare providers in occupational lung disease with emphasis in pneumoconioses remains the best options.

CONCLUSION

Relying on the symptoms (e.g. cough, fever) and CXR abnormalities will lead to high rate of false-positive TB. We discourage empirical TB treatment in ex-gold miners and call for a clear TB diagnostic algorithm in this population is to be established.

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CHAPTER 6: FACTORS ASSOCIATED WITH SILCOSIS, ACTIVE TUBERCULOSIS DISEASE AND HYPOXAEMIA

INTRODUCTION

Background

Ex-mineworkers from South African mines have a higher mortality rate than active mineworkers and the general population [Bloch et al., 2018]. They also carry a heavy burden of silicosis, TB, HIV and other chronic pulmonary diseases. All these conditions cause tissue hypoxia and hypoxaemia and are all associated with excess mortality [WHO, 2021; UNAIDS, 2021 WHO, 2022]. Understanding factors associated with these conditions would assist in finding ways to reduce excess mortality, i.e., by identifying cost-effective screening mechanisms in the context of finite healthcare resources. Studying the chronic health consequences of occupational lung disease would also strengthen the case for allocation of resources to prevention, care and surveillance.

To answer the following questions: 1. What are the cross-sectional associations between variables defined as pre-existing characteristics and the various outcomes 2. What are the cross-sectional associations between the outcome and variables defined as consequences? We pursued the objective below.

Objective

To examine factors associated with silicosis, active TB, and associated hypoxaemia in former gold miners to better understand occupational aetiology, the effects of comorbidity, determinants of severity, and health care implications.

RESEARCH METHODS - PARTICULARITIES OF THIS SUB-STUDY

Study design

Cross-sectional analytic study.

Sampling

During the study period, Mafeteng OHSC serviced 3 166 subjects, including active and ex-mineworkers, family and community members. To be included in this analysis, subjects had to be an ex-mineworker who had attended Mafeteng-OHSC between January 2017 and November 2018, and have worked underground for a minimum duration of 12 months in a South Africa gold mine. A total of 2 678 (84.6%) subjects met the inclusion criteria and were thus included in the analysis.

Statistical analysis

Computerisation used Numbers software (version 6.2.1, Apple Inc., 2008-2019). Statistical analysis was performed using Wizard Pro 1.9.38 (wizardmac.com). Multiple logistic regression modelling was performed with silicosis, active TB and hypoxaemia as the dependent variable in separate models. Independent variables were drawn from the other variables in Chapter 3 covering demographic and occupational characteristics, clinical features, comorbidity and past medical history. The modelling strategy was based on biological and epidemiological as well as statistical considerations, i.e. primarily causal modelling.

The silicosis adjusted model 1 included known risk factors (length of service, level of dust exposure, and the history of past TB treatment). HIV status was included in this model due to its potential interaction with the development of lung fibrosis, as suggested by the theory of interleukin-9 evoked earlier [Arras et al., 2006]. The silicosis adjusted model 2 included possible consequences of the condition (BMI, active TB, cough, shortness of breath, lung function performance parameters included percentage predicted FEV1 and FVC.

The active TB adjusted models included documented risk factors (length of service and level of exposure, BMI, HIV status, history of past TB treatment and silicosis) and possible consequences of TB (i.e., cough, shortness of breath, fever) .

Two adjusted models were developed for hypoxaemia. Model 1 included potential risk factors (age, history of past TB, history of smoking, silicosis BMI and HIV). Model 2 included possible consequences or clinical correlates (shortness of breath, and percentage predicted FEV1 and FVC).

RESULTS

Sample characteristics

Characteristics of this population, including the prevalence of silicosis, HIV, lung function impairment and tuberculosis (past- or current-TB) have been published elsewhere [Maboso et al., 2020] (See Tables 2 and 3, Chapter 5). A total of 2678 participants were included in this analysis. The median age was 62 years (range 28-98 years). The median length of service in the mining industry was 28 years (range 1-52 years).

Table 4 below shows the factors associated with silicosis. In the unadjusted logistic regression, with silicosis as the dependent variable, positive associations were found with almost all variables; except for BMI, especially overweight/obesity, 0.64 (0.52-0.76), and HIV, 0.80 (0.66-0.94), for which there were negative associations.

The first adjusted model ("aetiological") showed that length of service in the mines, level of dust exposure and history of past TB treatment were strongly associated with silicosis. However, HIV positive status was found to have a strong negative association with radiological silicosis.

The findings from the second model ("possible consequences of silicosis") revealed that ex-gold miners with silicosis may be suffer from shortness of breath and impaired lung function.

Table 4. Factors associated with silicosis (ILO grade >1/1): Unadjusted and adjusted models (N=2678).

Independent variable	Independent variable category	n=1139	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI) Model 1 - Risk factors/cause	Adjusted odd ratio (standard error) Model 2 - Consequences
Length of service in years					
	1-17	447	1 (0)		
	18-34	1499	2.44 (1.85-3.33)	**2.21 (1.68-2.74)**	
	35 plus	626	2.89 (2.13-3.65)	**2.61 (1.90-3.32)**	
Level of dust exposure					
	Low	701	1 (0)		
	High	1866	1.61 (1.32-1.90)	**1.57 (1.28-1.86**)	
BMI					
	Normal BMI	1500	1 (0)		
	Overweight and obesity	626	0.64 (0.52-0.76)		0.68 (0.52-0.84)
	Underweight	296	1.56 (1.17-1.95)		0.96 (0.69-1.23)
Current TB					
	No	2497	1 (0)		
	Yes	181	2.10 (1.45-2.75)		**1.94 (1.31-2.53)**
HIV Status					
	Negative	776	1 (0)		
	Positive	1781	0.80 (0.66-0.94)	**0.62 (0.50-0.73)**	
Past TB treatment					
	No	1163	1 (0)		
	Yes	1400	2.52 (2.11-2.93)	**2.66 (2.21-3.11)**	
Cough					
	No	1823	1 (0)		
	Yes	740	1.43 (1.18-1.68)		0.95 (0.73-1.17)
Shortness of breath					

	No	1791	1 (0)	
	Yes	767	1.92 (1.59-2.88)	**1.47 (1.14-1.80)**
FEV1				
	>= 80%	1379	1 (0)	
	61% - 79%	405	2.35 (1.82–2.88)	**1.88 (1.41-2.35)**
	<= 60%	316	4.04 (2.98-5.10)	**2.35 (1.55-3.15)**
FVC				
	>= 80%	1709	1 (0)	
	61% - 79%	299	2.78 (2.07-3.49)	**1.51 (1.04-1.98)**
	<= 60%	92	4.17 (2.23-6.11)	1.84 (0.85-2.82)

Table 5 presents the factors associated with active TB disease. Most of the findings in the adjusted and unadjusted analysis are imprecise because of the very wide confidence intervals due to the small sample size (positive TB, n=181). However, despite the small sample size, silicosis (OR: 2.30, 95% CI: 1.56-3.08) and HIV (OR: 1.57, 95% CI: 1.04-2.10) were significantly associated with active TB.

Table 5. Factors associated with active TB disease: Unadjusted and adjusted models (N=2678).

Independent variable	Independent variable category	n=181	Unadjusted Odd Ratio (standard error)	Adjusted Odd ratio (standard error) Moddel 1Risk factors/cause	Adjusted Odd ratio (standard error) Moddel 2 Consequences
Length of service					
	1-17 years	447	1 (0)		
	18-34 years	1499	1.20 (0.40-2.00)	1.02 (0.57-1.47)	
	35 years plus	626	1.38 (0.36–2.40)	0.93 (0.46-1.40)	
Level of dust exposure					
	Low	701	1 (0)		
	High	1866	1.05 (0.50-1.60)	1.28 (0.81-1.75)	
BMI					
	Normal BMI	1500	1 (0)		
	Overweight and obesity	626	0.79 (0.32-1.26)		0.80 (0.47-1.13)
	Underweight	296	0.90 (0.21-1.59)		1.12 (0.59-1.65)
HIV Status					
	Negative	1781	1 (0)		
	Positive	776	1.06 (0.53-1.59)	**1.57 (1.04-2.10)**	
Past TB treatment					
	No	1163	1 (0)		
	Yes	1400	1.12 (0.59-1.65)	**0.56 (0.38-0.74)**	
Cough					
	No	1823	1 (0)		
	Yes	740	2.09 (1.13-3.05)		1.17 (0.70-1.64)

Shortness of breath					
	No	1791	1 (0)		
	Yes	767	1.86 (0.98–2.74)		1.38 (0.81-1.95)
Silicosis					
	No	1493	1 (0)		
	Yes	1079	2.44 (1.28-3.60)	**2.30 (1.56-3.08)**	
Fever					
	No	2144			
	Yes	18	4.34 (2.15-10.83)		4.34 (0.11-8.79)

Factors associated with hypoxaemia (SpO2 <95%)

Table 6 presents variables associated with hypoxaemia. Of note, older ex-gold miners had elevated odds of hypoxaemia (OR: 2.89, 95% CI: 1.17-4.61), as did those with an abnormal BMI (either overweight/obese, OR: 1.30, 95% CI: 0.99–1.61; or underweight, OR: 1.49, 95% CI: 1.08-1.90). .

Other variables associated with elevated odds of hypoxaemia were a history of past TB (OR: 1.48, 95% CI: 1.17-1.79), silicosis (OR: 2.41, 95% CI: 1.92-2.90), shortness of breath (OR: 1.55, 95% CI: 1.20-1.90), and lung obstruction measured by FEV1 (moderate obstruction with OR: 2.17, 95% CI: 1.56-2.78; severe obstruction with OR 4.30, 95% CI: 2.77-5.83). . However, HIV positive status had a had an inverse association with hypoxaemia (OR: 0.84, 95% CI: 0.63-1.03).

Table 6. Factors associated with hypoxaemia (SpO2 < 95%): Unadjusted and adjusted models (N=2360).

Independent variable	Independent variable category	n=642	Unadjusted Odd Ratio (standard error)	Adjusted Odd ratio (standard error) Risk Factor/	Adjusted Odd ratio(standard error)
Age					
	28-49 years	141	1 (0)	1 (0)	
	50 years plus	2371	2.10 (0.74-4.94)	**2.89 (1.17-4.61)**	
Level of exposure					
	Low	701	1 (0)	1 (0)	
	High	1866	1.53 (0.82-2.24)	1.17 (0.92-1.43)	
BMI					
	Normal BMI	1500	1 (0)	1 (0)	
	Underweight	296	1.15 (0.60-1.70)	**1.49 (1.08-1.90)**	
	Overweight and obesity	626	2.10 (1.02-3.18)	**1.30 (0.99-1.61)**	
HIV Status					
	Negative	1781	1 (0)	1 (0)	
	Positive	776	0.60 (0.33-0.87)	0.84 (0.63-1.03)	
Active TB					

	No	2496	1 (0)		
	Yes	181	**1.70 (1.13-2.27)**		1.49 (0.86-2.12)
Past TB treatment					
	No	1163	1 (0)	1 (0)	
	Yes	1400	2.72 (1.52-3.92)	**1.48 (1.17-1.79)**	
History of smoking					
	Never smoked	697	1 (0)	1 (0)	
	Ever smoker	1847	1.95 (0.75-3.15)	1.15 (0.90-1.40)	
Shortness of breath					
	No	1791	1 (0)		
	Yes	767	4.16 (2.51-5.81)		**1.55 (1.20-1.90)**
FEV1					
	>= 80%	1379	1 (0)		
	61% - 79%	405	7.48 (2.03-12.93)		**2.17 (1.56-2.78)**
	<= 60%	316	21.42 (7.01-35.83)		**4.30 (2.77-5.83)**
FVC					
	>= 80%	1709	1 (0)		
	61% - 79%	299	4.42 (2.15-6.69)		1.15 (0.78-1.52)
	<= 60%	92	10.61 (3.81-17.41)		1.66 (0.78-2.54)
Silicosis					
	No	1493	1 (0)	1 (0)	
	Yes	1079	1.85 (1.14-2.56)	**2.41 (1.92-2.90)**	

DISCUSSION

Factors associated with silicosis

There were a number of expected associations found, notably years of exposure, dustiness of job and and lung function impairment, with a mixed pattern - obstruction and restriction. There are many risk factors for lung function impairment in this population: general dust effects, including chronic bronchitis, post TB lung impairment with severe fibrosis obstruction of large airways [Ross at al., 2010; Fan et al., 2021], a high rate of positive past TB history in this cohort, and the high recurrence rate of TB [Maboso et al., 2020]. Of note is that there was an association with breathlessness but not with cough.

With regard to the HIV finding, we know that the number of B lymphocyte cells increases with HIV disease progression [Rodrigueza set al., 2003]. Over expansion of B lymphocytes is associated with an expansion of interleukin (IL)-9 [Arras et al. 2001]. Furthermore, evidence exists that IL-9 controls lung fibrosis induced by silica particles [Arras et al., 2001]. Therefore, this pathway linking HIV disease progression to an antifibrotic effect may explain the association of HIV positive status with the “protective” effect against silicosis that was found. To my knowledge, this is the first published finding that is consistent with Arras’ experiment. However, selection bias could influence this association as the combined silicosis and HIV could result in strong early mortality. This could weaken any association, although admittedly not reverse it [Bloch et al., 2018].

Factors associated with active TB

Silicosis and HIV-positive status showed significant associations with active TB, despite the small number of active TB cases. These associations are well known [Ehrlich et al., 2021]. Although the mechanism by which silica dust increases the risk of TB is not completely clear, studies have established that chronic and immunomodulatory character of silica increase susceptibility to TB [Konecny et al., 2019]. The high prevalences of silicosis and HIV, and their combined action in this population [Maboso et al., 2020], and the fact that these ex-gold miners live in high TB burden communities [WHO, 2021], make TB a permanent threat. This requires a qui vive attitude and regular TB screening, which adds substantial burden to government responsibilities

Some of our results are surprising, such as the inverse association between past TB treatment and risk of active TB. Although the true reason for this remains uncertain, it may be because of survivorship bias. ,

Factors associated with hypoxaemia (SpO2 < 95%)

After adjustment, age, BMI, silicosis, a history of past TB, shortness of breath, lung obstruction (FEV1) remained positively associated with hypoxaemia. HIV status was negatively associated.

TB- and/or silica-induced lung damage (e.g. fibrosis) may impair gas exchange in the lungs and cause low oxygen saturation. Furthermore, human TB lesions are hypoxic, and hypoxia up-regulates matrix metalloproteinase (MMP)-mediated tissue inflammation [Belton et al. 2016]. MMPs are enzymes responsible for tissue destruction in different lung diseases including TB [Elkington and Friedland, 2006].

In addition, even if successfully treated, TB often leaves lung damage [Roy et al., 2010, Zubair et al., 2021]. Consequently, the association between hypoxaemia and a history of past TB as found in this study (SpO2 <95%, OR: 1.48 (1.17-1.79), may be bidirectional in that hypoxaemia and the corresponding lung hypoxia may be the cause and the consequence of TB-induced lung damage.

The strong association between the history of past TB, lung obstruction (e.g., FEV1) and hypoxaemia in one hand, and the modest association between silicosis and hypoxaemia on the other, add to the evidence that co-occurrence of these conditions results in a substantial combined impairment compared to that of silicosis alone, , with associated increased morbidity [Bloch et al., 2018; Ehrlich, 2010].

In contrast, HIV positive ex-gold miners were less likely to have a low oxygen saturation. This may be explained by the earlier evoked theory of IL-9 and B-lymphocytes expansion on lung-fibrosis control [Arras et al., 2001; Arras et al., 2006], resulting in relatively less fibrosis and therefore less hypoxaemia in HIV positive individuals..

CONCLUSION

The findings from this study demonstrate that indicators of dust exposure (i.e., silicosis, level of exposure) from mining work are predictors of disease, which is, in turn is associated, with markers of morbidity of ex-gold miners years after they leave the mines.

It is known that even if treated TB often leaves permanent lung lesions [Roy et al., 2010,;Zubair et al., 2021]. The finding of a high odds of silicosis and of a history of past TB among ex-gold miners who have hypoxaemia implies that these entities may be mutually sustaining in a vicious cycle (e.g., lung lesion-hypoxaemia-lung lesion).

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CHAPTER 7: THESIS DISCUSSION

Introduction

To contribute to efforts aimed at reducing morbidity and mortality among mineworkers from the South African gold mining, we designed three studies that included Basotho ex-gold miners who visited a TIMS (TB in the Mining Sector in Southern Africa) [TIMS, 2019] - Mafeteng Occupational Health Service Centre (OHSC) in Lesotho from January 2017 to November 2018. ,The objectives were to (1) present a case series illustrating the diagnostic and health service problems of distinguishing TB and silicosis clinically and radiologically; (2) assess the predictive value of the symptoms of fever and cough and the plain chest radiograph (CXR) in the diagnosis of active TB disease among ex-gold miners; and (3) examine factors associated with silicosis, active TB, and hypoxaemia in ex-gold miners to better understand occupational aetiology, the effects of comorbidity, determinants of severity, and health care implications.

The first study found that ex-gold miners from the South African mines present with complex lung diseases with poor agreement between radiological findings and clinical presentation, poor agreement between radiographs suggestive of TB and Xpert MTB/RIF sputum results, and overlap of clinical and radiological presentation of silicosis and TB.

The second study demonstrated that chronic symptoms and abnormal CXR findings are not reliable predictors of active TB in the population of ex-gold miners from South African industry. An abnormal plain CXR on screening, in this population, will identify almost all those with active TB, and a CXR negative for TB remains a valuable tool in ruling out active TB disease. However, most ex-miners with CXRs “suggestive of TB” will not have active TB. Symptoms on their own only identify about half of the active cases.

The third study showed that indicators of dust exposure from the mining are detectable predictors of disease, which, in turn are associated with markers of morbidity of ex-gold miners many years after they leave the mines. Silicosis, TB and hypoxaemia are mutually affecting in a vicious cycle (e.g., lung lesion – hypoxaemia - lung lesion). Of particular interest was that HIV infected ex-gold miners had lower odds of silicosis and hypoxaemia.

Relationship to other literature

The burden of silicosis and TB among ex-miners from South African industry has been reported to be very high [Trapido et al., 1998; Steen et al., 1997; Meel, 2002; Girdler-

brown et al., 2008; Maboso et al., 2020; Q(h)ubeka Trust, 2021]. Sophisticated means of diagnosis such as CT, that could help distinguish old healed TB from acute active TB and from silicosis in other settings [Liu et al., 2019], are not available to these ex-miners. As shown in our study the difficulty in distinguishing these conditions, especially in sub-Saharan Africa, has not changed [Taylor et al., 1938; Lee, 1948; Solomon and Rees, 2010; Franzblau et al., 2018]. The limited accessibility and high cost of CT scanning make the use of this tool impractical in the context of this ex-gold miner population. Respiratory medicine specialist care is equally inaccessible.

CXR is a cost effective tool in the screening for pulmonary TB in the general population [WHO, 2016; Mor et al., 2012; de Boon et al., 2006; van Clef et al., 2005]. Our study partially corroborates this with the finding of a CXR ("suggestive of TB") sensitivity that is similar to that reported in the general population (80 – 97%), i.e. non-occupational with no silicosis and a lower burden of past TB. [Mor et al. ,2012; de Boon et al., 2006; van Cleeff et al., 2005]. However, we found a CXR specificity (0.41) significantly lower than that in the general population, with only 5% of CXRs read as suggestive of TB having active TB disease confirmed bacteriologically. The high burden of confounding conditions such as silicosis and post TB lung lesions that characterise this population [Maboso et al., 2020; Q(h)ubeka trust, 2021] explains this low specificity, resulting in difficulty in distinguishing silicosis from TB, and active from inactive TB, on radiological grounds [Franzblau 2018, et al, Taylor and Alexander, 1938; Lee, 1948; Roy and Ellis, 2010; Solomon and Rees, 2010].

The low sensitivity and specificity of symptom screening in this population are similar to that in the general population [den Boon et al., 2006; van Cleeff et al., 2005; Mor et al., 2012]. A higher prevalence of non-TB related cough should be expected in this population of ex-gold miners, due to dust bronchitis, silica-induced chronic alveolitis, post TB fibrosis or emphysema [Barnes et al., 2019;].

The third study demonstrates that indicators and consequences of dust exposure from the mining remain strongly associated with morbidity of ex-gold miners many years after they leave the mines. These findings corroborate what has been reported previously on ex-miners in the region [Trapido et al., 1998; Girdler-Brown et al., 2008; Steen et al., 1997 Q(h)ubeka Trust, 2021].

The finding that HIV infection has a inverse association with radiological silicosis and hypoxaemia is novel and requires further studies for confirmation. There is biological plausibility, discussed earlier [Arras et al., 2001; Arras et al., 2006], but selection (cross-sectional) bias due to high mortality in those with combined disease could be an alternative explanation. Given the old age of ex-gold miners included in this study (i.e., median age 62 years) [Maboso et al., 2020], and given a higher likelihood of contracting HIV infection among younger individuals, and among miners compared to the general population [Rees et al., 2010], it is possible that many of these HIV-positive ex-gold miners had advanced HIV disease (i.e., infected while younger and or while still in the mines). Since Lesotho has good antiretreoviral coverage, this depends on long-term medication compliance. Immunosuppression could be associated with over expansion of B-lymphocyte stimulators with an over expression of IL-9 which reduces silica-induced lung fibrosis [Arras et al., 2001; Arras et al., 2006; Rodriguez et al., 2003].. Therefore, further studies to illuminate the negative association between silicosis and HIV infection are needed.

Implications for the Lesotho health system

We have estimated that the kingdom of Lesotho, as a small country of about 2.2 million inhabitants [World Bank, 2022], has of the order of 95 000 living ex-gold miners from the South African mines [Maboso et al., 2020]. We previously found that nearly half of such ex-gold miners attending invited examinations (42.5%) had silicosis, over half (53.4%) had been treated at least once for pulmonary TB in the past, 60% sample had CXR change suggestive of TB. A substantial proportion were HIV-infected (31%) [Maboso et al., 2020].

These findings highlight the burden of disease and the challenge that gold mining has imposed on the health system of this country, especially, as the lesions observed in the lungs of ex-gold miners are permanent and progressive in most, if not in all [Ehrlich 2012, Nandi et al., 2021]. Furthermore, as long as these ex-miners continue living in high TB burden communities [WHO, 2021], given their impaired lung defences due to silicosis and silica loading [Konecny et al., 2019; Pasula et al., 2009] and the high prevalence of latent TB infection (89%) [Hanifa et al., 2009] new TB infection, reactivation, and recurrence will remain a lifelong population burden.

Figure 7. Healthcare workers on an outreach visit.

A mountainous country with a land area of 30 355 Km^2 [World Bank, 2022], the Kingdom of Lesotho has no easy access to health services. Its government health system counts only 18 health facilities that offer radiological and/or bacteriological diagnosis of TB (i.e. conventional radiography, Xpert MTB/RIF and conventional smear TB test on sputum), and only one laboratory that processes TB cultures. Furthermore, as stated earlier, Lesotho has the world's highest incidence of TB and is one of the countries with the highest HIV prevalence [WHO, 2021]. An important contributor is the significant proportion of its population who are ex-gold miners with a high burden of occupational lung disease and HIV [Maboso and Ehrlich, 2020; Maboso et al., 2020]. The poor specificity of CXR in the diagnosis of active TB among ex-gold miners from the current study has an important implication for the End-TB strategy (i.e., TB screening, diagnosis and treatment) in Lesotho country. The fact that more than half of these ex-gold miners will present with a CXR suggestive of TB, i.e., due to silicosis, silicotuberculosis, and/or old healed TB lesion implies that most abnormal lung findings on screening will not signify active TB. MTB/RIF Xpert should thus be universally available, with a protocol for use of empirical therapy in ex-goldminers.

Strengths and limitations

The ILO guidelines for classification of pneumoconioses recommend that CXRs reading for pneumoconioses, in the case of epidemiological studies, is done by at least two readers [ILO, 2011]. A limitation is that CXRs reading used for the analysis in chapters 5 and 6, were done by only one medical practitioner. However, this reader received ILO training on reading CXRs for pneumoconioses, from the NIOH and MBOD in South Africa. Furthermore, a random sample of 300 CXRs were independently read by two occupational medicine specialists with extensive experience in reading CXRs for pneumoconioses. These readers reported an 80-90% agreement with the clinic reading.

The TIMS Mafeteng-OHSC serviced ex-gold miners, mostly coming from only half of Lesotho (i.e. from 5 out of 10 districts). Consequently, some ex-gold miners had to travel for up to 24 hours to reach the OHSC. Hence, factors including sickness, lack of transport or lack of accommodation (e.g., where to spend night near the OHSC). Many with advanced disease would have died without visiting the OHSC, limiting the representativeness of the OHSC sample accordingly.

The fact that our data included exposure history, symptoms and past medical history review, physical examination, radiological and bacteriological assessment for all participants (e.g., we obtained sputum Xpert MTB/RIF test from all ex-gold miners included in this study) is a major strength as it increased the potential to catch even asymptomatic active TB infection cases. However, less than 30% reported cough, and although we used a sputum induction technique to obtain sputum for those who could not spontaneously produce it, the quality of sputum might have been suboptimal. However, the ability of Xpert MTB/RIF test to provide TB diagnosis is much less dependent on sputum quality than smear [Mulengwa et al., 2022].

To our current knowledge, this is the first research of our era to study the value of the CXR in the screening for pulmonary TB and consider the challenge of distinguishing TB and silicosis, in a large sample of ex-gold miners from different gold mining companies, with a long mining service history in high dust jobs, analysed relatively long after exposure to dust ceased. The availability of HIV status information for almost all subjects enabled analysis of the association between HIV and silicosis in a large sample.

Conclusions and recommendations

These studies demonstrate that exposure to silica-dust continues to cause morbidity in ex-gold miners years after exposure ceased, imposing a health cost on poor ex-miners and the health system of the country. In addition, the findings of high odds of silicosis, history of past TB or active TB disease with hypoxaemia imply that these entities are mutually sustaining in a vicious cycle. These findings underscore the permanency of the damage caused by silica exposure and other mining related factors conducive to TB.

These effects are also likely progressive, requiring increased medical attention long after they leave the mines, and for some after the compensation funds received have been exhausted. These considerations highlight the fact that compensation, whether through the normal regulatory channel (i.e., The Compensation Commissioner for Occupational Diseases (CCOD)) or the settlement fund (i.e., Tshiamiso Trust), is not a long-term solution to the crisis of occupational lung disease in ex-miners from the South African mines.

Lump sum monetary compensation, has never been enough to provide for the silica-created health needs of low wage migrant workers, [Ehrlich 2012]. After payment, the system shifts the responsibility to ex-gold miners to deal with their silica-induced medical problems on their own. This is especially so for ex-gold miners living beyond South Africa's borders, such as those in Lesotho. An example highlighted in this study is the inability to afford long-term oxygen therapy when needed. To address this tragedy, legislation needs to provide for not only proper long-term medical surveillance but also medical care and support for these populations.

With regard to essential occupational and medical history, investment in systematic digital record keeping of CXRs, TB tests and treatment of miners, including while in service, is needed. This should be a collaborative arrangement between the mining industry, the South African government and compensation agencies or Trusts. An example in the compensation arena is the Compensation Claims Management System (CCMS) (www.recordables.com/workers-comp-claims-management-software/). The database should be extended to cover all ex-miners in South Africa and neighbouring countries and a system of digital access developed for local healthcare providers attending to these miners.

In order to avoid the burden of unnecessary TB treatment on ex-gold miners and the government, clinicians and policy makers need to consider the limitation of predictive values of symptoms and the CXR in identifying active TB among ex-gold miners. . Training of healthcare providers in the labour sending areas on mining lung disease including but not limited to silicosis, tuberculosis, silicotuberculosis, lung function deficit and related complications, is recommended; given the high prevalence of lung lesions among this population [Maboso et al., 2020]. Although mortality was not studied directly in this research, it is likely that HIV, progression of chronic disease, the vicious cycle of TB -hypoxaemia-TB, and a relatively high rate of hypoxaemia, all contribute to a high mortality rate among ex-miners [Bloch et al., 2018].

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ANNEXURES

Authorisation to use the data from Wits Health Consortium

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TIMS

TB in the Mining Sector in Southern Africa

01 October 2018

TO WHOM IT MAY CONCERN

Dear Sir/Madam

Re: Application by Dr Maboso for study clearance

This letter to confirm that Dr Maboso is currently employed as an Occupational Medicine Practitioner at our clinic in Lesotho. The aforementioned clinic is part of the TB In Mines In Southern Africa programme aimed at actively finding TB cases in mining key populations in Lesotho. This is part of a 10 country programme funded by the Global Fund against TB, HIV and Malaria.

Dr Maboso is currently studying for his Masters in Occupational Medicine and a component of this is a research study. Dr Maboso has elected to orientate his study towards assessing the burden of silicosis in Lesotho. This topic is chosen as Lesotho is a high burden TB country. The added burden of silicosis increases the risk of contracting TB and is an important factor in addressing the TB epidemic.

The objective of the study is to ascertain the burden of silicosis among ex-mineworkers in Lesotho; to ascertain the impact of the association silica exposure, silicosis and HIV on the burden of tuberculosis in Basotho ex-mineworkers in Lesotho and to determine the clinical profile of patient with silicosis and/or tuberculosis.

The methodology used will constitute a cross sectional survey of Basotho mineworkers who worked in South Africa will be employed. The sample shall include all miners attending the Mafeteng - Occupational Health Service Centre where Dr Maboso is stationed.

Wits Health Consortium is happy to support Dr Maboso's application for study clearance and looks forward to the study results.

Sincerely

Dr R Pillay

PROGRAMME MANAGER

TIMS

Clearance from the National Health Research Committee - Lesotho

LESOTHO

Ministry of Health
P.O. Box 514
Maseru 100

REF: ID142-2018 Renew 03
Date: 26th November 2021
To
Botembetume Maboso
WITS Health Programme
Occupational Health
Mafeteng Hospital

Category of Review:
[ ] Initial Review
[x] Continuing Annual Review
[ ] Amendment/Modification
[ ] Reactivation
[ ] Serious Adverse Event
[ ] Other _____

Dear Dr. Maboso,

RE: Assessing the Burden of Silicosis, Tuberculosis and HIV among Basotho Ex-mine workers

This is to inform you that the Ministry of Health Research and Ethics Committee reviewed and **APPROVED** the above named protocol for renewal and hereby authorizes you to continue the study according to the activities and population specified in the protocol. Departure from the approved protocol will constitute a breach of this permission.

This approval includes review of the following attachments:
[ ] Protocol
[ ] English consent forms
[ ] Sesotho consent forms
[ ] Data collection forms- English and Sesotho version
[ ] Participant materials
[x] **Other materials**: Letter of renewal request dated 21st November 2021 and Abstract Occup Environ Med: on 22nd October 2021

This approval is **VALID** until December 23, 2022

All serious adverse events associated with this study must be reported promptly to the MOH Research and Ethics Committee. Any modifications to the approved protocol or consent forms must be submitted to the committee prior to implementation of any changes.

We look forward to receiving your progress reports and a final report at the end of the study. If you have any questions, please contact the Research and Ethics Committee at rcumoh@gmail.com (or) 59037919/58800246.

Sincerely,

DR. 'NYANE LETSIE
Director General Health Services

DR. LLANG BRIDGET MAAMA-MAIME
Member, National Health Research Ethics Committee (NH-REC)

Clearance letter from Human Research Ethics Committee - University of Cape Town

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E50- Old Main Building
Groote Schuur Hospital
Observatory 7925
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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

30 November 2020

HREC REF: 699/2020

Prof R Ehrlich
School of Public Health & Family Medicine
Falmouth Building-FHS
Email: - Rodney.Ehrlich@uct.ac.za
Student: botembetume@gmail.com

Dear Prof Ehrlich

PROJECT TITLE: ILLUMINATING A NEGLECTED POPULATION: EPIDEMIOLOGIC AND CLINICAL FEATURES OF SILICOSIS AND TUBERCULOSIS AMONG FORMER GOLD MINERS FROM LESOTHO (MPHIL DEGREE - DR BOTEMBETUME MABOSO)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 November 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Dr Botembetume Maboso will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.