AMERICAN UNIVERSITY OF BEIRUT

SILICO-TUBERCULOSIS AMONG MINERS: A SCOPING REVIEW

by
ELIZABETH KOKA MUKONYO

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by
ELIZABETH KOKA MUKONYO

Approved by:

Dr. Rima Habib, Professor & Chairperson
Environmental Health Department
Advisor

Dr. Umayya Musharrafieh, Professor
Family Medicine Department
Member of Committee

Dr. Hassan Dhaini, Professor Assistant
Environmental Health Department
Member of Committee

Dr. Mey Jurdi, Professor
Environmental Health Department
Member of Committee

Date of thesis defense: May 04, 2021

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Date

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ABSTRACT
OF THE THESIS OF

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Title: Silico-Tuberculosis among Miners: A Scoping Review

Background: Silicotuberculosis is both a Public Health and Occupational Health problem within the twenty-first century. Although diagnostic procedures used to screen for tuberculosis have evolved over the years, the Sputum Test remains the GOLD Standard, particularly in resource-limited settings. Studies have identified several risk factors associated with silicotuberculosis outcomes. However, the associated risk factors, mechanism of action related to silica dust exposure, and infection or activation of tuberculosis with host iron status remain unanswered, especially in the mine settings.

Objectives: This scoping review aims to map out the risk factors associated with silicotuberculosis and identify diagnostic techniques used in the screening of silicotuberculosis.

Methods: A systematic search to identify the available international evidence was conducted in the following databases: Medline, Cochrane Library, Embase, Cinahl, Georef, and grey literature sources. The search was limited to articles published in the English language and between 2000 to 2020. The reference lists of included articles were also searched for relevant articles. We included all primary studies conducted on miners exposed to silica dust. Diagnostic techniques to screen silicosis and tuberculosis were included with silicotuberculosis as the outcome. The abstracts and full articles were screened independently and in duplicates by two reviewers. One reviewer conducted the data entry. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses: Extension for Scoping Reviews (PRISMA-ScR) was adopted as a guide to present the study results.

Results: Twenty-eight articles met our inclusion criteria. Seventeen studies were from Southern Africa, and four studies from China. The study population consisted mainly of miners. Risk factors associated with tuberculosis outcomes reported by the reviewed studies included demographic factors (> 50 years of age, migrants from neighboring/foreign country, and race), lifestyle behavior (smoking, daily alcohol intake, and opium addiction), clinical factors (history of tuberculosis (TB) in the last five years, previous TB retreatment, site of diagnosed TB, positive QFT, silicosis characteristics, HIV CD4 counts, and respiratory symptoms) and occupational health and safety factors (cumulative respirable quartz, continuity of silica dust exposure, and

exposure duration). A few studies used the occupational history and differential diagnostics to diagnose for silicotuberculosis. A few studies reported on NIOSH B readers in their methods of assessment. Several studies assessed silicotuberculosis outcome by the grading of silicotic nodules and a positive smear/culture result. A few studies highlighted latent tuberculosis, lung function loss and presence of *mycobacterium tuberculosis resistant strains* among miners.

Conclusion: This scoping review highlights substantial gaps in the reviewed literature. It outlines a series of recommendations urgently needed to inform research and practice. Capacity building in developing countries is needed to prioritize training to certify physicians and invest in diagnostic tools that screen for latent tuberculosis. The findings highlight an urgent need for legal frameworks in low- and middle-income countries to establish adequate workers' protection measures in small-scale mines. This scoping review identified a dearth of literature to explore risk factors that aggravate the consequences of silica dust exposure. Given the substantial deficit in studies assessing sex/gender differences within mine settings, there is an urgent research imperative for future studies to incorporate sex/gender analysis in investigating silico-tuberculosis among miners.

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ABBREVIATIONS

AIDS: Acquired Immune Deficiency Syndrome

ASGM: Artisanal and Small-Scale Gold Mining

BCG: Bacille Calmette Guerin

CFU: Colony Forming Units

CD4: Cluster of Differentiation 4

DOT: Direct Observed Therapy

EPTB: Extrapulmonary Tuberculosis

HIV: Human Immunodeficiency Virus

H37Rv: Standard Virulent Strain of *Mycobacterium tuberculosis*

IGRAs: Interferon-Gamma Release Assays

IFN γ: Interferon-gamma

INOS: Inducible nitric oxide synthase

LTBI: Latent tuberculosis infection

NIOSH: National Institute for Occupational Safety and Health

NKs: Natural Killer Cells

NRAMP1: Natural resistance macrophage protein 1

NTM: Nontuberculous *mycobacterium tuberculosis*

OSHA: Occupational Safety and Health Administration

OELs: Occupational Exposure Limits

PPE: Personal Protective Equipment

PEL: Permissible Exposure Limits

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PCC: Population Concept Context

PTB: Pulmonary Tuberculosis

PMF: Progressive Massive Fibrosis

QFT: QuantiFERON-TB Gold

REL: Recommended Exposure Limit

RTI: Respiratory Tract Infections

SiO_2: Silicon Dioxide

SPSS: Statistical Package for the Social Sciences

SCOEL: European Scientific Committee for Occupational Exposure Limits

TB: Tuberculosis

TST: tuberculin Skin Test

USA: United States of America

WHO: World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Silico-tuberculosis

1.1.1. Definition and problem statement

Silico-tuberculosis has become a critical public health concern in the twenty-first century because silicosis leads to tuberculosis infection and the spread of infection within the mines and communal environments (World Health Organization, 2016). Silicosis is an occupational disease that scars the lung tissues due to the inhalation of silica dust particulate matter (National Institute for Occupational Safety and Health, 2011). Tuberculosis is a communicable disease that mainly affects the lung and is caused by *Mycobacterium tuberculosis* (World Health Organization, 2019). The risk of developing tuberculosis among workers exposed to silica dust is 2.8 to 39-times higher than the general population. (Barboza, 2008; Cowie, 1994; teWaternaude et al., 2006). Silica particles in the lung may facilitate the initiation of tuberculous infection and progression to active tuberculosis (Konečny P, 2019). A person could acquire both silicosis and tuberculosis, and this is referred to as silico-tuberculosis. The disease often affects mine workers exposed to silica dust from the mining of coal, gold, copper, soapstone, and sand (Utembe, Faustman, Matatiele, & Gulumian, 2015).

The diagnosis of tuberculosis in silicotic patients can be difficult for two reasons: (1) because the clinical manifestations can be benign, or (2) the radiological alterations between tuberculotic and silicotic nodules can be indistinguishable due to silicosis (Konečny P, 2019; World Health Organization, 2016). Patients are often misdiagnosed, leading to multiple complications like respiratory failure and cor pulmonale

(Milovanović A, 2011; Sureka, Mittal, Mittal, & Thukral, 2013). Moreover, silico-tuberculosis is often misdiagnosed when physicians lack adequate knowledge on diagnostic techniques (Sureka, Mittal, Mittal, & Thukral, 2013).

Additionally, silicotuberculosis is also an occupational health concern as previous strategies to prevent tuberculosis among miners were ineffective (Konečny P, 2019). The tuberculosis prevention programs among miners included vaccination of workers with silicosis using mass treatment trials of gold miners with latent tuberculosis (LTBI), which is the dormant form of tuberculosis infection (Konečny P, 2019; Churchyard et al., 2014). Although BCG remains the only licensed vaccine for tuberculosis, there is a recognized risk of use in immune-compromised populations (Mendez-Samperio, 2019). Moreover, certain population groups like children, immuno-compromised workers, and older adults in the mining sector are among the most vulnerable groups affected by this disease entity (International Commission on Occupational Health, 2018).

40.5 million miners are situated in over 80 countries, especially within small-scale mines (Intergovernmental Forum on Mining, Minerals, Metals, and Sustainable Development, 2018). Most of the mining industry workforce consists of migrant workers (Fernández Álvarez et al., 2015; Ringshausen, 2013). Mine workers suffering from silicosis have a higher risk of contracting tuberculosis (TB) either in the mines because of unsafe underground working conditions or circular migration back and forth to their countries (Rees, Murray, Nelson, & Sonnenberg, 2010). Hence, silicotuberculosis presents a global challenge.

1.1.2 Disease burden

In the 2019 Global Tuberculosis Report, the WHO estimated a burden of 10 million tuberculosis cases worldwide. A study conducted in 195 countries found an increased prevalence rate of silicosis from 380 to 464 cases in the year per thousand of populations (Vos, 2017). However, despite the increasing rates of tuberculosis and silicosis globally, the global prevalence of silico-tuberculosis has not been estimated (Fernández Álvarez et al., 2015).

Nevertheless, the prevalence rates of silico-tuberculosis have been estimated at the country level. In developed countries like Germany, the silicotuberculosis incidence among coal workers was estimated at 33.9 cases per 100,000 (Ringshausen et al., 2013). In addition, the prevalence of silico-tuberculosis rates has also been assessed in some developing countries. A study conducted in Zambia in 2002 showed that 16 workers reported suffering from silico-tuberculosis among 2,114 surveyed workers (Mulenga, Miller, Sinkala, Hysong, & Burgess, 2005).

1.1.3 Risk factors

Risk factors associated with silico-tuberculosis outcomes vary from high-income to low-income countries. Studies found that older age, insurance status, type of mine settings, exposure duration to silica dust, and pulmonary disease were associated with silico-tuberculosis among miners in developed countries (Melo, 2016; Ringshausen et al., 2013). Meanwhile, in developing countries, the following risk factors were found to be associated with silico-tuberculosis: the high burden of Human immunodeficiency virus (HIV), unsafe working environments, age, oscillatory migration, smoking, in

addition to working in gold and copper mine settings (Rees, Murray, Nelson, & Sonnenberg, 2010; Utembe, Faustman, Matatiele, & Gulumian, 2015).

HIV is a risk factor for silicotuberculosis outcomes in low-income countries (Rees, Murray, Nelson, & Sonnenberg, 2010; Utembe, Faustman, Matatiele, & Gulumian, 2015). HIV infection suppresses the immune system, enhancing the risk of tuberculosis infection (Ahmed, Rakshit, & Vyakarnam, 2016). In addition, the deficiency or excess of iron in the body (referred to as iron status) influences the overall HIV viral increase (Haider et al., 2019; Abioye, Andersen, Sudfeld, & Fawzi, 2020). The excess of iron can also be due to HIV treatment and supplementation (Abioye, Andersen, Sudfeld, & Fawzi, 2020; Joann & Andrew, 2006). Consequently, the viral increase is dependent on the iron status of individuals and increases susceptibility to tuberculosis infection (Ghio, 2009; Joann & Andrew, 2006). Hence, the role of HIV in silicotuberculosis outcomes among miners.

Labor migration, the movement from rural areas within the same country or moving from a host country to neighboring countries to work in mines, is shown to increase silicotuberculosis outcome and, specifically within low-income countries (Rees, Murray, Nelson, & Sonnenberg, 2010). High-income countries face similar risks regarding migration status and silicotuberculosis outcomes (Demircigil et al., 2010; Ringshausen et al., 2013).

Globally, age, particularly older age, is a well-established risk factor for tuberculosis outcomes among silicotic miners (Melo, 2016; Ringshausen et al., 2013). Therefore, older age is a determining risk factor due to the time required to develop silicosis (Hnizdo, 1998; Melo, 2016). Additionally, older populations are considered a vulnerable group as they are at a higher risk of progressing from latent tuberculosis to

active tuberculosis disease (Salgame et al., 2015). However, only 5-10% of persons with latent tuberculosis infection will develop tuberculosis later in life (Center for Disease Control and Prevention, 2016).

Miners are at a greater risk of developing active tuberculosis due to silica dust exposure and other risk factors arising from mine settings and their work environment. Moreover, one million children work in small-scale mines (International Labor Organization, 2005; International Commission on Occupational Health, 2018). Children are particularly vulnerable to contracting respiratory tract infections (RTI) due to their iron status (Wander, Shell-Duncan, & Brindle, 2017). Also, acquiring RTI like tuberculosis among children is particularly dangerous as it may lead to meningitis, which in many cases could be fatal (Piccini, Chiappini, Tortoli, de Martino, & Galli, 2014).

Furthermore, the mine-setting and working environment can increase the risk of silicotuberculosis outcomes (Mulenga, Miller, Sinkala, Hysong, & Burgess, 2005). Globally, it is estimated that 40.5 million miners in over 80 countries work in artisanal and small-scale mines (Intergovernmental Forum on Mining, Minerals, Metals and Sustainable Development, 2018). The mine workers in artisanal and small-scale mines are at significant risk compared to large-scale mines due to the informal and unregulated sector (International Commission on Occupational Health, 2018). Additionally, the working environment of miners in most low-income countries is particularly unsafe due to lack of proper protection against silica exposure and lack of national regulations (Gottesfeld, 2015; Gottesfeld, Tirima, Anka, Fotso, & Nota, 2019; Maciejewska, 2008).

1.1.4 Diagnostic techniques

Although silicotic fibrosis among patients may prevent discharge of tubercle bacilli into the sputum, the Sputum Smear Microscopy test remains the GOLD Standard method for the diagnosis of tuberculosis, especially in resource-limited settings (World Health Organization, 2016; Achkar, Lawn, Moosa, Wright, & Kasprowicz, 2011). However, different diagnostic techniques are being used to diagnose tuberculosis in silicosis patients, including combined TB diagnostic and radiographic tests (Sureka, Mittal, Mittal, & Thukral, 2013). Other traditional methods used to screen for silicosis among workers include medical history, standard chest X-ray, and spirometry (National Institute of Occupational Safety and Health, 2014).

Over time, the use of Interferon-gamma release assays (IGRAs) has paved the way for diagnosing latent tuberculosis (Esmail et al., 2014; Salgame et al., 2015). However, studies have also revealed that latent tuberculosis detection using current immune assay technologies is limited as per Achkar, Lawn, Moosa, Wright, & Kasprowicz (2011) among immuno-compromised people like those living with HIV.

The diagnosis of tuberculosis among children is commonly conducted using TST and IGRAs because children have difficulty producing sputum (Piccini, Chiappini, Tortoli, de Martino, & Galli, 2014). However, there still lacks a GOLD Standard to diagnose latent tuberculosis infection among high-risk populations (Salgame et al., 2015).

1.2 Mechanistic of action

1.2.1 Mechanisms of cellular toxicity

Crystalline silica dust has specific properties that influence its absorption mechanism and toxicity pathways (Schapira, 1995; Castranova, 2000). Crystalline silica, specifically quartz, is a particulate matter of 3.87 ± 0.04 μm and contains silanol groups on its surface with an acidic PK_A (Schapira, 1995; Ghio, 1990). Hence, the physicochemical characteristic of crystalline silica determines its absorption within the respiratory system (Castranova, 2000).

Quartz uptake in the lungs and cytotoxicity is influenced by particle size, PH, and trace metals (IARC, 1997). Additionally, compared to aging quartz, freshly extracted quartz exhibit increased cytotoxicity during the absorption process by alveolar macrophages within the respiratory system (Vallyathan, 1988: as cited in IARC, 1997).

The pathways in which silica-dust induces lung inflammation, such as Fenton-like reaction, free radical oxygen species generation pathway, and genotoxicity mechanisms, are still being studied (Balmes 1990; Schapira, 1995; Churg, 1996; Mossman & Churg, 1998; Costantini, 2011; Chitra Thakur, 2015; Borm 2018).

1.2.1.1 Fenton-reaction and Reactive oxygen species mechanisms

Once absorbed, fractured silica dust particles generate radicals that are particle-related reactive oxygen species (Fubini & Hubbard, 2003; Mossman & Churg, 1998). However, other experimental model-based studies reported similar mechanisms in chemically inert and aged silica particles whereby, adsorption of hydroxyl radicals on aged quartz surface resulted in the generation of reactive surface radical (Robert Konecny, 2001; R. Konecny, Leonard, Shi, Robinson, & Castranova, 2001). According to Castranova (2000), there is a theoretical mechanism of silica-lung-induced toxicity

pathway involving silanol groups (Si-OH) from fractured silica, which causes cell damage in the lungs. On the other hand, In vivo studies depicted that upon exposure to small silica particulate matter; lung characteristics such as the presence of an aqueous media and a PH of 7 facilitates Fenton-like reaction induced macrophage injury (Schapira, 1995; Vincent Castranova & Donna Pack, 1997; Castranova, 2000).

A possible hypothesis by Ghio (1990) stipulates that iron made available from silicate-iron reactions may activate dormant tuberculosis as iron is considered a virulent component of mycobacteria (Ghio, 1990). However, Mara Ghiazza, Francesco Turci, and Fubini (2011) depicted contradictory findings relating to iron in quartz and the resulting inflammatory process, showing iron loading influences beneficial effects by reducing cytotoxicity of quartz. Another study by Murray (1978) observed reactivation of infectious diseases like tuberculosis, malaria, and brucellosis among Somali nomads not exposed to silica dust but replenished with iron compared to the iron-deficient study group. The study by Murray offers insight into the overall role of iron status in general populations like nomads in influencing the reactivation of infectious diseases. Hence, a similar extension on miners exposed to silica dust applies more so if their iron status is known. Increased iron concentration in cells catalyzes ROS production in macrophages (Ghio, 2009; Ganz & Nemeth, 2005). Silica dust exposure results in a Fenton-like reaction that induces macrophage injury (Vincent Castranova & Donna Pack, 1997; Castranova, 2000). Concurrently, increased iron levels and quartz provide a synergistic interplay. Whereby, iron accumulation in the macrophages induces oxidative stress (Ghio, 2009), and quartz, in the presence of iron, undergoes the Fenton reaction pathway generating oxidative stress (Robert Konecny, 2001).

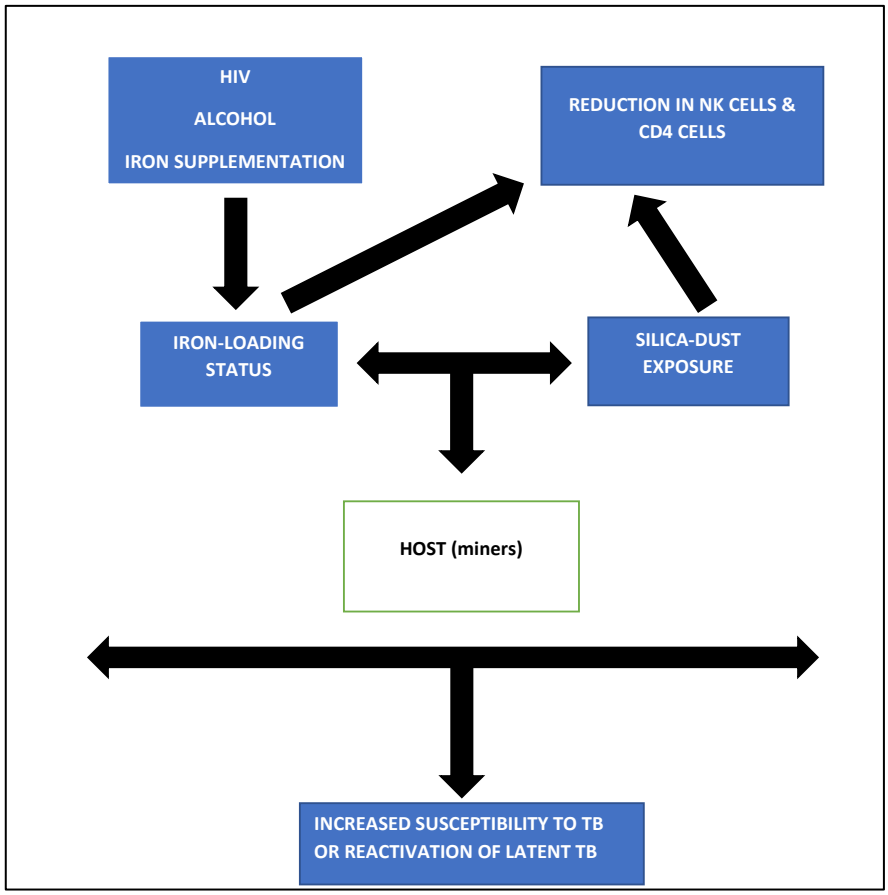

Figure 1 Host-Iron Status and Silica Dust Exposure Interplay in the Susceptibility of TB Infection

[1]

[1] Note (figure 1). Silica-dust exposure in an iron loading status influenced further by risk factors may increase the susceptibility of TB infection or reactivation of latent tuberculosis.
Reduction in NK cells and CD4 cells due to excess iron/iron loading (Joann, 2006). Reduction in NK cells and CD4 cells due to silica dust exposure (Konecny, 2019) Risk factors promoted an iron loading status in the host (Joann, 2006; Ioannou, 2004; Haider et al., 2019).

1.2.1.2 Genotoxicity mechanisms

IARC has classified crystalline silica as a Group 1 carcinogen (IARC, 2012). Recent toxicological profiling identified silica as a genotoxic agent in mammalian cells (Roney et al., 2019). Previous In Vitro studies elaborate that the parent compound, which is silica particle, directly induces cell death in macrophages via DNA damage (Costantini, 2011; Guidi et al., 2015). However, some studies noted attribution to other exposures like smoking in enhancing the DNA damage process among other workers exposed to silica dust (Başaran, Shubair, Ündeğer, & Kars, 2003; Peluso et al., 2015). Human studies assessing DNA damage related to occupational exposure to crystalline silica focused on foundry and pottery workers, stone crushers, sandblasters, glass, and industry workers but lacked focus on miners (Başaran et al., 2003; Demircigil et al., 2010; Roney et al., 2019; Sobti & Bhardwaj, 1991). Basaran et al. (2003) reported on an increase in DNA damage among foundry and pottery workers exposed to silica dust as compared to the controls ($P< 0.0001$). However, the study showed cigarette smoking attributed to more significant DNA damage among smokers than non-smokers (Başaran et al., 2003). On the other hand, Peluso et al. (2015) found that mixed exposure related to silica dust, solvents, welding, and exhaust fumes among pottery, ceramic, marble, and stone workers showed more significant damage in DNA strand compared to controls ($P=0.014$).

It is widely known that Alveolar macrophages play a crucial role in the defense against tuberculosis infection. However, other first-line defense cells, such as natural killer cells (NKs), also play a role in protecting against tuberculosis (P. Konecny, Ehrlich, Gulumian, and Jacobs, 2019). NKs cells are crucial in Interferon-gamma (IFN γ) production, which is a gene-mediated immunity against tuberculosis mycobacterial

infections (P. Konecny, Ehrlich, Gulumian, and Jacobs, 2019; Boisson-Dupuis, 2020). However, P. Konecny, Ehrlich, Gulumian, and Jacobs (2019) reports on the need for a detailed understanding of silica dust's role in altering NKs production. Boisson-Dupuis (2020) show that IFN γ deficiencies are because of genetic makeup in different populations. Both studies offer further insight into the different tuberculosis infection pathways and the need to explore silica dust exposure pathways related to NKs production or possible IFN γ deficiencies.

On the other hand, experimental studies have shown that macrophage plays a role in silicotuberculosis outcome (V. A. Shkurupy, 2010; Dong et al., 2014). One study showed an increase in the size of nodules arising from macrophages in mice exposed to silica and mice exposed to both silica and mycobacterium tuberculosis bacteria from the BCG vaccine (V. A. Shkurupy, 2010). However, it remains unclear why the nodules kept increasing in both mice compared to mice injected only with the BCG vaccine (V. A. Shkurupy, 2010). Similarly, another rat model study by Dong et al. (2014) showed that progression of silicosis worsened the tuberculosis outcome in rats injected with the standard virulent Strain of *Mycobacterium tuberculosis* (H37Rv). Dong et al.'s (2014) study offers future exploration for specific pathogenicity of silicosis in tuberculosis outcome.

1.3 Occupational safety and regulations

Recording of silicosis cases in most occupational health databases rely on compensation records hence leading to under-estimation of silicosis cases (De Klerk, 2002; Deslauriers & Redlich, 2018) , specifically since not all workers are covered by a social security system, espacially among small-scale workers (Demircigil et al., 2010). Additionally, small-scale mines situated in Asia, Africa, and South America are

reported to have a high incidence of tuberculosis despite a deficit of silica exposure data in most artisanal and small scale mines (Yassin, Yebesi, & Tingle, 2005; Gottesfeld, 2015; Tsang, Lockhart, Spiegel, & Yassi, 2019). Similarly, data on secondary tuberculosis infection is also limited in Switzerland in a database from the national accident and insurance fund among workers exposed to quartz (Koller, Scholz, Pletscher, & Miedinger, 2018; Knuchel, Lador, Soccal, & Janssens, 2016).

Recently, the Occupational Health and Safety Administration (OSHA) revised its initial exposure limit standard for silica dust previously set at 0.1mg/m³ and published a new limit set at 0.05mg/m³ due to the challenges faced within construction settings regarding increased exposure to silica dust (Deslauriers & Redlich, 2018; Occuaptional Safety and Health Administration, 2019). In addition, the European Scientific Committee for Occupational Exposure Limits (SCOEL) recommends a limit below 0.05mg/m³ exposure limit for silica dust (Stacey, 2007). However, different countries have implemented varying occupational exposure limits (OELs) for silica dust at the national level. European countries like Austria, Finland, Luxembourg, New Zealand, Slovenia, and Switzerland have set national exposure limits ranging from 0.15-0.2mg/m³ (Maciejewska, 2008). Other countries like Germany do not have standards because crystalline silica has been added as a category one carcinogen, making it impossible to establish a safety standard for such carcinogenic substances (Maciejewska, 2008). On the other hand, most developing countries have not established standards for silica dust exposure at the workplace (Gottesfeld, 2015; Gottesfeld, Tirima, Anka, Fotso, & Nota, 2019).

1.4 Significance for policy and research

Silicotuberculosis is a concern for both Public health and Occupational health (World Health Organization, 2016; Intergovernmental Forum on Mining, Minerals, Metals, and Sustainable Development, 2018). Therefore, in 2018, the International Commission on Occupational Health (ICOH) has emphasized the need for prioritizing research on silicosis and tuberculosis. The findings of this research will add to the existing knowledge in research and identify gaps related to risk factors associated with silicotuberculosis outcomes and available diagnostic techniques used to screen for the disease. Additionally, such research findings will inform healthcare workers, policymakers, and researchers.

1.5 Thesis objectives

The present study aims to map available evidence on the risk factors and diagnostic techniques for silico-tuberculosis among miners.

1.5.1 Review questions

1. What are the risk factors associated with silico-tuberculosis among miners?
2. What are the diagnostic techniques for screening silico-tuberculosis among miners?

CHAPTER 2

METHODS

2.1 Study Design

A scoping review was conducted to meet the objectives of this study. The scoping review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: Extension for scoping reviews (PRISMA-ScR), Joanna Briggs Institute guidelines and Levac, (2010) methodological framework (Peters et al., 2020; Tricco et al., 2018; Levac, Colquhoun, & O'Brien 2010). In line with the study's objectives, a scoping review aims to identify existing research gaps in the literature and map out studies available to the research area of interest with the aim to summarize our findings to guide researchers, health practitioners and policy makers (Arksey & O'Malley, 2005; Levac, Colquhoun, & O'Brien 2010).

2.2 Protocol

Using the PRISMA-ScR checklist item, a protocol for this scoping review was developed (Tricco et al., 2018). PRISMA-ScR checklist item offers an improved and transparent way of reporting the findings of scoping reviews (refer to appendix 1). Additionally, the list contains 22 items that guide each section of the review, such as title, abstract, introduction, methods, results, discussion, and funding sections.

2.3 Eligibility criteria

We included studies that met the following criteria:

- Type of participant(s): miners of any age and gender.

- Type of exposure: exposure to silica dust.
- Type of intervention: diagnostic techniques to screen for silico-tuberculosis.
- Type of outcome: the primary outcome was silico-tuberculosis occurrence among miners.
- Type of study: primary studies, including randomized clinical trials, non-randomized clinical trials, case-control, cohort, cross-sectional studies, case studies, and qualitative studies. We excluded any research that was not considered primary such as scoping reviews, systematic reviews, literature reviews, editorials, and commentaries.
- Language: English

2.4 Information sources and search strategy

Using a simplified search strategy and specific filters, we searched MEDLINE to check for any other reviews that have been conducted on this topic. The PROSPERO database was also searched for any similar existing registered protocol. The search did not identify any review with similar research questions.

Additionally, with the help of a medical librarian and experts in the field, a comprehensive search strategy was prepared and finalized on the 3rd of March 2020 (Refer to the detailed search strategy from all databases in Appendix 2). The following electronic databases were searched: MEDLINE, EMBASE, CINAHL, COCHRANE LIBRARY, and GEOREF. Grey literature databases were also searched including Google Scholar, Science.gov, and WHO Global Index Medicus. Two concepts were used in the search strategy – silico-tuberculosis and miners. The search strategy entailed the use of medical subject headings (MeSH), keywords, and Boolean operators like

"OR" and "AND" to combine the two concepts. The search was limited to English articles published between 2000 and 2020. Publications before the year 2000 were excluded because screening techniques for tuberculosis have improved since then.

Keywords used for the silico-tuberculosis concept included: *pulmonary tuberculosis, lung tuberculosis, lung phthisis or phthises, pulmonary phthisis or phthises, pulmonary consumption, Koch disease, etc.*

Keywords used for miners included: *mineworker, mining, mine labor or labor etc.*

2.5 Study selection

Records obtained from electronic databases were exported directly to the Endnote library. Duplicates of records were removed using the Endnote library feature and manually. Records were screened using two independent reviewers guided by the pre-established eligibility criteria (Refer to appendix 3). Calibration exercises were conducted by the two reviewers to assess and refine the screening questions, if necessary, and ensure the validity of the selection process. The title and abstract screening process were assessed for consistency between reviewers using the Cohen Kappa method in SPSS V26.0 (Refer to appendix 5). Kappa showed an agreement score of 0.868, which indicates a strong level of agreement. Additionally, there was no change in the eligibility criteria, and the two reviewers had no disagreements after the abstract and title screening.

Two reviewers conducted the full-text screening independently, and any disagreements were resolved through discussion until consensus was reached between

both reviewers (Refer to Supplemental Materials). The reference lists of all included articles were searched to identify relevant articles.

2.6 Data abstraction

In line with the eligibility criteria and study objectives, a data abstraction form was developed and reviewed by the research team (Refer to appendix 6). Data were abstracted from ten random articles as part of a calibration exercise to assess and refine the form, if needed.

Guided by the Joanna Briggs Institute guidelines (Peters et al., 2020; Tricco et al., 2018) and Levac (2010), the data items extracted from the articles included: author, year of publication, country of origin, the aim of the study, study intervention, outcomes, and key findings. Data abstraction was conducted by one reviewer and modified based on the feedback given by the research team. The following information were extracted from the included studies:

- Study characteristics: Extracted information from studies on geographical distribution of published articles, year of publication, study designs, population characteristics, type of mine-settings and mine-scale.
- Risk factors: Assessed studies based on various grouped categories for risk factors such as demographics, lifestyle, clinical, occupational health, and safety. Comparisons between significant and non-significant risk factors from all categories of risk factors.
- Diagnostic techniques: Studies assessed on the types of screening techniques used and methods of assessment applied to the techniques.
- Diagnostic results: Results were extracted from diagnostic techniques outcome.

- Limitations: Limitations from assessed studies were documented where available.

2.7 Data synthesis

We used a descriptive analysis approach to present the study characteristics, risk factors and diagnostic techniques. First, we evaluated the geographical distribution of the published articles. We then analyzed the study population characteristics regarding the gender and child context. Secondly, we presented all risk factors based on the demographic, clinical, lifestyle, occupational health, and safety categories. A narrative approach to summarize the detection of silico-tuberculosis, key findings, and limitations was applied.

CHAPTER 3

RESULTS

3.1 Literature search

6,414 records were identified from the searches. After the removal of duplicates, 5,175 titles and abstracts were screened (Refer to Figure 2). After title and abstract screening, 112 potentially relevant articles were included for full-text screening, of which 28 articles were included in the final review. Also, 84 items were excluded with reasons, as shown in figure 2.

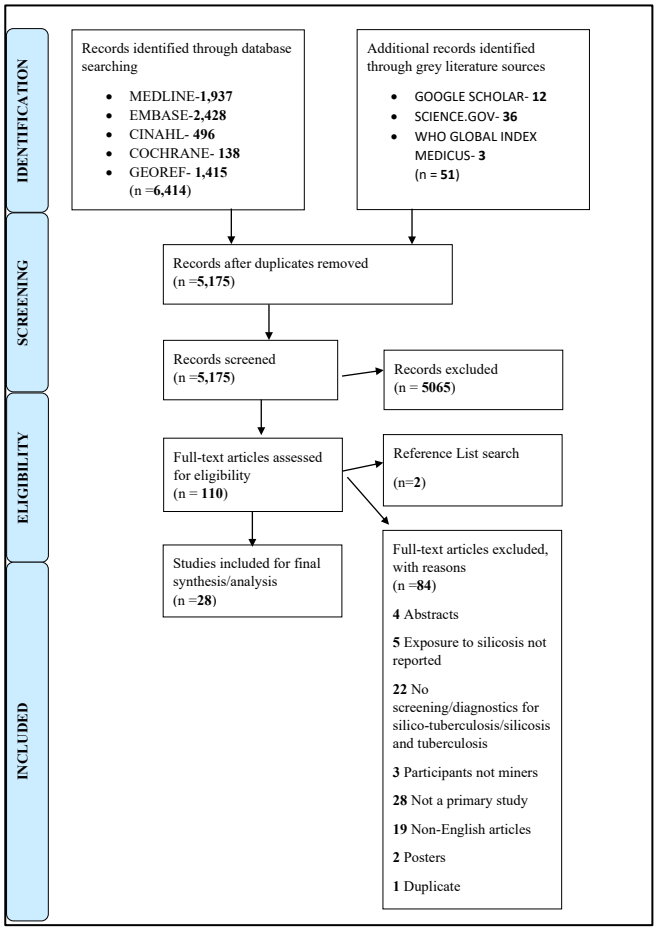

Figure 2 PRISMA Flow Chart

3.2 Study characteristics

The 28 studies were distributed between 2000 and 2018, as per figure 3. There was an increase of >50% in the number of articles assessing silico-tuberculosis/silicosis and tuberculosis outcomes in the last decade. The number of publications mainly peaked in 2000 mainly from South Africa (Churchyard, 2000; Corbett et al., 2000; Hnizdo, 2000; Sonnenberg et al., 2000) then gradually between 2007-2008 from China and India (Tse, 2007; Qu et al., 2007; Dixit & Dave, 2007; Charalambous et al., 2008; Glynn et al., 2008; Girdler-Brown et al., 2008) and 2014-2015 from China, Iran and India (Cheraghvandi et al., 2014; Tse, 2014; Feng et al., 2014; Farazi & Jabbariasl, 2015; Oni & ehrlich, 2015; Murlidhar, 2015).

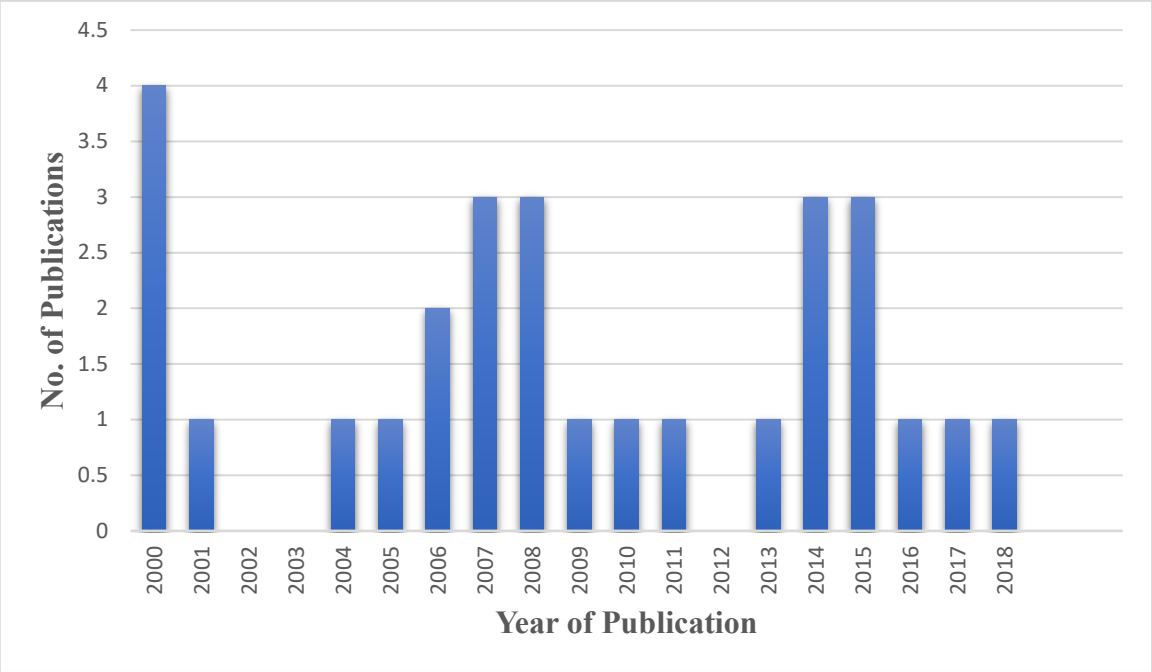

Figure 3 Number of Published Articles from the Year 2000 to 2018

Figure 4 maps the number of published articles included in this review for each country. Most of the articles (53%) were from South Africa (Cairncross & Kisting,

2016; Charalambous, Churchyard, Murray, De Cock, & Corbett, 2001; Charalambous et al., 2008; Churchyard, 2000; Corbett et al., 2004; Corbett et al., 2000; Ehrlich, 2011; Franzblau, 2018; Girdler-Brown, White, Ehrlich, & Churchyard, 2008; Hnizdo, 2000; Naidoo, Robins, Seixas, Lalloo, & Becklake, 2005; Oni & Ehrlich, 2015; Park, Girdler-Brown, Churchyard, White, & Ehrlich, 2009; Ross, Ehrlich, Hnizdo, White, & Churchyard, 2010; Sonnenberg et al., 2000; teWaternaude et al., 2006); four studies (14%) from China (Feng et al., 2014; Qu et al., 2007; L. A. Tse, Li, Wong, Fu, & Yu, 2007; L. A. Y. Tse, I. T. S.; Qiu, H.; Leung, C. C., 2014). Additionally, two studies (7%) were from India (Dixit & Dave, 2007; Murlidhar, 2015) and two (7%) from Iraq (Cheraghvandi et al., 2014; Farazi & Jabbariasl, 2015). One study was carried out in Zimbabwe (Carneiro, Barreto, Siqueira, Cavariani, & Forastiere 2006), one in in Brazil (Moyo & Kgalamono 2017), and another in Germany (Ringshausen et al., 2013).

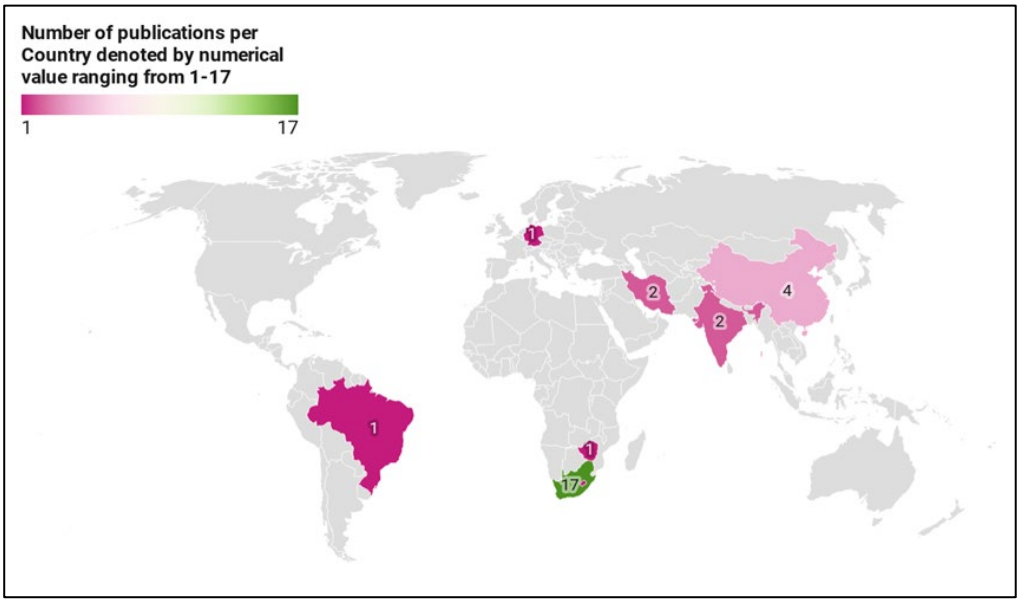

Figure 4 Overview of the Geographical Distribution of Publications Per Country

[2]

Eight of the reviewed studies (29%) were cross-sectional (Ehrlich, 2011; Farazi & Jabbariasl, 2015; Feng et al., 2014; Franzblau et al., 2018; Naidoo, 2005; Girdler-Brown et al., 2008; teWaternaude et al., 2006; Tse et al., 2007), seven studies (21%) were retrospective cohort (Carneiro et al., 2006; Churchyard, 2000; Corbett et al., 2000; Glynn et al., 2008; Hnizdo, 2000; Ross et al., 2010; Tse, 2014), five articles (18%) were case studies (Cheraghvandi et al., 2014; Dixit & Dave, 2007; Moyo & Kgalamono, 2017; Murlidhar, 2015; Oni & Ehrlich, 2015), two studies (7%) were prospective cohort (Charalambous et al., 2008; Park et al., 2009). In addition, one study (4%) was a case-control (Sonnenberg et al., 2000), one (4%) was a case-study (Cairncross & Kisting, 2016), one study (4%) was a case-series (Charalambous et al., 2001), one (4%) was a mixed- method study (Corbett et al., 2004), and one (4%) was an observational cohort study (Ringshausen et al., 2013). Eight studies (29%) had a sample size of less than 50 (Cairncross & Kisting, 2016; Charalambous et al., 2001; Cheraghvandi et al., 2014; Dixit & Dave, 2007; Feng et al., 2014; Moyo & Kgalamono, 2017; Murlidhar, 2015; Oni & Ehrlich, 2015), five studies (18%) had a sample size between 100-499 (Carneiro et al., 2006; Franzblau, 2018; Qu et al., 2007; Ringshausen et al., 2013; Ross et al., 2010), eight studies (29%) had between 500-999 (Charalambous et al., 2008; Ehrlich, 2011; Girdler-Brown et al., 2008; Naidoo et al., 2005; Park et al., 2009; Sonnenberg et al., 2000; teWaternaude et al., 2006; Tse, 2007), and seven studies (25%) had a sample size of more than 1000(Churchyard, 2000; Corbett et al., 2004; Corbett et al., 2000; Farazi & Jabbariasl, 2015; Glynn et al., 2008; Hnizdo, 2000; Tse, 2014). The summary of the descriptive characteristics is presented in Table 1.

[2] Note (figure 4). The map is available at (//www.datawrapper.de/_/JEJOm/)

The articles reported different study population characteristics, as shown in Table 1. The male population represented the majority (68%) of study participants of the reviewed articles (Charalambous et al., 2001; Charalambous et al., 2008; Churchyard, 2000; Corbett et al., 2000; Dixit & Dave, 2007; Ehrlich, 2011; Farazi & Jabbariasl, 2015; Feng et al., 2014; Franzblau, 2018; Moyo & Kgalamono, 2017; Oni & Ehrlich, 2015; Park et al., 2009; Qu et al., 2007; Ringshausen et al., 2013; Ross et al., 2010; Sonnenberg et al., 2000; Tse et al., 2007; Tse, 2014). Gender was not specified in seven (25%) articles (Cairncross & Kisting, 2016; Corbett et al., 2004; Girdler-Brown et al., 2008; Hnizdo, 2000; Naidoo, 2005; teWaternaude et al., 2006; Carneiro et al., 2006). In addition, only one study (4%) reported one female miner (Murlidhar, 2015). Four studies (14%) entailed mixed populations of different occupations, including miners (Cairncross & Kisting, 2016; Tse, 2014; Murlidhar, 2015; Farazi & Jabbariasl, 2015). Five articles (18%) assessed silico-tuberculosis outcomes among internal migrants (Cairncross & Kisting, 2016; Oni & Ehrlich, 2015; Ross et al., 2010; Sonnenberg et al., 2000; Tse, 2014), while four records assessed silico-tuberculosis outcomes among external migrants (Ehrlich, 2011; Carneiro et al., 2006; Ringshausen et al., 2013; Park et al., 2009). One study (4%) did not specify if the migrant population was external or internal (Charalambous et al., 2008). Also, only one study (4%) reported that the study population was insured (Ringshausen et al., 2013).

Overall, terminologies used to describe the type of exposure included either silica or quartz in the studies (68%) reviewed (Cairncross & Kisting, 2016; Charalambous et al., 2001; Charalambous et al., 2008; Churchyard, 2000; Corbett et al., 2004; Corbett et al., 2000; Dixit & Dave, 2007; Cheraghvandi et al., 2014). Also, a few studies referred to the type of exposure as dust/silica (Ehrlich, 2011; Girdler-Brown et

al., 2008; Feng et al., 2014; teWaternaude et al., 2006; Tse et al., 2007; Carneiro et al., 2006; Ringshausen et al., 2013) and coal/quartz (Naidoo, 2005).

On the other hand, eighteen articles (64%) assessed miners working in Goldmines (Carneiro et al., 2006; Charalambous et al., 2001; Charalambous et al., 2008; Churchyard, 2000; Corbett et al., 2004; Corbett et al., 2000; Ehrlich, 2011; Franzblau, 2018; Girdler-Brown et al., 2008; Hnizdo, 2000; Oni & Ehrlich, 2015; Park et al., 2009; Ross et al., 2010; Sonnenberg et al., 2000; teWaternaude et al., 2006; Qu et al., 2007; Tse et al., 2007; Glynn et al., 2008), while two studies (7%) assessed miners working in Gold and platinum mines (Cairncross & Kisting, 2016) and Gold/Granite mines (Moyo & Kgalamono, 2017). Other studies assessed miners working in stone mines (Murlidhar, 2015), iron mines (Qu et al., 2007), and coal mines (Naidoo, 2005; Ringshausen et al., 2013). Out of all the studies, one article (4%) specified the mine as large-scale (Franzblau, 2018) and another article specified the mine as small scale (Tse et al., 2007). Twelve studies (43%) assessed silica dust exposure among underground miners (Charalambous et al., 2008; Churchyard, 2000; Corbett et al., 2000; Ehrlich, 2011; Hnizdo, 2000; Oni & Ehrlich, 2015; Park et al., 2009; Ross et al., 2010; Sonnenberg et al., 2000; Qu et al., 2007; Carneiro et al., 2006; Moyo & Kgalamono, 2017). Two studies (7%) assessed exposure among miners engaged in underground and surface mining (Naidoo, 2005; Ross et al., 2010), while three articles (11%) assessed exposure among miners involved in rock-drilling mine work (Moyo & Kgalamono, 2017; Tse et al., 2007; Cairncross & Kisting, 2016). Only one study (4%) assessed exposure among miners involved in underground mining, rock-drilling, and open-cast mining (Cairncross & Kisting, 2016).

Study characteristics	**N***	**(%)***
Study design		
Cross-sectional	8	29
Case-control	1	4
Retrospective cohort	7	25
Prospective cohort	2	7
Case-study	1	4
Case-series	1	4
Case-report	5	18
Mixed (cross-sectional, retrospective and prospective)	1	4
Observation cohort	1	4
Sample size		
≤ 50	8	29
100-499	5	18
500-999	8	29
≥1000	7	25
Characteristics of the study population		
Mixed population	4	14
Female	1	4
Male	19	68
Gender not specified	7	25
Migrant status		
Internal	5	18
External	4	14
Not specified	1	4
Insurance Status		
Insured	1	4
Exposure		
Dust	1	7
Quartz/silica	19	68
Both dust and silica	7	25
Coal and quartz	1	4
Type of mine		
Gold	18	64
Gold and Platinum	1	4
Gold and Granite	1	4
Stone	1	4
Iron	1	4
Coal	2	7
Scale of mine		
Small-scale	1	4
Large-scale	1	4
Type of mining work		
Underground	12	43
Underground and surface	2	7
Rock drilling	3	11
Underground, rock drilling, and open cast	1	4

Table 1 Summary of Study Characteristics

[3]

3.3. Risk factors associated with Silico-tuberculosis outcome

3.3.1 Demographics

Reviewed studies identified various demographic characteristics as risk factors for silicosis and tuberculosis outcomes (refer to table 2). Age was considered a significant risk factor in four studies (Churchyard, 2000; Corbett et al., 2000; Farazi & Jabbariasl, 2015; Moyo & Kgalamono, 2017). However, no significant results were seen in by age categories when comparing HIV +ve to HIV -ve participants (Charalambous et al., 2008; Churchyard, 2000; Corbett et al., 2000).

Migrant status and race appeared to influence silicosis and tuberculosis outcomes significantly. Migrants from neighboring or foreign countries was a significant risk factor as reported by one study (Ringshausen et al., 2013) and non-significant risk factor as shown by two studies (Sonnenberg et al., 2000; Farazi & Jabbariasl, 2015). Additionally, skin color was significantly associated with advanced grading of silicosis and opacities (Carneiro et al., 2006). Also, educational background seemed to be a non-significant risk factor, especially for the primary and secondary levels (Sonnenberg et al., 2000). Interestingly, gender was not reported as a risk factor in the studies reviewed.

Demographic Risk Factors Related to Silico-Tuberculosis/Silicosis and Tuberculosis	N*	%	Significant Association (Measure of Association,	Non-Significant Association (Measure of Association,

[3] Note (table 1). (%) * for percentages are rounded. N* for number of studies.

			Confidence Interval, P-Value)	Confidence Interval, P-Value)
Age in yrs.				
General in yrs. (all ages).	3	11	OR=1.97, CI=1.12-3.46, P=0.02 (Farazi & Jabbariasl, 2015)	OR=1.05, CI=1.01-1.09 (Park et al., 2009) OR=1.3 CI=0.75-2.4, P=0.3 (Sonnenberg et al., 2000)
0-29	1	4	[4]OR=1.1, CI=0.4-3.0 (Churchyard, 2000)	-
18-29	1	4	-	IRR=0.4, CI=0.2-0.7 (Corbett et al., 2000)
35-44	1	4	-	[1]HR=0.9, CI=0.4-2.1 (Charalambous et al., 2008) [2]HR=5.5, CI=0.6-2.1 (Charalambous et al., 2008)
≥45	1	4	-	[1]HR=0.9, CI=0.4-2.1 (Charalambous et al., 2008) [2]HR=1.8, CI=0.6-5.9 (Charalambous et al., 2008)
>50	1	4	IRR=1.3, CI=0.8-2.2 (Corbett et al., 2000) [8]OR=5.8, CI=2.04–16.26, P <0.001 (Ringshausen et al., 2013) [9]OR=8.1, CI=2.22–29.21, P= 0.001 (Ringshausen et al., 2013)	[4]OR=1.0, CI=0.4-2.3 (Churchyard, 2000) [5]OR=0.5, CI=0.2-1.4 (Churchyard, 2000)
Migrant status				
Neighboring/Foreign country	3	11	[8]OR=6.8, CI=1.91–24.0, P= 0.003 (Ringshausen et al., 2013) [9]OR=4.8, CI=1.26–18.07, P= 0.022	OR=0.65, CI=0.27-1.56, P=0.37 (Farazi & Jabbariasl, 2015) OR=1.2, CI=0.67-2.2 (Sonnenberg et al., 2000)

			(Ringshausen et al., 2013)	
Education level				
Primary education	1	4	-	OR=0.76, CI=0.41-1.4 (Sonnenberg et al., 2000)
Secondary education	1	4	-	OR=0.46, CI=0.18-1.2 (Sonnenberg et al., 2000)
Race				
Skin color	1	4	[1]OR=19.99, CI=3.05-131.16, P=0.002 (Carneiro et al., 2006) [2]OR=5.51, CI=1.25-24.38, P=0.024 (Carneiro et al., 2006)	[3]OR=1.58, CI=038-6.57, P=0.529 (Carneiro et al., 2006)

Table 2 Demographic Risk Factors Related to Silico-Tuberculosis/Silicosis and Tuberculosis

[4]

3.3.2 Lifestyle behavior Factors

Seven studies assessed the association between silico-tuberculosis outcomes and lifestyle behavioral risk factors (refer to Table 3). Smoking was significantly associated with silicosis and tuberculosis in two studies (Tse, 2014; Farazi & Jabbariasl, 2015). On the other hand, three studies found a non-significant association between smoking and TB or latent TB and decline in FEV_1 (Naidoo, 2005; Park et al., 2009; Ross et al., 2010; Sonnenberg et al., 2000). In addition, one study reported previous smoking status (ex-

[4] Note (table 2). Abbreviations:

[1]OR is the odds ratio for silicosis category 3. [2]OR is the odds ratio for either coalescence or large opacities. [3]OR is the odds ratio for TB. [4]OR is the odds ratio for all participants. [5]OR is the odds ratio for HIV +ve group. [8]OR is the odds ratio for +ve QFT. [9]OR is odd ratio for +ve T-SPOT. [1]HR for the hazard ratio for both HIV +ve and -ve participants; [2]HR is hazard ratio for HIV +ve sub-groups. * for risk factors without a measure of association. (%) * for percentages are rounded. N* for number of studies.

smokers) as a significant risk factor for the decline in FEV_1 (Naidoo, 2005). Daily and occasional alcohol drinking was also found to be significantly associated with TB in one study (Sonnenberg et al., 2000). On the other hand, one study revealed opium addiction as a non-significant lifestyle behavioral risk factor associated with latent TB or TB (Farazi & Jabbariasl, 2015).

Lifestyle Risk Factors Related to Silico-Tuberculosis/Silicosis and Tuberculosis	N*	%	Significant Association (A Measure of Association, Confidence Interval, P-Value)	Non-Significant Association (A Measure of Association, Confidence Interval, P-Value)
Smoking characteristics				
Smoking	7	25	[10]OR=1.80, CI= 1.20-2.60 (Tse, 2014) [11]OR=2.54, CI=1.24-5.22 (Tse, 2014) OR=3.11, CI=1.30-7.44, P=0.01 (Farazi & Jabbariasl, 2015)	[6]OR=1.39, CI=0.68-2.85 (Dixit & Dave, 2007) [7]OR=1.00, CI=0.68-1.47 (Dixit & Dave, 2007) OR=0.83, CI=0.54-1.26 (Park et al., 2009) [8]OR=3.5, CI=0.92–13.60, P= 0.066 (Ringshausen et al., 2013) [9]OR=2.6, CI=0.65-10.65, P= 0.18 (Ringshausen et al., 2013) OR=2.04, CI=1.33-3.12 (Ross et al., 2010) OR=1.1, CI=0.55-2.3 (Sonnenberg et al., 2000)
Ex-smokers	1	4	[6]OR=2.65, CI=1.21-5.81 (Dixit & Dave, 2007)	-
Alcohol characteristics				
Weekends	1	4	OR=0.91, CI=0.48-1.7, P=0.8 (Sonnenberg et al., 2000)	-
Daily	1	4	OR=0.12, CI=0.02-0.93, P=0.04	-

			(Sonnenberg et al., 2000)	
Opium				
Opium addiction	1	4	-	OR=0.45, CI=0.12-1.76, P=0.32 (Farazi & Jabbariasl, 2015)

Table 3 Lifestyle Risk Factors Related to Silico-Tuberculosis/Silicosis and Tuberculosis

[5]

3.3.3 Clinical Factors

Nine studies reported clinical factors that may influence the risk of silico-tuberculosis outcomes as per Table 4. Two studies reported non-significant findings among miners who had a history of TB in the last five years (Corbett et al., 2000; Park et al., 2009) and one study showed significant results (Dixit & Dave, 2007). Additionally, participants with TB for more than five years were deemed significant to silico-tuberculosis outcome (Corbett et al., 2000). Previous TB treatment was a significant risk factor in one study (Sonnenberg et al., 2000), and post-treatment characteristics like scarring in the zones and cavitation were non-significant (Charalambous et al., 2008). Additionally, Previous TB retreatment was a significant risk factor in HIV +ve groups compared to all participants reported in one study (Churchyard, 2000).

[5] Note (table 3). Abbreviations:

[6]OR is odd ratio for $FEV_1 < 65\%$. [7]OR is odd ratio for $FEV_1 < 65\%$. [8]OR is odd ratio for +ve QFT. [9]OR is odd ratio for +ve T-SPOT. [10]OR is odd ratio for silicosis mortality. [11]OR is odd ratio for TB mortality. (%) * for percentages are rounded. N* for number of studies.

On the other hand, (1) radiological pattern for TB (atypical) was significant in HIV +ve group in one study (Churchyard, 2000) while (2) radiological pattern for TB (cavitation) was non-significant in another study (Sonnenberg et al., 2000).

The site of diagnosed tuberculosis, such as pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB), were significant risk factors in HIV +ve groups (Churchyard, 2000). Radiological evidence of previously healed TB as a risk factor depicted mixed reports from one study (Ringshausen et al., 2013). Those with a positive QuantiFERON-TB Gold (QFT) diagnosis posed significantly higher risk when compared to those with a positive T-SPOT (Ringshausen et al., 2013). Whereas risk factors related to last TB characteristics in terms of duration and treatment depicted mixed findings. Drug-resistance TB was reported as a non-significant risk factor for all participants and HIV +ve sub-groups (Charalambous et al., 2008; Churchyard, 2000). Confirmed TB and duration of active TB were reported as significant risk factors (Corbett et al., 2004). All diagnosed TB and COPD were reported as non-significant risk factors by three studies (Corbett et al., 2004; Park et al., 2009; Ringshausen et al., 2013).

Silicosis was a clinical risk factor based on the staging and the characteristics displayed. Silicosis characteristics referred to as possible for silicosis and probable for silicosis were a significant risk factor for TB (Corbett et al., 2000; Sonnenberg et al., 2000). Whereas silicosis staging referred to as early silicosis and advanced silicosis was a significant risk factor for TB in one study (Corbett et al., 2000) and a non-significant risk factor for TB among HIV +ve and HIV-ve groups in another study (Charalambous et al., 2008).

HIV as a clinical risk factor was significant based on CD4 cell count and period of HIV infection, respectively (Charalambous et al., 2008; Churchyard, 2000; Corbett et al., 2000). Two studies reported clinical assessments using sputum tests and found contradictory results. One study found a -ve sputum test as a significant clinical risk factor for HIV +ve groups compared to all participants (Churchyard, 2000), while the other study revealed a +ve smear test as a significant risk factor (Corbett et al., 2004).

Respiratory symptoms such as cough, phlegm, and wheezing were reported as non-significant risk factors except for breathlessness (Ross et al., 2010). On the other hand, history assessment for asthma, pneumonia, and bronchitis were reported as risk factors but non-significant by one study (Ross et al., 2010). Additionally, self-presentation on clinical assessment was identified to be significant by one study (Churchyard, 2000).

Clinical Risk Factors Related to Silico-Tuberculosis/Silicosis and Tuberculosis	**N***	**%**	**Significant Association (A Measure of Association, Confidence Interval, P-Value)**	**Non-Significant Association (A Measure of Association, Confidence Interval, P-Value)**
Previous TB in yrs. characteristics				
0-5	3	11	[6]OR=8.091, CI=3.34-19.61 (Dixit & Dave, 2007) [7]OR=5.29, CI=2.37–11.78 (Dixit & Dave, 2007)	IRR=1.3, CI=0.6-2.8 (Corbett et al., 2000) OR=1.45, CI=0.93-2.26 (Park et al., 2009)
>5	1	4	IRR=2.6, CI=1.5-4.4 (Corbett et al., 2000)	-
Previous TB treatment characteristics				
Previous TB treatment (general)	2	7	OR=3.61, CI=1.9-6.9, P<0.001 (Sonnenberg et al., 2000)	OR=1.42, CI= 0.36-5.59 (Park et al., 2009)
Post-treatment scarring (one zone)	1	4	-	[1]HR=0.7, CI=0.2-2.9 (Charalambous et al., 2008)

				[2]HR=0.7, CI=0.2-2.8 (Charalambous et al., 2008)
Post-treatment scarring (Two or more zones)	2	7	-	[1]HR=1.0, CI= 0.2-4.4 (Charalambous et al., 2008) [2]HR=0.7, CI=0.2-2.6 (Charalambous et al., 2008) [4]OR=1.1, CI=0.6-1.9 (Churchyard, 2000) [5]OR=0.97, CI=0.5-1.7 (Churchyard, 2000)
Cavitation end of treatment	1	4	-	[1]HR=1.1, CI=0.5-2.5 (Charalambous et al., 2008) [2]HR=0.4, CI=0.1-2.6 (Charalambous et al., 2008)
Site of disease PTB +EPTB	1	4	[5]OR=3.1, CI=1.7–5.6 (Churchyard, 2000)	-
Radiological evidence of prior healed TB	1	4	[8]OR=5.0, CI=1.69–14.98, P= 0.004 (Ringshausen et al., 2013)	[9]OR=3.0, CI=0.96–9.15, P= 0.059 (Ringshausen et al., 2013)
Treatment category				
Retreatment	1	4	[5]OR=1.5, CI=0.8–2.9 (Churchyard, 2000)	[4]OR=1.5, CI=0.8–2.8 (Churchyard, 2000)
Drug-resistant TB characteristics				
Drug-resistant TB (any/general)	2	7	-	[1]HR=0.8, CI=0.2-3.4 (Charalambous et al., 2008) [2]HR=1.4 CI=0.3-6.1 (Charalambous et al., 2008) [4]OR=1.2, CI=0.5–3.0 (Churchyard, 2000)
Single resistance (S/R)	1	4	-	[4]OR=0.9, CI=0.3-3.0 (Churchyard, 2000)
Multi-drug resistance (MDR)	1	4	-	[4]OR=1.2, CI=0.1–13.8 (Churchyard, 2000)
Confirmed TB	2	7	RR=5.1, CI=3.0-9.0 (Corbett et al., 2004) DDR=0.33, CI=0.14-0.72 (Corbett et al., 2004)	OR=1.7, CI=0.89-3.3 (Corbett et al., 2004)
Duration of active TB disease before diagnosis	1	4	DDR=0.16, CI=0.00-0.73 (Corbett et al., 2004)	-
All diagnosed TB	1	4	-	OR=1.6, CI=0.83-3.1 (Corbett et al., 2004)

				RR=5.2, CI=3.2-8.5 (Corbett et al., 2004) OR=3.09, CI=1.42-6.69 (Park et al., 2009)
COPD	1	4	-	[8]OR=1 (Ringshausen et al., 2013) [9]OR=1 (Ringshausen et al., 2013)
Silicosis characteristics				
Silicosis (possible)	2	7	OR=1.4, CI=0.62-3.0, P=0.5 (Sonnenberg et al., 2000) IRR=1.4, CI=1.0-2.2 (Corbett et al., 2000)	-
Silicosis (probable)	1	4	IRR=1.8, CI=1.0-3.0 (Corbett et al., 2000)	-
Silicosis (yes)	4	14	OR=12.6, CI=2.2-71, P=0.004 (Sonnenberg et al., 2000) [4]OR=3.0, CI=1.4-6.3 (Churchyard, 2000) [5]OR=2.8, CI=1.2-6.8 (Churchyard, 2000)	[8]OR=1.8, CI=0.75–4.28, P= 0.19 (Ringshausen et al., 2013) [9]OR=1.5, CI=0.63–3.55, P= 0.36 (Ringshausen et al., 2013) OR=1.86, CI=1.03-3.37 (Ross et al., 2010)
Silicosis (early)	2	7	IRR=2.2, CI=1.3-3.7 (Corbett et al., 2000)	[1]HR=0.8, CI=0.3-2.3 (Charalambous et al., 2008) [2]HR=0.9, CI=0.3-3.0 (Charalambous et al., 2008)
Silicosis (advanced)	2	7	IRR=2.5, CI=1.6-4.0 (Corbett et al., 2000)	[1]HR=0.6, CI=0.2-1.9 (Charalambous et al., 2008) [2]HR=0.9, CI=0.3-3.0 (Charalambous et al., 2008)
HIV characteristics				
HIV (general status)	3	11	[1]HR=2.5, CI=1.2-5.3 (Charalambous et al., 2008) [4]OR=15.0, CI=7.4-30.6 (Churchyard, 2000)	OR=0.74, CI=0.38-1.49 (Park et al., 2009) OR=0.67, CI= 0.35-1.3, P=0.2 (Sonnenberg et al., 2000)
CD4 <200 count/cells/ul	1	4	[5]OR=28.2, CI=11.5-72.3 (Churchyard, 2000)	-

CD4 200-500 count/cells/ul	1	4	[2]HR=0.4, CI=0.1-1.1 (Charalambous et al., 2008)	-
CD4 >500 count/cells/ul	1	4	[2]HR=0.1, CI=0.0-1.1 (Charalambous et al., 2008)	-
CD4 14-28%	1	4	-	OR=0.98, CI=0.35-2.8 (Sonnenberg et al., 2000)
CD4 < 14%	1	4	-	OR=0.36, CI=0.04-3.0 (Sonnenberg et al., 2000)
HIV infection period 1991-1994	1	4	IRR= 2.8, CI=1.5-5.0 (Corbett et al., 2000)	-
HIV infection period 1995-1997	1	4	IRR=5.9, CI=4.2-8.2 (Corbett et al., 2000)	-
Radiological characteristics				
Radiological Pattern atypical	1	4	[5]OR=1.4, CI=0.7–2.8 (Churchyard, 2000)	-
Chest radiography for cavitation	1	4	-	OR=2.1, CI=1.1-3.8 (Sonnenberg et al., 2000)
Respiratory symptom characteristics				
Cough	1	4	-	OR=1.59, CI=0.90-2083 (Ross et al., 2010)
Phlegm	1	4	-	OR=1.45, CI=0.78-2.68 (Ross et al., 2010)
Breathlessness	1	4	OR=2.20, CI=1.18-4.11 (Ross et al., 2010)	-
Wheezing	1	4	-	OR=1.67, CI=0.92-3.03 (Ross et al., 2010)
Other characteristics				
Sputum -ve	1	4	[5]OR=0.3, CI=0.1-0.8 (Churchyard, 2000)	[4]OR=0.9, CI=0.4-2.0 (Churchyard, 2000)
Smear +ve	1	4	DDR:0.16 CI=0.00-0.73 (Corbett et al., 2004) OR:0.8 CI=0.082-4.2 (Corbett et al., 2004) [I]RR:5.5 CI=2.6-12.2 (Corbett et al., 2004)	-
Culture +ve	1	4	-	OR=2.1, CI=0.98-4.2 (Corbett et al., 2004) RR=4.4, CI=2.2-9.1 (Corbett et al., 2004)
Self-presentation	1	4	[4]OR=5.6, CI=2.6-12.2 (Churchyard, 2000)	-

			[5]OR=4.3, CI=1.9-9.6 (Churchyard, 2000)	
History of asthma	1	4	-	OR=3.411, CI=22-9.51 (Ross et al., 2010)
History of pneumonia	1	4	-	OR=1.36, CI=0.56 to 3.30 (Ross et al., 2010)
History of bronchitis	1	4	-	OR=1.51, CI=0.25-9.13 (Ross et al., 2010)

Table 4 Clinical Risk Factors Related to Silico-Tuberculosis/Silicosis and Tuberculosis

[6]

3.3.4 Occupational health and safety

Nine studies (Charalambous et al., 2008; Corbett et al., 2000; Naidoo, 2005; Farazi & Jabbariasl, 2015; Carneiro et al., 2006; Ross et al., 2010; Sonnenberg et al., 2000; teWaternaude et al., 2006; Qu et al., 2007) reported occupational health and safety risk factors related to chemical exposure (silica/dust exposure, intensity, and duration) Refer to Table 5. Additionally, one study showed current miners exposed to high or medium dust as a non-significant risk factor for reduced lung function referred to as low FEV_1< 65% and low FEV_1< 80% (Naidoo, 2005). Also, other studies reported significant risks related to high dust exposure over time compared to medium dust exposure over time (Naidoo, 2005; teWaternaude et al., 2006). Respirable quartz/silica exposure over time was a significant risk for both silicosis category 3 and large opacities compared to TB (teWaternaude et al., 2006; Carneiro et al., 2006). The

[6] Note (table 4). Abbreviations:

[4]OR is the odds ratio for all participants. [5]OR is the odds ratio for HIV +ve group. [6]OR is the odds ratio for FEV_1 < 65%; [7]OR is the odds ratio for FEV_1 < 65. [8]OR is the odds ratio for +ve QFT. [9]OR is odd ration for +ve T-SPOT; IRR is incidence rate ratio. [1]HR for the hazard ratio for both HIV +ve and -ve participants. [2]HR is hazard ratio for HIV +ve sub-groups. [I]RR is rate ratio for TB incidence. DDR is disease duration ratio. * for risk factors without a measure of association. (%) * for percentages are rounded. N* for number of studies.

continuity of exposure to silica dust and duration was a significant risk factor by two studies (Farazi & Jabbariasl, 2015; Carneiro et al., 2006). On the other hand, the concentration of chemical factors (silica/dust), such as the average intensity of silica and dust, were also found to be significant risk factors (teWaternaude et al., 2006).

Several studies reported the length of service as a risk factor based on years of work. Two studies reported work duration as non-significant among HIV +ve and HIV -ve groups (Charalambous et al., 2008; Corbett et al., 2000). On the other hand, one study showed work duration to be a significant risk among HIV +ve groups. Additionally, one study showed work duration as non-significant when adjusted for age and smoking. Underground work duration and surface work were also identified as significant risk factors as reported by two studies.

In addition, a few studies recognized and reported potential occupational risk factors associated with increased risk of silico-tuberculosis (no measure of association reported). The potential risk factors included social factors, such as inferior houses made of zinc for mine workers with no ventilation (Cairncross & Kisting, 2016), human factors like lack of frequent use of respiratory PPE's (Tse et al., 2007; Moyo & Kgalamono, 2017), and safety risk factors mainly mechanical ventilation in underground pits (Tse et al., 2007).

3.3.5 Genetic polymorphs

Out of all the reviewed studies, only one study reported genotype polymorphisms associated with alveolar macrophage response genes (Qu et al., 2007). The study found non-significant association between the role of single polymorphisms with the increased risk of silicosis and tuberculosis (Qu et al., 2007). However, significant associations were identified for the different polymorphisms like tumor

necrosis factor (TNF) of variant type TNF-a-308 G/G and natural resistance macrophage protein 1 (NRAMP1) INT4 polymorphisms with increased TB risk and interaction between NRAMP1 INT4 and D543N G/A+A/A polymorphisms to PTB (Qu et al., 2007).

Genetic Polymorphs Related to Silico-Tuberculosis/Silicosis and Tuberculosis	N*	%	Significant Association (A Measure of Association, Confidence Interval, P-Value)	Non-Significant Association (A Measure of Association, Confidence Interval, P-Value)
NRAMP1 INT4 Genotypes (TB)				
G/C	1	4	OR=2.53, CI=1.21-5.31 (Qu et al., 2007)	-
G/C + C/C	1	4	OR=2.66, CI=1.27-5.54 (Qu et al., 2007)	
C/C*	1	4	-	- (Qu et al., 2007)
NRAMP1 D543N Genotypes (TB)				
G/A*	1	4	-	- (Qu et al., 2007)
A/A	1	4	-	OR=1.06, CI=0.09-12.74 (Qu et al., 2007)
G/G + A/A	1	4	-	OR=1.81, CI=0.84-3.93 (Qu et al., 2007)
TNF-a-308 Genotypes (TB)				
G/A	1	4	-	OR=0.83, CI=0.34-2.03 (Qu et al., 2007)
A/A*	1	4	-	- (Qu et al., 2007)
G/A + A/A	1	4	-	OR=0.81, CI=0.33-1.95 (Qu et al., 2007)
iNOS Ser608Leu Genotypes (TB)				
C/T	1	4	-	OR=1.46, CI=0.69-3.09 (Qu et al., 2007)
T/T	1	4	-	OR=3.00, CI=0.17-54.03 (Qu et al., 2007)
C/T +T/T	1	4	-	OR=1.50, CI=0.71-3.15 (Qu et al., 2007)
TNF-a-308 Genotypes (Silicosis)				
G/A	1	4	-	OR=1.59, CI=0.80-3.19 (Qu et al., 2007)
A/A	1	4	-	OR=1.12, CI=0.16-7.78 (Qu et al., 2007)

G/A + A/A	1	4	-	OR=1.52, CI=0.79-2.95 (Qu et al., 2007)
iNOS Ser608Leu Genotypes (Silicosis)				
C/T	1	4	-	OR=0.45, CI=0.27-0.77 (Qu et al., 2007)
T/T	1	4	-	OR=0.92, CI=0.16-5.42 (Qu et al., 2007)
C/T + T/T	1	4	-	OR=0.47, CI=0.28-0.79 (Qu et al., 2007)
Interaction of TNF-a-308 G/G and NRAMP1 INT4 polymorphisms to PTB				
NRAMP1 INT4 G/G & G/C+C/C	1	4	OR=2.38, CI=1.14-4.98, P<0.01 (Qu et al., 2007)	-
Interaction of TNF-a-308 G/A+A/A and NRAMP1 INT4 polymorphisms to PTB				
NRAMP1 INT4 G/G & G/C + C/C	1	4	-	OR=5.71, CI=0.45-73.19 (Qu et al., 2007)
Interaction of TNF-a-308 G/G and NRAMP1 D543N polymorphisms to PTB				
NRAMP1 D543N G/G & G/A+A/A	1	4	-	OR=1.59, CI=0.72-3.50 (Qu et al., 2007)
Interaction of TNF-a-308 G/A + A/A and NRAMP1 D543N polymorphisms to PTB				
NRAMP1 D543N G/G & G/A+A/A	1	4	-	OR=1.25, CI=0.23-6.70 (Qu et al., 2007)
Interaction of NRAMP1 INT4 and D543N G/G polymorphisms to PTB				
NRAMP1 D543N G/G & G/C + C/C	1	4	OR=3.26, CI=1.47–7.23, P<0.01 (Qu et al., 2007)	-
Interaction of NRAMP1 INT4 and D543N G/A+A/A polymorphisms to PTB				
NRAMP1 D543N G/G & G/C+C/C	1	4	-	OR= 1.23, CI= 0.28–5.45 (Qu et al., 2007)
Miner characteristics				
Current miner	1	4	-	[6]OR=0.65, CI=0.23-1.81 (Naidoo, 2005) [7]OR=1.35, CI=0.73-2.52 (Naidoo, 2005)
Current miner × high dust exposure	1	4	-	[6]OR=0.51, CI=0.076-3.39 (Naidoo, 2005) [7]OR=0.21, CI=0.06-0.74 (Naidoo, 2005)
Current miner × medium dust exposure	1	4	-	[6]OR=0.47, CI=0.11-2.01 (Naidoo, 2005) [7]OR=0.41, CI=0.16-0.98 (Naidoo, 2005)
Dust exposure characteristics				
Cumulative respirable dust	1	4	[c1]POR=1.45, CI=1.14-1.85 (teWaternaude et al., 2006)	-
High cumulative dust exposure	1	4	[7]OR=4.21, CI=1.31-13.51 (Naidoo, 2005)	-
Medium cumulative dust exposure	1	4	-	[6]OR=1.36, CI=0.48-3.83 (Naidoo, 2005)

				[7]OR=1.43, CI=0.69-2.93 (Naidoo, 2005)
Average intensity respirable dust	1	4	[c1]POR: 1.48 (1.13-1.95 (teWaternaude et al., 2006)	-
Cumulative respirable quartz/silica dust	2	7	[1] OR=1.06, CI=1.01-1.08, P=0.005 (Carneiro et al., 2006) [2] OR=1.01, CI=0.99-1.03, P=0.012 (Carneiro et al., 2006) [c1]POR=1.47, CI=1.14-1.89 (teWaternaude et al., 2006)	[3]OR=1.04, CI=1.01-1.06, P=0.338 (Carneiro et al., 2006)
Average intensity of quartz/silica dust	1	4	[c1]POR=1.44, CI=1.11-1.87 (teWaternaude et al., 2006)	-
Continuity of silica exposure	1	4	[1]OR=6.42, CI=1.20-34.27, P=0.029 (Carneiro et al., 2006) [2]OR= 3.85, CI=1.07-13.93, P=0.040 (Carneiro et al., 2006) [3]OR=4.61, CI=1.14-18.71, P=0.032 (Carneiro et al., 2006)	-
Exposure duration	1	4	OR=2.07, CI=1.10-3.88, P=0.03 (Farazi & Jabbariasl, 2015)	-
Length of service in yrs. characteristics				
General in yrs.	3	11	OR=2.32, CI=1.32-4.10, P=0.004 (Farazi & Jabbariasl, 2015)	OR=1.03, CI=0.99-1.07 (Park et al., 2009) [c1]POR=1.31, CI=1.00-1.72 (teWaternaude et al., 2006)
0-4	1	4	-	IRR=1.8, CI=0.9-3.5 (Corbett et al., 2000)
10-19	2	7	[2]HR=2.1, CI=0.4-9.9 (Charalambous et al., 2008)	[1]HR=1.1, CI=0.4-3.2 (Charalambous et al., 2008) IRR=1.6, CI=1.0-2.5 (Corbett et al., 2000)
> 20	1	4	-	IRR=1.3, CI=0.8-2.3 (Corbett et al., 2000)
20-24 yrs.	1	4	[2]HR=3.0, CI=0.6-14.0 (Charalambous et al., 2008)	[1]HR=1.5, CI=0.5-4.2 (Charalambous et al., 2008)

≥ 25 yrs.	1	4	[2]HR=4.0, CI=0.9-17.9 (Charalambous et al., 2008)	[1]HR=1.5, CI=0.5-4.4 (Charalambous et al., 2008)
Underground work duration characteristics				
10-19yrs.	1	4	OR=1.1, CI=0.43-2.8, P=0.8 (Sonnenberg et al., 2000)	-
≥ 2yrs.	1	4	OR=3.2, CI=0.95-10.8, P=0.06 (Sonnenberg et al., 2000)	-
Surface work	1	4	IRR=0.5, CI=0.3-0.9 (Corbett et al., 2000)	-

Table 5 Genetic polymorphs Related to Silico-Tuberculosis/Silicosis and Tuberculosis

[7]

3.4 Diagnostic techniques and method of assessment for screening silico-tuberculosis

Three main diagnostic criteria were used to screen for silicosis and tuberculosis from the reviewed studies as per Table 6. Over 50% of the studies reported the use of medical or clinical history in the screening process (Carneiro et al., 2006; Cheraghvandi et al., 2014; Dixit & Dave, 2007; Farazi & Jabbariasl, 2015; Feng et al., 2014; Franzblau, 2018; Girdler-Brown et al., 2008; Hnizdo, 2000; Murlidhar, 2015; Oni & Ehrlich, 2015; Park et al., 2009; Qu et al., 2007; Ringshausen et al., 2013; Ross et al., 2010; Tse, 2014), while more than 60% described their diagnostic criteria using chest radiography (Charalambous et al., 2008; Churchyard, 2000; Corbett et al., 2004; Corbett

[7] Note (table 5). Abbreviations:

[c1]POR is odd prevalence ratio adjusted for age and smoking. [1]OR is the odds ratio for silicosis category 3. [2]OR is the odds ratio for either coalescence or large opacities. [3]OR is the odds ratio for TB. [6]OR is the odds ratio for $FEV_1 < 65\%$. [7]OR is the odds ratio for $FEV_1 < 80\%$. [1]HR for the hazard ratio for both HIV +ve and -ve participants. [2]HR is hazard ratio for HIV +ve sub-groups. [I]IRR is rate ratio for TB incidence. * for risk factors without a measure of association. NRAMP1 is natural resistance macrophage protein 1. iNOS is inducible nitric oxide synthase gene. TNF is tumor necrosis factor. (%) * is percentages are rounded. N* is number of studies.

et al., 2000; Ehrlich, 2011; Farazi & Jabbariasl, 2015; Franzblau, 2018; Girdler-Brown et al., 2008; Glynn et al., 2008; Hnizdo, 2000; Oni & Ehrlich, 2015; Park et al., 2009; Ringshausen et al., 2013; Ross et al., 2010; Sonnenberg et al., 2000; teWaternaude et al., 2006; Tse et al., 2007). Also, several studies used the sputum test to screen for tuberculosis (Corbett et al., 2004; Charalambous et al., 2001; Churchyard, 2000; Corbett et al., 2000; Dixit & Dave, 2007; Farazi & Jabbariasl, 2015; Feng et al., 2014; Glynn et al., 2008; Hnizdo, 2000; Moyo & Kgalamono, 2017; Murlidhar, 2015; Naidoo, 2005; Qu et al., 2007; Sonnenberg et al., 2000). Moreover, only a few studies used spirometry (Carneiro et al., 2006; Dixit & Dave, 2007; Farazi & Jabbariasl, 2015; Girdler-Brown et al., 2008; Naidoo, 2005; Park et al., 2009; Moyo & Kgalamono, 2017; Ehrlich, 2011), respiratory clinical examination (Dixit & Dave, 2007; Moyo & Kgalamono, 2017; Oni & Ehrlich, 2015; Park et al., 2009), high resolution computed tomography (Cheraghvandi et al., 2014; Oni & Ehrlich, 2015), differential diagnostics (Cheraghvandi et al., 2014; Moyo & Kgalamono, 2017), and self-reported history (teWaternaude et al., 2006; Carneiro et al., 2006; Churchyard, 2000).

Out of all the reviewed studies, only two reported on genotyping analysis for TB (Feng et al., 2014; Charalambous et al., 2008), whereby one study showed IS6110 genotype analysis (Charalambous et al., 2008) and the other reported MIRU-VNTR genotyping technique (Feng et al., 2014), respectively. Only three studies reported the use of occupational history in the diagnosis process (Moyo & Kgalamono, 2017; Naidoo, 2005; Tse et al., 2007), while one study reported CT Scan (Moyo & Kgalamono, 2017), Skiagram chest test (Dixit & Dave, 2007), Mantoux/tuberculin test (Dixit & Dave, 2007; Farazi & Jabbariasl, 2015), and IGRA (Ringshausen et al., 2013).

Several reviewed articles used the following assessment methods as presented in Table 7. Most of the studies reported using ILO criteria for chest radiography diagnostics (Carneiro et al., 2006; Charalambous et al., 2001; Charalambous et al., 2008; Churchyard, 2000; Corbett et al., 2004; Corbett et al., 2000; Ehrlich, 2011; Farazi & Jabbariasl, 2015; Franzblau, 2018; Girdler-Brown et al., 2008; Hnizdo, 2000; Murlidhar, 2015; Oni & Ehrlich, 2015; Park et al., 2009; Ringshausen et al., 2013; Ross et al., 2010; Sonnenberg et al., 2000; teWaternaude et al., 2006; Tse, 2014). Also, some studies used +ve smear for TB in sputum test diagnostics (Charalambous et al., 2001; Churchyard, 2000; Corbett et al., 2000; Dixit & Dave, 2007; Farazi & Jabbariasl, 2015; Glynn et al., 2008; Qu et al., 2007; Sonnenberg et al., 2000). A few studies assessed their diagnostics criteria using American Thoracic Society criteria (Farazi & Jabbariasl, 2015; Girdler-Brown et al., 2008; Naidoo, 2005; Park et al., 2009; Ringshausen et al., 2013), FEV_1 and FVC results (Ehrlich, 2011; Hnizdo, 2000; Moyo & Kgalamono, 2017; Park et al., 2009; Naidoo, 2005), occupational questionnaire (Carneiro et al., 2006; Tse et al., 2007), respiratory symptom questionnaire (Carneiro et al., 2006; Girdler-Brown et al., 2008; Park et al., 2009), and two reader evaluation (Charalambous et al., 2001; Churchyard, 2000; Moyo & Kgalamono, 2017; Naidoo, 2005; Sonnenberg et al., 2000). Additionally, two studies reported on using only National Institute for Occupational Safety and Health (NIOSH) B readers (Ehrlich, 2011; teWaternaude et al., 2006). In contrast, one study had either a mix of an experienced reader with a B reader for diagnostic evaluation or one experienced reader (Carneiro et al., 2006). Similarly, a few studies reported more than two reader evaluations (Feng et al., 2014; Franzblau, 2018; Girdler-Brown et al., 2008; Park et al., 2009). Only one article reported using Chinese criteria for silicosis (Qu et al., 2007).

Screening Tools Used to Diagnose Silico-Tuberculosis/Silicosis and Tuberculosis	N*	(%)*
Diagnostic tests		
Sputum test (smear/culture)	14	50
IS6110 genotyping analysis	1	4
MIRU-VNTR genotyping tool	1	4
Chest X Ray	6	21
Mini Chest X-Ray	1	4
Self-reported history	3	11
Occupational history	3	11
Medical/clinical history	15	54
Chest radiography	17	60
Lung function test/Spirometry	9	32
High resolution computed tomography (HRCT)	2	7
CT-Scan	1	4
Respiratory clinical examination	4	14
Mantoux test	1	4
Skiagram chest test	1	4
Tuberculin skin test (TST)	1	4
IGRA (QFT and/or T-SPOT)	1	4
Differential diagnostic tests	2	7

Table 6 Screening Tools Used to Diagnose Silico-Tuberculosis/Silicosis and Tuberculosis

[8]

[8] Note (table 6). Abbreviations:
N* is for number of studies. (%) * is percentages are rounded.

Method of Assessment	N*	(%)*
One experienced reader evaluation	2	7
Specialists' evaluation (number of readers not specified)	2	7
ILO classification (silicosis)	19	68
Culture +ve cases for TB	4	14
Culture +ve cases (TB or non-tuberculous mycobacteria (NTM) or Mixed infections of TB/NTM)	2	7
Smear +ve cases (TB)	8	29
History of TB cases	1	4
+ve smear/culture for TB cases	1	4
M. tuberculosis isolates	1	4
+ve TST cases	1	4
Two reader evaluation	5	18
Two reader evaluation (NIOSH B readers)	2	3
Three reader evaluation (One experienced and one B reader)	1	4
More than two reader evaluation	4	14
Chinese diagnostic criteria (silicosis)	1	4
Comparison of previous CT scans	1	4
In-depth interviews	1	4
Structured interviews	1	4
Occupational questionnaire	2	7
Respiratory symptom questionnaire	3	11
Brazilian guidelines (spirometry)	1	4
Strain identification using bands identity or differentiation	1	4
Genome variants identification	1	4
20mm induration within 72hrs	1	4
FEV_1 and FVC losses/results	5	18
American Thoracic Society criteria	5	18
WHO criteria	1	4
IFN-γ response of TB antigen minus nil control ≥0.35 IU/ml	1	4
≥6 SFCs	1	4

Table 7 Method of Assessment

3.5 Diagnostic techniques outcome

The term definition for disease varied among articles reviewed as some studies referred to the term as silicotuberculosis or silicosis and tuberculosis (refer to appendix 6, Table 2: Study results of detection of silico-tuberculosis, key findings, and limitation). Out of the twenty-eight articles reviewed, two studies reported on latent TB outcome (Farazi & Jabbariasl, 2015; Ringshausen et al., 2013). Most studies assessed silicosis by grading the stage of silicosis and examined tuberculosis outcome by smear/culture-positive cases by comparing HIV +ve and HIV -ve groups (Charalambous et al., 2001; Charalambous et al., 2008; Churchyard, 2000; Corbett et al., 2004; Corbett et al., 2000). A few studies reported on lung function loss (Ross et al., 2010; Park et al., 2009; Oni & Ehrlich, 2015; Naidoo, 2005; Moyo & Kgalamono, 2017; Hnizdo, 2000; Girdler-Brown et al., 2008). On the other hand, one study reported silico-tuberculosis qualitatively from miners who stated they had symptoms of TB and were usually told they had HIV and TB when they visited the mines hospital (Cairncross & Kisting, 2016). A few studies reported on the follow-up duration of participants diagnosed with silicosis and tuberculosis (Charalambous et al., 2001; Hnizdo, 2000; Oni & Ehrlich, 2015; Moyo & Kgalamono, 2017; Park et al., 2009).

3.5.1 Other relevant findings

The reviewed studies revealed other key findings (refer to appendix 6, Table 2: Study results of detection of silico-tuberculosis, key finding and limitation). Two studies reported TB outcome association with continued exposure to silica dust, and progressive silicosis by grading (Carneiro et al., 2006; Corbett et al., 2000). Similarly, one study reported an increase in TB prevalence associated with silica and dust

exposure despite the absence of silicosis among the non-silicotic group (teWaternaude et al., 2006). Only two studies reported on differential diagnostic outcomes (Moyo & Kgalamono, 2017; Cheraghvandi et al., 2014). One article revealed differentials for silicosis and multi-drug resistant TB using transbronchial lung biopsy (Cheraghvandi et al., 2014). The other study showed possible PTB reactivation and silicosis with PMF upon second reader evaluation (Moyo & Kgalamono, 2017). Also, only one study distinguished Mycobacterium *tuberculosis resistant strains* as higher in the silico-tuberculosis group than the PTB group (Feng et al., 2014). Importantly, only one study reported a case of suspected silicosis and confirmed tuberculosis in a child whose mother was a miner but refused to admit that she took the child to the mines (Murlidhar, 2015). This is the only study highlighting a case of "alleged child labor" and secondary silicotuberculosis in the findings.

3.6 Limitations reported in the published studies

Reviewed studies reported several limitations, and the significant setbacks reported revolved around a health worker effect, recall bias, diagnostic screening challenges, methodology, and sample-size (Carneiro et al., 2006; Charalambous et al., 2008; Churchyard, 2000; Ehrlich, 2011; Farazi & Jabbariasl, 2015; Franzblau, 2018; Hnizdo, 2000; Ross et al., 2010; Sonnenberg et al., 2000; teWaternaude et al., 2006; Tse, 2014).

Although most of the studies reported diagnostics outcomes, a few articles reported on some challenges with the diagnostic screening process or lack of specific assessments. One study acknowledged the absence of a GOLD standard for screening LTBI and challenges in distinguishing between MTB and NTM when using IGRAs

(Ringshausen et al., 2013). Another article revealed a lack of lung function assessments as a limit (Charalambous et al., 2001).

Additionally, another study reported that hard copy images were two-thirds the size of both film and soft copy, contributing to a loss of detection accuracy (Franzblau, 2018). Only two studies reported difficulties in diagnosing silico-tuberculosis (Churchyard, 2000; Farazi & Jabbariasl, 2015). And one of the two studies further showed similar radiographic presentations as a limitation (Churchyard, 2000).

CHAPTER 4

DISCUSSION

This scoping review mapped out studies related to silicotuberculosis among miners. The main objectives were to identify risk factors associated with silicotuberculosis and diagnostic techniques used to screen silicosis and tuberculosis. Also, we identified relevant findings and gaps in the reviewed literature to hence inform research and practice and expand further on the existing knowledge about silicotuberculosis.

4.1 Geographical distribution of reviewed articles

Although we did not limit the scope of our study selection criteria in low- and middle-income countries, the findings show that most of the published work was conducted among miners in Southern Africa and China. The geographical scope of our reviewed articles was limited. Other literature have shown that several low-income countries are engaged in mining like Ghana, Tanzania, Northern Nigeria, DR Congo, Mali, Uganda, and Burkina Faso (Basu et al., 2015; Bratveit, Moen, Mashalla, & Maalim, 2003; P. Gottesfeld, Tirima, Anka, Fotso, & Nota, 2019; Kayembe-Kitenge et al., 2020; Luis Sagaon-Teyssier et al., 2017; Mpagi, Ssamula, Ongode, Henderson, & Robinah, 2017; Porgo & Gokyay, 2017; Zhang et al., 2016). Yet, studies on silico-tuberculosis among miners in these countries is limited. Studies in those countries addressed various other issues related to miners, including the HIV prevalence among miners Luis Sagaon-Teyssier et al. (2017), respiratory outcomes like wheezing and

exposure to heavy metals in artisanal mines Keyembe-Kitenge et al. (2020) and women in mining (Mpagi, Ssamula, Ongode, Henderson, & Robinah, 2017).

4.2 Insurance status

Our findings revealed that only one study reported on the insurance status of the miners. In general, previous, and current literature have documented sufficient evidence to suggest that small-scale workers like sandblasters and stone miners exposed to silica dust lack insurance coverage like the social security system or medical schemes (Nandi, Dhatrak, & Sarkar, 2021; Demircigil et al. 2010). According to a recent study by Ohnishi, Tembo, Nakao, Matsuura, & Fujita (2021), 78.6% (n=158) of miners who were regular employees received sickness insurance compared to 47.8% of the temporary miners on a contract (n=55). Miners are predisposed to occupational diseases like silicotuberculosis which is debilitating and mine accidents. Hence, our findings provide a crucial insight to the role of insurance as a safety net for miners at risk of silicosis and tuberculosis.

4.3 Opium addiction

Our findings show that most studies lacked focus on opium addiction as a risk factor among miners. A recent analytical case-control study among pure opium addicts and controls revealed many pulmonary tuberculosis cases among opium addicts compared to the controls (Safari, Reazai, Tangestaninejad, Mafi, & Mousavi, 2016). Our reviewed literature lacks focus on miners and opium addiction, yet; current literature reveals tuberculosis infection among opium addicts. Further, opium is categorized as a group 1 carcinogen (Warnakulasuriya et al., 2020). These data

highlight that miners who are opium addicts are at a risk of pulmonary diseases like tuberculosis. According to our findings and current literature, there is a clear need for additional research to determine if opium addiction among miners is common around different mine settings and country context.

4.4 Occupational health and safety

NRAMP1 INT4 Genotypes were identified to be an occupational health and safety risk factor among miners by one study (Qu et al., 2007). Similarly, previous literature showed NRAMPI as an iron-regulatory gene that influences the course of certain infectious diseases like tuberculosis and HIV based on its allele variants (Canonne-Hergaux, Gruenheid, Govoni, & Gros, 1999; Joann & Andrew, 2006). In addition, a study showed how the NRAMPI polymorphism gene is a risk factor for tuberculosis among the pediatric population using a family-based association study (Malik et al., 2005). However, none of our reviewed literature have assessed on NRAMPI polymorphism gene as a risk factor among child miners.

Due to social, human, and safety characteristics, potential occupational risk factors continue to exist among workers exposed to silica dust, as revealed in our findings (Cairncross & Kisting, 2016; Tse et al., 2007; Moyo & Kgalamono, 2017). The lack of frequent use of respiratory protective personnel equipment and poor mechanical ventilation remains daunting not only among miners, but other workers exposed to silica (Başaran et al., 2003). Additionally, continuous exposure to silica dust and cumulative respirable quartz was a risk factor for silicotuberculosis outcomes (teWaternaude et al., 2006; Carneiro et al., 2006). These findings suggest that miners are still exposed to silica dust exposure. Previous studies indicate that industrialized

countries have more strict regulations and standards compared to less industrialized countries (Maciejewska, 2008; Gottesfeld, 2015; Gottesfeld, Tirima, Anka, Fotso, & Nota, 2019).

4.5 Diagnostic techniques, method of assessment, and results

4.5.1 Chest radiography evaluators

The findings revealed a lack of trained physicians certified by NIOSH (B reader) assessments while using chest radiography techniques since a few studies reported having a B reader evaluator (Ehrlich, 2011; teWaternaude et al., 2006). In contrast, some studies had a mix of B readers and non-B reader evaluators (Carneiro et al., 2006). These findings align with the previously recommended surveillance approach by the National Institute of Occupational Safety and Health (2014), which requires a trained physician certified by NIOSH, to interpret radiographs. Our findings shed light on the lack of adequate B readers within the screening process. The lack of B readers signifies a risk on accurate radiograph interpretations. The World Health Organization (2016) has shown that most physicians in low-income countries lack training on the diagnosis and management of occupational diseases like silicotuberculosis.

4.5.2 Occupational history

The standard methods of screening silicosis among workers included medical history, normal chest X-ray, and spirometry (National Institute of Occupational Safety and Health, 2014). However, a few studies reported on the occupational history of patients (Moyo & Kgalamono, 2017; Naidoo, 2005; Tse et al., 2007). Two studies also documented using an occupational questionnaire (Carneiro et al., 2006; Tse et al.,

2007). Apart from its use as an assessment tool for silicotuberculosis the occupational questionnaire reveals the history of silica exposure in detail, ventilation techniques in place for dust extraction, and other individual protective measures used (Fernández Álvarez et al., 2015). Strategies for silica dust prevention or lack thereof are documented in an occupational questionnaire which shows if prevention measures are in place or need further attention.

4.5.3 IGRAs and TST diagnostic techniques

A few studies reported using IGRAs and TST (Ringshausen et al., 2013; Farazi & Jabbariasl, 2015). Additionally, we noted only two studies reporting latent tuberculosis outcomes (Farazi & Jabbariasl, 2015; Ringshausen et al., 2013). Previous literature warrants the need to address latent tuberculosis (World Health Organization, 2016). This is important because 1.7 billion people are infected with latent tuberculosis, of which 11% have isoniazid-resistant strains due to previous isoniazid preventive treatment (Houben & Dodd, 2016). However, the literature reveals that such prevention mechanisms failed among miners relating to isoniazid prevention treatment (Konečny P, 2019; Churchyard, 2014). Hence, our findings show a gap concerning detecting latent tuberculosis among miners. It is important to note that this gap may be due to the lack of a Gold Standard on diagnosing latent tuberculosis infection (Salgame et al., 2015). Also, detecting tuberculosis among certain groups like children is commonly obtained using TST and IGRAs (Piccini, Chiappini, Tortoli, de Martino, & Galli, 2014).

4.5.4 Differential diagnostics and follow-ups

Our findings showed only two studies reporting genotyping analysis of tuberculosis (Feng et al., 2014; Charalambous et al., 2008). A few studies reported differential diagnosis in their reports (Cheraghvandi et al., 2014; Moyo & Kgalamono, 2017; Feng et al., 2014). Such results reveal the advanced and evolved nature of diagnostics relating to tuberculosis screening and available differentials for silicotuberculosis detection. Additionally, we noted only one study distinguishing Mycobacterium *tuberculosis resistant strains* as higher in the silico-tuberculosis group than the PTB group (Feng et al., 2014). Previous literature depicts the widened threat of multi-drug resistant tuberculosis due to the presence of drug-resistant strains among populations infected with latent tuberculosis (Houben & Dodd, 2016). Similarly, other studies show a slight increase in multi-drug-resistant tuberculosis in industrialized country settings (Knuchel, Lador, Soccal, & Janssens, 2016). However, our findings reveal a lack of focus on screening for tuberculosis strain characteristics among miners.

Additionally, our findings revealed silicotuberculosis outcome was reported based on the number of positive smear/culture cases, grading of silicosis, and lung function loss. However, our results showed very few studies reporting follow-up duration upon positive smear/culture cases and grading of silicosis outcome. Follow-up of miners leads to early onset of treatment and delays the progression of further complications (Milovanović A, 2011). Nevertheless, these findings may be due to the nature of study designs, as most studies were cross-sectional.

4.6 Gaps identified from reviewed literature

4.6.1 Sex and gender analysis

The reviewed studies lacked focus in assessing sex differences among miners exposed to silica dust. Yet a study assessing tuberculosis among populations attending a hospital revealed that tuberculosis drug complications was common among women compared to their male counterparts (Safwat et al., 2019). Also, women showed a fill up of fluid within the linings of the lungs (pleural effusion), skin and stomach complications after receiving anti-tuberculous treatment and this led to loss of follow up in most females (Safwat et al., 2019). Other studies indicate a clear need to further investigate biological differences between men and women populations infected with HIV in relation to drug tolerance and viral resistance to line-one regimens (Godfrey, 2020).

Gender-based cultural differences may exacerbate silicotuberculosis outcome in women compared to men miners. It is widely known that women take on the role of caregivers in the family. Equally important, men are usually considered the providers in a typical household. However, due to a patriarchal system in most low- and middle-income countries, women may face an increased burden when accessing healthcare services for the treatment of tuberculosis compared to men. A study by Gradmann & Manyazewa (2020) showed that TB disease is accompanied by mental distress due to the exhaustive treatment and stigma associated with drug resistant tuberculosis. Also, in the cases of multi-drug resistant tuberculosis, patients are strictly isolated in hospitals and denied access with the outside world or community (Gradmann & Manyazewa, 2020). Psychological stress is also rampant in women due to fear of community alienation (Gyimah & Dako-Gyeke, 2019). Patients with tuberculosis are usually

abandoned by their family, while others undergo self-denial of the disease to cope with mental stress (Gradmann & Manyazewa, 2020). In the context of our reviewed studies, women are understudied in the mine setting. Yet, other studies that mainly focused on mercury and lead exposure within the gold mining sector, have assessed child labor and women's role in mines (Hayes, 2012; Hilson, 2012; S. Allen Counter, 2003) . The statistics on women engagement in mine work differ throughout the world (Jennifer J. Hinton, 2003). In Asia, women contribute to less than 10% of the mining workforce, while in Latin America and Africa, they constitute up to 50% of the mining workforce (Jennifer J. Hinton, 2003). In their study, Kabongo & Naidoo (2021) found that 553 women were engaged in both underground mine work and surface mine work within the South Africa Gold mines (n=553). Hence, if women are infected with tuberculosis, the disease may deter them from accessing the direct observed therapy services (DOT) in fear of isolation from their families and children as caregivers.

Directly observed therapy is a form of medical monitoring whereby patients infected with drug-resistant tuberculosis are observed by the healthcare worker in clinics to ensure they swallow their pills (Gradmann; & Manyazewa, 2020). DOT is a rigid program that lacks the counseling component for patients and results in non-adherence to prescribed medications (Gradmann; & Manyazewa, 2020). The disease is accompanied by mental distress due to the exhaustive treatment and stigma associated with drug-resistant tuberculosis. In multi-drug-resistant tuberculosis cases, patients are strictly isolated in hospitals and not allowed access to the outside world or community. The World Health Organization (2007) mandates that a trained healthcare worker undertake DOT to ensure patients with tuberculosis do not develop drug resistance tuberculosis due to non-adherence to the treatment. Also, the report noted that family

observation lacks effectiveness in controlling TB at a large scale and due to patriarchal structures in most of the communities (World Health Organization, 2007). However, cultural differences among men and women exist, hindering the effectiveness of the DOT program.

4.6.2 Child labor

It is recognized that child labor exists in small-scale mines (International Labor Organization, 2005; International Commission on Occupational Health, 2018). Children engage in hazardous tasks not limited to digging, crushing, removing waste from mines, and mining in general, which is considered by the International Labor Organization (2019) as the worst forms of child labor. Previous literature has shown that children are at increased risk of contracting meningitis due to tuberculosis infection (Piccini, Chiappini, Tortoli, de Martino, & Galli, 2014). A recent scoping review mapping out health studies in artisanal and small scale mining has shown a few health studies investigating women, children and pregnant mothers as working in the mines (Cossa et al., 2021). Further, mercury exposure was the most investigated health topic and little attention was drawn to infectious diseases like HIV, tuberculosis and malaria (Cossa et al., 2021). There's need for further research on infectious diseases like silicotuberculosis among vulnerable groups within the mines.

4.6.3 Gaps in Mine-settings

Few of the studies we reviewed delved further to report whether the mines were large-scale or small-scale. Only two articles specified large-scale mines (Franzblau, 2018) or small-scale mines (Tse et al., 2007). Increased attention to documenting mine settings would significantly add further to the research as previous literature indicates

small-scale artisanal mines are risky because the sector is unregulated and has low levels of mechanization unlike the large-scale mine sectors (Bratveit et al., 2003; P. Gottesfeld, Andrew, & Dalhoff, 2015; Mpagi et al., 2017; P. Gottesfeld, Tirima, Anka, Fotso, & Nota, 2019; Basu et al., 2015). Further, over 40.5 million miners are engaged in artisanal and small-scale mining compared to only 7 million within the large-scale mines (International Institute for Sustainable Development, 2019).

Previous studies focusing on artisanal and small-scale mines assessed heavy metal exposure among small-scale miners (Kayembe-Kitenge et al., 2020 & S. Allen Counter, 2003). However, in a recent review investigating poverty and health impacts in artisanal and small-scale mining world-wide, Schwartz, Lee, & Darrah (2021) documented various determinants of health affecting miners. Schwartz, Lee, & Darrah, (2021) has shown occupational health risks exist among miners including silica dust exposure and silicosis from reviewed studies (Burki, 2019; Chi Chiu Leung, 2012; Cowie, 1994). Thus, further studies are required to investigate silicotuberculosis in small-scale mines.

4.6.4 Gaps in the interplay of iron status and tuberculosis outcome

4.6.3.1 Alcohol and iron status

The influence of alcohol intake and resulting iron loading was nearly uncharted territory among our reviewed literature as only one study reported alcohol behavior as a risk factor. Previous literature showed that more than two alcoholic drinks are associated with increased iron levels among the general United States adult populations (Ioannou, 2004). Similarly, a recent study conducted among 877 South African women revealed an increase in iron levels ($p<0.0001$) among women who reported drinking

(Schutte et al., 2019). In addition, studies show a link between increased iron levels and infectious disease outcomes (Murray, 1978; Joann, 2006; Haider et al., 2019). Our reviewed literature lacked a focus on alcohol intake within an iron status approach. Hence, no conclusions were made regarding the role of iron status among alcohol-consuming miners.

4.6.4.2 HIV and iron status

Human Immunodeficiency Virus (HIV) is a risk factor for silico-tuberculosis among miners (Rees, Murray, Nelson, & Sonnenberg, 2010; Utembe, Faustman, Matatiele, & Gulumian, 2015). Findings of our review showed that HIV infection as a risk factor was based on characteristics like CD4 cell count, the period of HIV infection, and sputum test outcome. On the other hand, the literature reveals the role of HIV in predisposed tuberculosis outcomes (Ghio, 2009). Low CD4 cell count results in a high viral load among HIV groups, increasing iron levels, thus increasing the risk of acquiring bacterial infections (Joann and Andrew, 2006). Importantly, our reviewed articles' findings suggest a lack of focus on iron status among HIV predisposed miners. It remains unclear from our reviewed articles if miners were under any HIV treatment or iron supplementation. Previous studies have shown HIV patients with low CD4 counts of either <350cells/μL or <200cells/ μL were put on HIV treatment and given iron supplementation based on their blood iron levels (Haider et al., 2019). Such findings indicate increased attention is required among HIV miners on whether they are given iron supplementation, increasing iron levels among miners at risk of tuberculosis. Other studies have shown that increased iron levels result in the formation of reactive oxygen species (Ganz, 2015).

Further, the generation of reactive oxygen species by macrophage cells is iron-dependent (Drakesmith & Prentice, 2012). Thus, the interplay between the iron status of an individual and silica dust exposure may lead to tuberculosis infection or activation of latent tuberculosis. Hence, our findings suggest a further consideration in research related to HIV and iron status among miners at risk of infectious diseases like tuberculosis.

4.6.4.3 Mechanism of action (interplay of iron status and silica dust exposure)

Reviewed articles were deficient in reporting the pathophysiological mechanism through which silica dust exposure results in either tuberculosis infection or reactivation of previous latent tuberculosis. Despite other research indicating pathways of induced lung inflammation via silica-dust exposure, studies lack clear evidence on silica-dust induced pathway in reactivating latent tuberculosis from an iron-status approach (Balmes 1990; Schapira, 1995; Churg, 1996; Mossman & Churg, 1998; Costantini, 2011; Chitra Thakur, 2015; Borm 2018). Our findings are in line with a recent study by Lanzafame and Vento (2021) that describes the pathophysiology mechanism as incompletely identified. However, the interplay between iron status and silica dust exposure in the activation of tuberculosis deserves further exploration in future research. Because iron is a trace metal, it induces oxidative stress (Ghio, 2009). Previous studies showed that there is an increased risk of respiratory infections associated with the iron levels of an individual (Wander, Shell-Duncan, & Brindle, 2017). Other studies indicate that increased iron levels in the body facilitate increased iron within the macrophages that results in fenton reaction pathways which produces free radicals that injure cells (Ganz & Nemeth, 2005). Silica dust exposure among miners who may have increased iron levels due to different reasons, could be exposed

to free radicals due to increased iron interacting with silica particles within the macrophages. There is need to address the issue of iron status among miners exposed to silica dust in future research.

4.6.4.4 Bi-directional relationship between silica dust exposure and tuberculosis infection

Miners exposed to silica dust are at a higher risk for contracting tuberculosis (Barboza, 2008; Cowie, 1994; teWaternaude et al., 2006). Given substantial evidence on the increased risk of contracting tuberculosis if exposed to silica dust, there is need to investigate further if previous infection with the tuberculosis bacteria increases the risk of tuberculosis reinfection. A bi-directional approach entails investigating miners with previously healed TB scars and eventual infectious disease. However, our findings suggest that other risk factors in play may contribute to this bi-directional relationship. HIV infection weakens the immune system and may increase the risk to tuberculosis infection (Ahmed, Rakshit, & Vyakarnam, 2016). Additionally, previous literature highlights that iron levels in the body were shown to contribute to infectious diseases inclusive of tuberculosis (Ghio, 2009; Joann & Andrew, 2006). Current literature lacks this phenomena on bi-directional realtionship between silica dust exposure and tuberculosis infection or reactivation. Further investigation of this phenomenon may offer insights in understanding silicotuberculosis related pathways and may provide more insight for the protection of vulnerable workers.

4.7 Limitations reported in the published studies

Our findings revealed healthy worker effect, recall bias, and sample size as setbacks for some studies. These findings may be due to the nature of the study design,

such as retrospective cohorts, cross-sectional and prospective studies. Additionally, a healthy worker effect finding suggests selection bias due to occupational settings.

Nevertheless, our findings showed a few studies reporting the challenges in diagnosing silicotuberculosis. Challenges noted included: similar radiographic presentations as the limiting case, challenges distinguishing between tuberculosis and non-tuberculous mycobacteria when using IGRAs, lack of lung function assessments, and lack of a GOLD standard in screening latent tuberculosis. These findings are in line with previous studies denoting that misdiagnosis of patients may lead later to further respiratory complications (Milovanović A, 2011; Sureka, Mittal, Mittal, & Thukral, 2013). Additionally, previous studies reveal that radiological alterations caused by tuberculosis and silicosis may be indistinguishable (Konečny P, 2019). Similarly, previous literature showed that silicosis fibrosis might prevent the tubercle bacilli from being discharged during sputum testing (World Health Organization, 2016; Achkar, Lawn, Moosa, Wright, & Kasprowicz, 2011).

4.8 Strengths and limitations of this scoping review

The scoping review has several strengths. Importantly, and to the best of our knowledge, this is the first scoping review mapping out available literature on risk factors associated with silicotuberculosis and diagnostic techniques used to screen for the disease. Further, we conducted a standardized method of review using the PRISMA-ScR protocol. Finally, we conducted a search strategy using more than two databases. While our study highlighted important findings, limitations need to be considered. First, some of the reviewed articles had a mixed population characteristic. Secondly, the selection criteria of articles were limited to only those published in English. Hence, the

selection criteria may have excluded exploring other studies published in a different language that may have tackled the concept of silicotuberculosis. Finally, the scoping review lacked the consultation phase as part of the methodology. However, (Arksey & O'Malley, 2005) suggested the consultation phase, whereby stakeholders and consumers contribute more information to the scoping review findings. However, this phase is optional in a scoping study.

4.9 Recommendations and Implication for future research

4.9.1. Legal framework in low and middle income countries

There is an increased need for countries to either set national standards or comply with existing occupational health standards to prevent silica dust exposure. The legal framework from a national context will necessitate the enforcement of regulations in artisanal and small-scale mines. The National Institute of Occupational Health and Safety overview of risk management entails eliminating a hazard from the workplace as the highest form of regulatory control (National Institute of Occupational Health, 2015). Without national standards, miners will continue to be exposed to silica dust as a hazard because controls to eliminate dust exposure are absent in small-scale mines. Instituting a legal framework informs various stakeholders such as governments, mine owners, and mine employees. The International Labor Organization has emphasized the importance of engaging these stakeholders in labor-related standards (International Labor Organization, 2021).

4.9.2 Capacity building

There is a need for increased training of physicians to qualify as B-readers as mandated by NIOSH. Also, differentials, a GOLD standard to test for latent tuberculosis, and occupational questionnaires deserve further attention when assessing silico-tuberculosis outcomes among mines. The World Health Organization has set out to eliminate tuberculosis by acknowledging the need for increased financial investment in TB (Reid et al., 2019). This is particularly crucial in low- and middle-income countries. Further, this study sets forth a call of action to WHO to strengthen their efforts in eliminating silica exposure among miners. Developing countries need to set out financial commitments towards acquiring new diagnostics that facilitate preventative screening, which entails diagnosing patients for latent tuberculosis before progression to active disease to end the tuberculosis pandemic.

4.9.3 Future work

Further investigations on risk factors such as HIV and alcohol intake are required among miners by assessing their iron status. Such future research may be relevant to inform stakeholders such as public health officials engaged in behavioral change and iron supplementation programs. Also, our findings indicate a need for further research on the pathophysiological mechanisms related to silica dust exposure within an iron status approach. We anticipate the results of this study will shape further research on the role of increased iron levels in facilitating susceptibility to tuberculosis infection and reactivation of latent tuberculosis among miners. Given the substantial evidence on silicotic miners having tuberculosis, there is need to investigate further a bi-directional relationship between silica dust exposure and tuberculosis infection.

In this scoping review, we identified gaps in research namely the lack of gender and sex integration in the reviewed studies. Gender considerations in research and policies can be incorporated through training programs for researchers and reviewers (Van Hagen, Muntinga, Appelman, & Verdonk, 2021). Therefore, there is a dire need for further research exploring both the biological and cultural differences among men and women exposed to silica dust.

CHAPTER 5

CONCLUSION

This scoping review highlights substantial gaps in the reviewed literature. It outlines a series of recommendations urgently needed to inform research and practice. The study assessed numerous risk factors associated with silicotuberculosis among miners and diagnostic techniques used to screen for the disease. The study highlighted deficits in certified physicians and a lack of a GOLD standard for screening latent tuberculosis infection within the mine environment. Hence, capacity building in developing countries is needed to prioritize training among physicians and financial investment in diagnostic tools that screen for latent tuberculosis. Also, the study highlighted gaps relating to informal mines. The findings address an urgent need for legal frameworks in low- and middle-income countries to enforce preventive health and safety measures among small-scale mines. The results indicate a need for future work investigating iron status among miners. This scoping review identified a lack of articles exploring iron status among miners who were HIV positive and those who were alcohol drinkers. HIV infected persons receiving iron supplementation are at risk of increased iron levels while alcohol drinkers have elevated iron levels that leads to increased risk of free iron to pathogens leading to infections. In addition, Silica dust exposure in the presence of increased iron levels may lead to tuberculosis infection or reinfection. Given the substantial deficit in studies assessing sex/gender differences within mine settings, there is also an urgent research imperative for future studies to incorporate sex/gender analysis in their investigations among miners.

APPENDIX

Appendix 1. PRISMA-SCR CHECKLIST

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	vi
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	vi-vii
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	1-13
Objectives	4	Provide an explicit statement of the questions and objectives being addressed regarding their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	13
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	14
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	14-15
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	15-18
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	67-68

Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	16-17
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	17
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	17
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	18
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	20-21
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	84-105
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that was charted that relate to the review questions and objectives.	21-49
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	21-49
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	50-59
Limitations	20	Discuss the limitations of the scoping review process.	60
Conclusions	21	Provide a general interpretation of the results concerning the review questions and objectives, as well as potential implications and/or next steps.	60-63

FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	N/A

Adopted source: (Tricco et al., 2018)

Appendix 2. SEARCH STRATEGY

Date of Searches: 3 March 2020
Database 1: MEDLINE Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily
Search Strategy: --- exp TUBERCULOSIS, PULMONARY/ OR (((consumption OR pthis?s OR tuberculos?s) adj1 (pulmonar* OR lung*)) OR silicotuberculos?s OR silico-tuberculos?s).mp. OR BRONCHOSCOPY/ OR ((bronchoscop* OR broncho-scop* OR (fiberoptic adj bronchoscop*) OR (bronchial OR laryngotracheo OR trachea)) adj endoscop*).mp. OR exp BIOPSY, NEEDLE/ OR ((aspiration OR needl* OR puncture* OR core OR fine OR (bone adj marrow)) adj biops*).mp. OR (endoscopic adj1 (aspiration* OR needl*)).mp. OR MASS CHEST X-RAY/ OR (mass adj (x-ray* OR xray)).mp. OR BRONCHOALVEOLAR LAVAGE FLUID/ OR (((bronch* OR lung* OR pulmonary OR alveolar) adj1 fluid*) OR BALF).mp. OR TOMOGRAPHY, X-RAY COMPUTED/ OR ((beam* OR comput* OR assist* OR axial OR electron*) adj1 (tomogra* adj transmission*)).mp. OR ((cat or ct) adj1 (xray OR x-ray)).mp. OR tomodensitometr*.mp. OR FOUR-DIMENSIONAL COMPUTED TOMOGRAPHY/ OR ((4d OR (four adj dimensional)) adj1 (ct OR (cat adj scan*))).mp. OR POSITRON EMISSION TOMOGRAPHY COMPUTED TOMOGRAPHY/ OR ((ct OR scan*) adj tomogra*).mp. OR SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY COMPUTED TOMOGRAPHY/ OR (single adj photon* adj emission* adj comput* adj tomogra*).mp. OR exp SPIROMETRY/ OR (spirometr* OR bronchospirometr* OR (maneuver* adj valsalva*) OR (breathing adj1 work*)).mp. OR (sputum adj (test* OR culture*)).mp. OR ((acid adj fast adj (bacill* OR stain*)) or AFB).mp. OR exp FORCED EXPIRATORY VOLUME/ OR ((forced adj vital adj capacit* adj timed) OR (Forced adj Expiratory adj Volume*) OR fevt OR FVC OR FEV1).mp. OR (((maxim* OR voluntary) adj1 capacit*) OR mvv or mbc).mp. OR RESPIRATORY FUNCTION TESTS/ OR (test* adj1 (lung* OR respirat* or pulmunar*)).mp. OR PULMONARY DIFFUSING

CAPACITY/ OR ((pulmonar* OR lung*) adj diffus* adj capacit*).mp. OR PULMONARY GAS EXCHANGE/ OR (((pulmonar* OR lung*) adj gas* adj exchang*) OR (ventilation adj perfusion adj Ratio)).mp. OR ((blood adj gas* adj analys?s) OR (oximetr* adj pulse) OR (oxygen* adj saturat*) OR (arter* adj oxygen*)).mp. OR POLYMERASE CHAIN REACTION/ OR ((anchor* OR nest* OR invers*) adj (polymerase adj chain adj reaction*)).mp. OR AMPLIFIED FRAGMENT LENGTH POLYMORPHISM/ OR ((amplify* adj fragment* adj length adj polymorph* adj analys?s) OR aflp).mp. OR POLYMORPHISM, RESTRICTION FRAGMENT LENGTH/ OR ((restrict* adj fragment* adj length adj (polymorph* OR pcr)) OR rflp*).mp. OR DNA FINGERPRINTING/ OR ((dna OR (deoxyribonucleic adj acid)) adj1 (print* OR profil* OR typing*)).mp. OR LIGASE CHAIN REACTION/ OR (liga?e* adj chain adj reaction*).mp. OR CONTRAST MEDIA/ OR ((radio-contrast OR radiocontrast OR contrast OR radiopaque OR radio-paque) adj (media* OR medium)).mp. OR "EXTRAVASATION OF DIAGNOSTIC AND THERAPEUTIC MATERIALS"/ OR (extravasation adj1 (material* OR media* OR medium)).mp. OR X-RAYS/ OR ((grenz OR roentgen) adj ((x adj ray*) OR x-ray* OR x-radiation)).mp. OR RADIOGRAPHY/ OR (diagnostic* adj1 (radiolog* OR roentgenography OR radiograph*)).mp. OR TECHNOLOGY, RADIOLOGIC/ OR (radiolog* adj technolog*).mp. OR LUNG INJURY/ OR (pulmonar* OR lung*) adj1 injur*).mp. OR ACUTE LUNG INJURY/ OR PNEUMOCONIOSIS/ OR pneumoconios?s.mp. OR exp SILICOSIS/ OR (((si OR quartz OR cristobalite OR tridymite) adj dust) OR anthracosilicos?s OR silicos?s).mp. OR PULMONARY FIBROSIS/ OR ((alveoli* OR fibros* OR lung* OR hamman OR pulmonar*) adj1 syndrom*).mp. OR TUBERCULIN TEST/ OR (tuberculin adj test*).mp. OR INTERFERON-GAMMA RELEASE TESTS/ OR (((IGRA OR T) adj spot) OR QuantiFERON OR PPD OR Mantoux OR TST OR (protein adj derivative* adj test*) OR (Interfer* adj gam?a adj release adj (test* OR assay*))).mp. OR INTERFERON-GAMMA/ OR (interferon* adj (immune* OR type ii OR gamma) adj test*).mp. OR ENZYME-LINKED IMMUNOSORBENT ASSAY/ OR ((enzyme adj1 assay) OR ELISA).mp. OR MINERS/ OR (mine adj worker*).mp. OR exp MINING/ OR (miner? OR mining? OR (mine adj1 (worker? OR labo?r)) OR coal OR uranium).mp.
Database 2: EMBASE

miner?:ti,ab,kw OR mining?:ti,ab,kw OR ((mine NEAR/1 (worker? OR labo?r)):ti,ab,kw) OR coal:ti,ab,kw OR uranium:ti,ab,kw
OR 'mining'/de OR (mine NEXT/1 worker*):ti,ab,kw OR 'miner'/de AND ((enzyme NEAR/1 assay):ti,ab,kw) OR elisa:ti,ab,kw OR 'enzyme
linked immunosorbent assay'/de OR ((interferon* NEXT/1 immune* NEXT/1 test*):ti,ab,kw) OR ((interferon* NEXT/1 type):ti,ab,kw)
OR ((ii NEXT/1 test*):ti,ab,kw) OR ((interferon* NEXT/1 gamma NEXT/1 test*):ti,ab,kw) OR 'gamma interferon'/de OR (((igra OR t)
NEXT/1 spot):ti,ab,kw) OR quantiferon:ti,ab,kw OR ppd:ti,ab,kw OR mantoux:ti,ab,kw OR tst:ti,ab,kw OR
((protein NEXT/1 derivative* NEXT/1 test*):ti,ab,kw) OR ((interfer* NEXT/1 gam?a NEXT/1 release NEXT/1 (test* OR assay*)):ti,ab,kw)
OR 'interferon gamma release assay'/de OR (tuberculin NEXT/1 test*):ti,ab,kw OR 'tuberculin test'/de
OR ((alveoli* OR fibros* OR lung* OR hamman OR pulmonar*) NEAR/1 syndrom*):ti,ab,kw OR 'lung fibrosis'/de
OR (((si OR quartz OR cristobalite OR tridymite) NEXT/1 dust):ti,ab,kw) OR anthracosilicos?s:ti,ab,kw OR silicos?s:ti,ab,kw OR 'silicosis'/de
OR pneumoconios?s:ti,ab,kw OR 'pneumoconiosis'/de OR 'acute lung injury'/de OR ((pulmonar* OR lung*) NEAR/1 injur*):ti,ab,kw
OR 'lung injury'/de OR (radiolog* NEXT/1 technolog*):ti,ab,kw OR 'radiology'/de OR (diagnostic* NEAR/1
OR (radiolog* OR roentgenography OR radiograph*)):ti,ab,kw OR 'radiography'/de OR ((grenz NEXT/1 (xray* OR xradiation)):ti,ab,kw) OR
((roentgen NEXT/1 (xray* OR xradiation)):ti,ab,kw) OR 'x ray'/de OR (extravasation NEAR/1 (material* OR media* OR medium)):ti,ab,kw
OR 'contrast medium extravasation'/de OR (('radio contrast' OR radiocontrast OR contrast OR radiopaque OR 'radio paque') NEXT/1
(media* OR medium)):ti,ab,kw OR 'contrast medium'/de OR (liga?e* NEXT/1 chain NEXT/1 reaction*):ti,ab,kw OR 'ligase chain reaction'/de
OR ((dna NEXT/1 (print* OR profil* OR typing*)):ti,ab,kw) OR ((deoxyribonucleic NEXT/1 acid NEXT/1 print*):ti,ab,kw) OR
((deoxyribonucleic NEXT/1 acid NEXT/1 profil*):ti,ab,kw) OR ((deoxyribonucleic NEXT/1 acid NEXT/1 typing*):ti,ab,kw) OR 'dna
fingerprinting'/de OR ((restrict* NEXT/1 fragment* NEXT/1 length NEXT/1 (polymorph* OR pcr)):ti,ab,kw) OR rflp*:ti,ab,kw OR 'restriction
fragment length polymorphism'/exp OR ((amplify* NEXT/1 fragment* NEXT/1 length NEXT/1 polymorph* NEXT/1 analys?s):ti,ab,kw)
OR aflp:ti,ab,kw OR 'amplified fragment length polymorphism'/de
OR ((anchor* NEXT/1 polymerase NEXT/1 chain NEXT/1 reaction*):ti,ab,kw) OR
((nest* NEXT/1 polymerase NEXT/1 chain NEXT/1 reaction*):ti,ab,kw) OR

((invers* NEXT/1 polymerase NEXT/1 chain NEXT/1 reaction*):ti,ab,kw) OR 'polymerase chain reaction'/de
OR ((blood NEXT/1 gas* NEXT/1 analys?s):ti,ab,kw) OR ((oximetr* NEXT/1 pulse):ti,ab,kw) OR ((oxygen* NEXT/1 saturat*):ti,ab,kw) OR
((arter* NEXT/1 oxygen*):ti,ab,kw) OR (((pulmonar* OR lung*) NEXT/1 gas* NEXT/1 exchang*):ti,ab,kw) OR
((ventilation NEXT/1 perfusion NEXT/1 ratio):ti,ab,kw) OR 'lung gas exchange'/de OR ((pulmonar* OR lung*)
NEXT/1 diffus* NEXT/1 capacit*):ti,ab,kw OR
'lung diffusion capacity'/de OR (test* NEAR/1 (lung* OR respirat* OR pulmunar*)):ti,ab,kw OR 'lung function test'/de OR
(((maxim* OR voluntary) NEAR/1 capacit*):ti,ab,kw) OR mvv:ti,ab,kw OR mbc:ti,ab,kw
OR ((forced NEXT/1 vital NEXT/1 capacit* NEXT/1 timed):ti,ab,kw) OR ((forced NEXT/1 expiratory NEXT/1 volume*):ti,ab,kw)
OR fevt:ti,ab,kw OR fvc:ti,ab,kw OR fev1:ti,ab,kw OR 'forced expiratory volume'/de OR
afb:ti,ab,kw OR ((acid NEXT/1 fast NEXT/1 stain*):ti,ab,kw) OR ((acid NEXT/1 fast NEXT/1 bacill*):ti,ab,kw) OR
(sputum NEXT/1 (test* OR culture*)):ti,ab,kw OR
spirometr*:ti,ab,kw OR bronchospirometr*:ti,ab,kw OR ((maneuver* NEXT/1 valsalva*):ti,ab,kw) OR ((breathing NEAR/1 work*):ti,ab,kw)
OR 'spirometry'/de OR
(single NEXT/1 photon* NEXT/1 emission* NEXT/1 comput* NEXT/1 tomogra*):ti,ab,kw OR 'positron emission tomography-computed
tomography'/de OR ((4d OR 'four dimension*') NEXT/1 (cat OR ct)):ti,ab,kw 'four dimensional computed tomography'/de
OR tomodensitometr*:ti,ab,kw OR ((cat OR ct) NEAR/1 (xray OR 'x ray')):ti,ab,kw OR
((beam* NEAR/1 tomogra* NEXT/1 transmission*):ti,ab,kw) OR ((comput* NEAR/1 tomogra* NEXT/1 transmission*):ti,ab,kw) OR
((assist* NEAR/1 tomogra* NEXT/1 transmission*):ti,ab,kw) OR ((axial NEAR/1 tomogra* NEXT/1 transmission*):ti,ab,kw) OR
((electron* NEAR/1 tomogra* NEXT/1 transmission*):ti,ab,kw) OR 'x-ray computed tomography'/de
OR (((bronch* OR lung* OR pulmonary OR alveolar) NEAR/1 fluid*):ti,ab,kw) OR balf:ti,ab,kw OR 'bronchoalveolar lavage fluid'/de
OR (mass NEXT/1 xray*):ti,ab,kw OR (endoscopic NEAR/1 (aspiration* OR needl*)):ti,ab,kw

OR (bone NEXT/1 marrow NEXT/1 biops*):ti,ab,kw OR ((aspiration OR needl* OR puncture* OR core OR fine) NEXT/1 biops*):ti,ab,kw OR 'biopsy needle'/exp OR (fiberoptic NEXT/1 bronchoscop* NEXT/1 endoscop*):ti,ab,kw OR ((bronchoscop* OR bronchial OR laryngotracheo OR trachea) NEXT/1 endoscop*):ti,ab,kw OR 'bronchoscopy'/de OR (((consumption OR pthis?s OR tuberculos?s) NEAR/1 (pulmonar* OR lung*)):ti,ab,kw) OR silicotuberculos?s:ti,ab,kw OR 'silico tuberculos?s':ti,ab,kw OR 'lung tuberculosis'/de
Database 3: CINAHL
TI ((miner# OR mining# OR (mine N1 (worker# or labo#r)) OR coal OR uranium)) OR AB ((miner# OR mining# OR (mine N1 (worker# or labo#r)) OR coal OR uranium)) OR MW ((miner# OR mining# OR (mine N1 (worker# or labo#r)) OR coal OR uranium)) OR (MH "Mining") OR TI (mine W1 worker*) OR AB (mine W1 worker*) OR MW (mine W1 worker*) OR TI (((enzyme N1 assay) OR ELISA)) OR AB (((enzyme N1 assay)) OR MW (((enzyme N1 assay) OR ELISA)) OR (MH "Enzyme-Linked Immunosorbent Assay") OR TI (((interferon* W1 (immune* OR type ii OR gamma) W1 test*)) OR AB (((interferon* W1 (immune* OR type ii OR gamma) W1 test*)) OR MW (((interferon* W1 (immune* OR type ii OR gamma) W1 test*)) OR TI ((((IGRA OR T) W1 spot) OR QuantiFERON OR PPD OR Mantoux OR TST OR (protein W1 derivative* W1 test*) OR (Interfer* W1 gam#a W1 release W1 (test* OR assay*)))) OR AB ((((IGRA OR T) W1 spot) OR QuantiFERON OR PPD OR Mantoux OR TST OR (protein W1 derivative* W1 test*) OR (Interfer* W1 gam#a W1 release W1 (test* OR assay*)))) OR MW ((((IGRA OR T) W1 spot) OR QuantiFERON OR PPD OR Mantoux OR TST OR (protein W1 derivative* W1 test*) OR (Interfer* W1 gam#a W1 release W1 (test* OR assay*)))) OR (MH "Interferon-Gamma Release Tests") OR TI (tuberculin W1 test*) OR AB (tuberculin W1 test*) OR MW (tuberculin W1 test*) OR (MH "Tuberculin Test") OR TI (((alveoli* OR fibros#s OR lung* OR hamman OR pulmonar*) N1 syndrom*)) OR AB (((alveoli* OR fibros#s OR lung* OR hamman OR pulmonar*) N1 syndrom*)) OR MW (((alveoli* OR fibros#s OR lung* OR hamman OR pumonar*) N1 syndrom*)) OR (MH "Pulmonary Fibrosis") OR TI ((((si OR quartz OR cristobalite OR tridymite) N1 dust) OR anthracosilicos#s OR silicos#s)) OR AB ((((si OR quartz OR cristobalite OR tridymite) N1 dust) OR anthracosilicos#s OR silicos#s)) OR MW ((((si OR quartz OR cristobalite OR tridymite) N1 dust) OR anthracosilicos#s OR silicos#s)) OR TI

pneumoconios#s OR AB pneumoconios#s OR MW pneumoconios#s OR (MH "Pneumoconiosis") OR (MH "Acute Lung Injury") OR TI (((pulmonar* OR lung*) W1 injur*)) OR AB (((pulmonar* OR lung*) W1 injur*)) OR MW (((pulmonar* OR lung*) W1 injur*)) OR (MH "Lung Injury") OR TI ((radiolog* W1 technolog*)) OR AB ((radiolog* W1 technolog*)) OR MW ((radiolog* W1 technolog*)) OR (MH "Technology, Radiologic") OR TI ((diagnostic* N1 (radiolog* OR roentgenography OR radiograph*))) OR AB ((diagnostic* N1 (radiolog* OR roentgenography OR radiograph*))) OR MW ((diagnostic* N1 (radiolog* OR roentgenography OR radiograph*))) OR (MH "Radiography") OR TI (((grenz OR roentgen) W1 ((x W1 ray* OR x-ray* OR x-radiation#))) OR AB (((grenz OR roentgen) W1 ((x W1 ray* OR x-ray* OR x-radiation#))) OR MW (((grenz OR roentgen) W1 ((x W1 ray* OR x-ray* OR x-radiation#))) OR (MH "X-Rays") OR TI ((extravasation N1 (material* OR medi# OR medium))) OR AB ((extravasation N1 (material* OR medi# OR medium))) OR MW ((extravasation N1 (material* OR medi# OR medium))) OR (MH "Extravasation of Diagnostic and Therapeutic Materials") OR TI (((radio-contrast OR radiocontrast OR contrast OR radiopaque OR radio-paque) W1 (media* OR medium))) OR AB (((radio-contrast OR radiocontrast OR contrast OR radiopaque OR radio-paque) W1 (media* OR medium))) OR MW (((radio-contrast OR radiocontrast OR contrast OR radiopaque OR radio-paque) W1 (media* OR medium))) OR (MH "Contrast Media") OR TI (liga#e* W1 chain W1 reaction*) OR AB (liga#e* W1 chain W1 reaction*) OR MW (liga#e* W1 chain W1 reaction*) OR TI (((dna OR (deoxyribonucleic W1 acid)) N1 (print* OR profil* OR typing*))) OR AB (((dna OR (deoxyribonucleic W1 acid)) N1 (print* OR profil* OR typing*))) OR MW (((dna OR (deoxyribonucleic W1 acid)) N1 (print* OR profil* OR typing*))) OR (MH "DNA Fingerprinting") OR TI (((restrict* W1 fragment* W1 length W1 (polymorph* OR pcr)) OR rflp*)) OR AB (((restrict* W1 fragment* W1 length W1 (polymorph* OR pcr)) OR rflp*)) OR MW (((restrict* W1 fragment* W1 length W1 (polymorph* OR pcr)) OR rflp*)) OR TI (((amplify* W1 fragment* W1 length W1 polymorph* W1 analys#s) OR aflp)) OR AB (((amplify* W1 fragment* W1 length W1 polymorph* W1 analys#s) OR aflp)) OR MW (((amplify* W1 fragment* W1 length W1 polymorph* W1 analys#s) OR aflp)) OR TI ((((anchor* OR nest* OR invers*) W1 (polymerase W1 chain W1 reaction*)) OR pcr)) OR AB ((((anchor* OR nest* OR invers*) W1 (polymerase W1 chain W1 reaction*)) OR pcr)) OR MW ((((anchor* OR nest* OR invers*) W1 (polymerase W1 chain W1 reaction*)) OR pcr)) OR (MH "Polymerase Chain Reaction") OR TI (((blood W1 gas* W1 analys#s) OR (oximetr* W1 pulse) OR (oxygen* W1 saturat*) OR (arter* W1 oxygen*))) OR AB (((blood W1 gas* W1 analys#s) OR (oximetr* W1 pulse) OR

(oxygen* W1 saturat*) OR (arter* W1 oxygen*))) OR MW (((blood W1 gas* W1 analys#s) OR (oximetr* W1 pulse) OR (oxygen* W1 saturat*) OR (arter* W1 oxygen*))) OR TI ((((pulmonar* OR lung*) W1 gas* W1 exchang*) OR (ventilation W1 perfusion W1 Ratio))) OR AB ((((pulmonar* OR lung*) W1 gas* W1 exchang*) OR (ventilation W1 perfusion W1 Ratio))) OR MW ((((pulmonar* OR lung*) W1 gas* W1 exchang*) OR (ventilation W1 perfusion W1 Ratio))) OR (MH "Pulmonary Gas Exchange+") OR TI (((pulmonar* OR lung*) W1 diffus* W1 capacit*)) OR AB (((pulmonar* OR lung*) W1 diffus* W1 capacit*)) OR MW (((pulmonar* OR lung*) W1 diffus* W1 capacit*)) OR TI (test* N1 (lung* OR respirat* OR pulmunar*))) OR AB (test* N1 (lung* OR respirat* OR pulmunar*))) OR MW (test* N1 (lung* OR respirat* OR pulmunar*))) OR (MH "Respiratory Function Tests") OR TI ((((maxim* OR voluntary) N1 capacit*) OR mvv OR mbc)) OR AB ((((maxim* OR voluntary) N1 capacit*) OR mvv OR mbc)) OR MW ((((maxim* OR voluntary) N1 capacit*) OR mvv OR mbc)) OR TI (((forced W1 vital W1 capacit* W1 timed) OR (Forced W1 Expiratory W1 Volume*) OR fevt OR FVC OR FEV1)) OR AB (((forced W1 vital W1 capacit* W1 timed) OR (Forced W1 Expiratory W1 Volume*) OR fevt OR FVC OR FEV1)) OR MW (((forced W1 vital W1 capacit* W1 timed) OR (Forced W1 Expiratory W1 Volume*) OR fevt OR FVC OR FEV1)) OR (MH "Forced Expiratory Volume") OR TI (((acid W1 fast W1 (bacill* OR stain*)) OR AFB)) OR AB (((acid W1 fast W1 (bacill* OR stain*)) OR AFB)) OR MW (((acid W1 fast W1 bacill* OR stain*)) OR AFB)) OR TI ((sputum W1 (test* OR culture*))) OR AB ((sputum W1 (test* OR culture*))) OR MW ((sputum W1 (test* OR culture*))) OR TI ((spirometr* OR bronchospirometr* OR (maneuver* W1 valsalva*) OR (breathing N1 work*))) OR AB ((spirometr* OR bronchospirometr* OR (maneuver* W1 valsalva*) OR (breathing N1 work*))) OR MW ((spirometr* OR bronchospirometr* OR (maneuver* W1 valsalva*) OR (breathing N1 work*))) OR (MH "Spirometry") OR TI (((ct OR scan*) OR (single W1 photon* W1 emission* W1 comput* W1 tomogra*))) OR AB (((ct OR scan*) OR (single W1 photon* W1 emission* W1 comput* W1 tomogra*))) OR MW (((ct OR scan*) OR (single W1 photon* W1 emission* W1 comput* W1 tomogra*))) OR (MH "Tomography, Emission-Computed, Single-Photon") OR TI (((ct OR scan*) N1 tomogra*)) OR AB (((ct OR scan*) N1 tomogra*)) OR MW (((ct OR scan*) N1 tomogra*)) OR TI (((4d OR (four W1 dimensional)) N1 (ct OR (cat W1 scan*))) OR AB (((4d OR (four W1 dimensional)) N1 (ct OR (cat W1 scan*))) OR MW (((4d OR (four W1 dimensional)) N1 (ct OR (cat W1 scan*))) OR TI tomodensitometr* OR AB tomodensitometr* OR MW tomodensitometr* OR TI (((cat OR ct) N1 (xray OR x-ray))) OR AB (((cat OR ct) N1 (xray OR x-ray))) OR MW (((cat OR ct) N1 (xray OR

x-ray))) OR TI (((beam* OR comput* OR assist* OR axial OR electron*) N1 (tomogra* W1 transmission*))) OR AB (((beam* OR comput* OR assist* OR axial OR electron*) N1 (tomogra* W1 transmission*))) OR MW (((beam* OR comput* OR assist* OR axial OR electron*) N1 (tomogra* W1 transmission*))) OR (MH "Tomography, X-Ray Computed") OR TI ((((bronch* OR lung* OR pulmonary OR alveolar) N1 fluid*) OR BALF)) OR AB ((((bronch* OR lung* OR pulmonary OR alveolar) N1 fluid*) OR BALF)) OR MW ((((bronch* OR lung* OR pulmonary OR alveolar) N1 fluid*) OR BALF)) OR (MH "Bronchoalveolar Lavage") OR TI ((mass W1 (x-ray* OR xray*))) OR AB ((mass W1 (x-ray* OR xray*))) OR MW ((mass W1 (x-ray* OR xray*))) OR TI ((endoscopic N1 (aspiration* OR needl*))) OR AB ((endoscopic N1 (aspiration* OR needl*))) OR MW ((endoscopic N1 (aspiration* OR needl*))) OR TI (((aspiration or needl* or puncture* or core or fine or (bone W1 marrow)) W1 biops*)) OR AB (((aspiration or needl* or puncture* or core or fine or (bone W1 marrow)) W1 biops*)) OR MW (((aspiration or needl* or puncture* or core or fine or (bone W1 marrow)) W1 biops*)) OR (MH "Biopsy, Needle") OR TI (((bronchoscop* OR broncho-scop* OR (fiberoptic W1 bronchoscop*) OR (bronchial OR laryngotracheo OR trachea)) W1 endoscop*)) OR AB (((bronchoscop* OR broncho-scop* OR (fiberoptic W1 bronchoscop*) OR (bronchial OR laryngotracheo OR trachea)) W1 endoscop*)) OR MW (((bronchoscop* OR broncho-scop* OR (fiberoptic W1 bronchoscop*) OR (bronchial OR laryngotracheo OR trachea)) W1 endoscop*)) OR (MH "Bronchoscopy") OR TI ((((consumption or pthis?s or tuberculos?s) N1 (pulmonar* or lung*)) or silicotuberculos?s or silico-tuberculos?s)) OR AB ((((consumption or pthis?s or tuberculos?s) N1 (pulmonar* or lung*)) or silicotuberculos?s or silico-tuberculos?s)) OR MW ((((consumption or pthis?s or tuberculos?s) N1 (pulmonar* or lung*)) or silicotuberculos?s or silico-tuberculos?s)) OR (MH "Tuberculosis, Pulmonary")

Database 4: GEOREF

TI ((miner# OR mining# OR (mine N1 (worker# or labo#r)) OR coal OR uranium)) OR AB ((miner# OR mining# OR (mine N1 (worker# or labo#r)) OR coal OR uranium)) OR TI (mine W1 worker*) OR AB (mine W1 worker*) OR TI (((enzyme N1 assay) OR ELISA)) OR AB (((enzyme N1 assay) OR ELISA)) OR DE "ELISA" OR TI (((interferon* W1 (immune* OR type ii OR gamma) W1 test*)) OR AB (((interferon* W1 (immune* OR type ii OR gamma) W1 test*)) OR TI ((((IGRA OR T) W1 spot) OR QuantiFERON OR PPD OR Mantoux

OR TST OR (protein W1 derivative* W1 test*) OR (Interfer* W1 gam#a W1 release W1 (test* OR assay*)))) OR AB ((((IGRA OR T) W1 spot) OR QuantiFERON OR PPD OR Mantoux OR TST OR (protein W1 derivative* W1 test*) OR (Interfer* W1 gam#a W1 release W1 (test* OR assay*)))) OR TI (tuberculin W1 test*) OR AB (tuberculin W1 test*) OR TI (((alveoli* OR fibros#s OR lung* OR hamman OR pulmonar*) N1 syndrom*)) OR AB (((alveoli* OR fibros#s OR lung* OR hamman OR pulmonar*) N1 syndrom*)) OR TI ((((si OR quartz OR cristobalite OR tridymite) W1 dust) OR anthracosilicos#s OR silicos#s)) OR AB ((((si OR quartz OR cristobalite OR tridymite) W1 dust) OR anthracosilicos#s OR silicos#s)) OR TI pneumoconios#s OR AB pneumoconios#s OR TI (((pulmonar* OR lung*)N1 injur*)) OR AB (((pulmonar* OR lung*) N1 injur*)) OR TI ((radiolog* W1 technolog*)) OR AB ((radiolog* W1 technolog* OR TI ((diagnostic* N1 (radiolog* OR roentgenography OR radiograph*))) OR AB ((diagnostic* N1 (radiolog* OR roentgenography OR radiograph*)) **S31** DE "radiography" OR TI (((grenz OR roentgen) W1 ((x W1 ray*) OR x-ray* OR x-radiation#))) OR AB (((grenz OR roentgen) W1 ((x W1 ray*) OR x-ray* OR x-radiation#))) OR DE "X-rays" OR TI (((radio-contrast OR radiocontrast OR contrast OR radiopaque OR radio-paque) W1 (media* OR medium))) OR AB (((radio-contrast OR radiocontrast OR contrast OR radiopaque OR radio-paque) W1 (media* OR medium))) OR TI (liga#e* W1 chain W1 reaction*) OR AB (liga#e* W1 chain W1 reaction*) OR TI (((dna OR (deoxyribonucleic W1 acid)) N1 (print* OR profil* OR typing*))) OR AB (((dna OR (deoxyribonucleic W1 acid)) N1 (print* OR profil* OR typing*))) OR TI (((restrict* W1 fragment* W1 length W1 (polymorph* OR pcr)) OR rflp*)) OR AB (((restrict* W1 fragment* W1 length W1 (polymorph* OR pcr)) OR rflp*)) OR TI (((amplify* W1 fragment* W1 length W1 polymorph* W1 analys#s) OR aflp)) OR AB (((amplify* W1 fragment* W1 length W1 polymorph* W1 analys#s) OR aflp)) OR TI ((((anchor* OR nest* OR invers*) W1 (polymerase W1 chain W1 reaction*)) OR pcr)) OR AB ((((anchor* OR nest* OR invers*) W1 (polymerase W1 chain W1 reaction*)) OR pcr)) OR TI (((blood W1 gas* W1 analys#s) OR (oximetr* W1 pulse) OR (oxygen* W1 saturat*) OR (arter* W1 oxygen*))) OR AB (((blood W1 gas* W1 analys#s) OR (oximetr* W1 pulse) OR (oxygen* W1 saturat*) OR (arter* W1 oxygen*))) OR TI ((((pulmonar* OR lung*) W1 gas* W1 exchang*) OR (ventilation W1 perfusion W1 Ratio))) OR AB ((((pulmonar* OR lung*) W1 gas* W1 exchang*) OR (ventilation W1 perfusion W1 Ratio))) OR TI (((pulmonar* OR lung*) W1 diffus* W1 capacit*)) OR AB (((pulmonar* OR lung*) W1 diffus* W1 capacit*)) OR TI ((test* N1 (lung* OR respirat* OR pulmunar*))) OR AB ((test* N1 (lung* OR respirat* OR pulmunar*))) OR TI ((((maxim* OR voluntary) N1 capacit*) OR mvv OR mbc))

OR AB ((((maxim* OR voluntary) N1 capacit*) OR mvv OR mbc)) OR TI (((forced W1 vital W1 capacit* W1 timed) OR (Forced W1 Expiratory W1 Volume*) OR fevt OR FVC OR FEV1)) OR AB (((forced W1 vital W1 capacit* W1 timed) OR (Forced W1 Expiratory W1 Volume*) OR fevt OR FVC OR FEV1)) OR TI (((acid W1 fast W1 (bacill*OR stain*)) OR AFB)) OR AB (((acid W1 fast W1 (bacill*OR stain*)) OR AFB)) OR TI ((sputum W1 (test* OR culture*))) OR AB ((sputum W1 (test* OR culture*))) OR TI ((spirometr* OR bronchospirometr* OR (maneuver* W1 valsalva*) OR (breathing N1 work*))) OR AB ((spirometr* OR bronchospirometr* OR (maneuver* W1 valsalva*) OR (breathing N1 work*))) OR TI (((ct OR scan*) OR (single W1 photon* W1 emission* W1 comput* W1 tomogra*))) OR AB (((ct OR scan*) OR (single W1 photon* W1 emission* W1 comput* W1 tomogra*))) OR TI (((ct OR scan*) N1 tomogra*)) OR AB (((ct OR scan*) N1 tomogra*)) OR TI (((4d OR (four W1 dimensional)) N1 (ct OR (cat W1 scan*))) OR AB (((4d OR (four W1 dimensional)) N1 (ct OR (cat W1 scan*))) OR TI tomodensitometr* OR AB tomodensitometr* OR TI (((cat OR ct) W1 (xray OR x-ray))) OR AB (((cat OR ct) W1 (xray OR x-ray))) OR TI (((beam* OR comput* OR assist* OR axial OR electron*) N1 (tomogra* W1 transmission*))) OR AB (((beam* OR comput* OR assist* OR axial OR electron*) N1 (tomogra* W1 transmission*))) OR DE "computed tomography" OR TI ((((bronch* OR lung* OR pulmonary OR alveolar) N1 fluid*) OR BALF)) OR AB ((((bronch* OR lung* OR pulmonary OR alveolar) N1 fluid*) OR BALF)) OR TI ((mass W1 (x-ray* OR xray*))) OR AB ((mass W1 (x-ray* OR xray*))) OR TI ((endoscopic N1 (aspiration* OR needl*))) OR AB ((endoscopic N1 (aspiration* OR needl*))) OR TI (((aspiration OR needl* OR puncture* OR core OR fine OR (bone W1 marrow)) W1 biops*)) OR AB (((aspiration OR needl* OR puncture* OR core OR fine OR (bone W1 marrow)) W1 biops*)) OR TI (((bronchoscop* OR broncho-scop* OR (fiberoptic W1 bronchoscop*) OR (bronchial OR laryngotracheo OR trachea)) W1 endoscop*)) OR AB (((bronchoscop* OR broncho-scop* OR (fiberoptic W1 bronchoscop*) OR (bronchial OR laryngotracheo OR trachea)) W1 endoscop*)) OR TI ((((consumption OR pthis#s OR tuberculos#s) N1 (pulmonar* OR lung*)) OR silicotuberculos#s OR silico-tuberculos#s)) OR AB ((((consumption OR pthis#s OR tuberculos#s) N1 (pulmonar* OR lung*)) OR silicotuberculos#s OR silico-tuberculos#s))
Database 5: COCHRANE LIBRARY

MeSH descriptor: [Tuberculosis, Pulmonary] explode all trees OR ((((consumption or pthis?s or tuberculos?s) NEAR/1 (pulmonar* or lung*)) or silicotuberculos?s or silico-tuberculos?s)):ti,ab,kw OR MeSH descriptor: [Bronchoscopy] this term only OR (((bronchoscop* or broncho-scop* or (fiberoptic NEXT/1 bronchoscop*) or (bronchial or laryngotracheo or trachea)) NEXT/1 endoscop*)):ti,ab,kw OR MeSH descriptor: [Biopsy, Needle] explode all trees OR (((aspiration or needl* or puncture* or core or fine or (bone NEXT/1 marrow)) NEXT/1 biops*)):ti,ab,kw OR ((endoscopic NEAR/1 (aspiration* or needl*))):ti,ab,kw OR MeSH descriptor: [Mass Chest X-Ray] this term only OR ((mass NEXT/1 (x-ray* or xray))):ti,ab,kw OR MeSH descriptor: [Bronchoalveolar Lavage Fluid] this term only OR ((((bronch* or lung* or pulmonary or alveolar) NEAR/1 fluid*) or BALF)):ti,ab,kw OR MeSH descriptor: [Tomography, X-Ray Computed] this term only OR (((beam* or comput* or assist* or axial or electron*) NEAR/1 (tomogra* NEXT/1 transmission*))):ti,ab,kw OR (((cat or ct) NEAR/1 (xray or x-ray))):ti,ab,kw OR (tomodensitometr*):ti,ab,kw OR MeSH descriptor: [Four-Dimensional Computed Tomography] this term only OR (((4d or (four NEXT/1 dimensional)) NEAR/1 (ct or (cat NEXT/1 scan*)))):ti,ab,kw OR MeSH descriptor: [Positron Emission Tomography Computed Tomography] this term only OR (((ct or scan*) NEXT/1 tomogra*)):ti,ab,kw OR MeSH descriptor: [Single Photon Emission Computed Tomography Computed Tomography] this term only OR ((single NEXT/1 photon* NEXT/1 emission* NEXT/1 comput* NEXT/1 tomogra*)):ti,ab,kw OR MeSH descriptor: [Spirometry] explode all trees OR ((spirometr* or bronchospirometr* or (maneuver* NEXT/1 valsalva*) or (breathing NEAR/1 work*))):ti,ab,kw OR ((sputum NEXT/1 (test* or culture*))):ti,ab,kw OR (((acid NEXT/1 fast NEXT/1 (bacill* or stain*)) or AFB)):ti,ab,kw OR MeSH descriptor: [Forced Expiratory Volume] this term only OR (((forced NEXT/1 vital NEXT/1 capacit* NEXT/1 timed) or (Forced NEXT/1 Expiratory NEXT/1 Volume*) or fevt or FVC or FEV1)):ti,ab,kw OR ((((maxim* or voluntary) NEAR/1 capacit*) or mvv or mbc)):ti,ab,kw OR MeSH descriptor: [Respiratory Function Tests] this term only OR ((test* NEAR/1 (lung* or respirat* or pulmunar*))):ti,ab,kw OR MeSH descriptor: [Pulmonary Diffusing Capacity] this term only OR (((pulmonar* or lung*) NEXT/1 diffus* NEXT/1 capacit*)):ti,ab,kw OR MeSH descriptor: [Pulmonary Gas Exchange] explode all trees OR ((((pulmonar* or lung*) NEXT/1 gas* NEXT/1 exchang*) or (ventilation NEXT/1 perfusion NEXT/1 Ratio))):ti,ab,kw OR (((blood NEAR/ gas* NEXT/1 analys?s) or (oximetr* NEXT/1 pulse) or (oxygen* NEXT/1 saturat*) or (arter* NEXT/1 oxygen*))):ti,ab,kw OR MeSH descriptor: [Polymerase Chain Reaction] this term only OR (((anchor* or nest* or invers*) NEXT/1 (polymerase NEXT/1 chain NEXT/1 reaction*))):ti,ab,kw OR (((amplify* NEXT/1

fragment* NEXT/1 length NEXT/1 polymorph* NEXT/1 analys?s) or aflp)):ti,ab,kw OR MeSH descriptor: [Polymorphism, Restriction Fragment Length] this term only OR (((restrict* NEXT/1 fragment* NEXT/1 length NEXT/1 (polymorph* or pcr)) or rflp*)):ti,ab,kw OR MeSH descriptor: [DNA Fingerprinting] this term only OR (((dna or (deoxyribonucleic NEXT/1 acid)) NEXT/1 (print* or profil* or typing*))):ti,ab,kw OR MeSH descriptor: [Ligase Chain Reaction] this term only OR ((liga?e* NEXT/1 chain NEXT/1 reaction*)):ti,ab,kw OR MeSH descriptor: [Contrast Media] this term only OR (((radio-contrast or radiocontrast or contrast or radiopaque or radio-paque) NEXT/1 (media* or medium))):ti,ab,kw OR MeSH descriptor: [Extravasation of Diagnostic and Therapeutic Materials] this term only OR ((extravasation NEAR/1 (material* or media* or medium))):ti,ab,kw OR MeSH descriptor: [X-Rays] this term only OR (((grenz or roentgen) NEXT/1 ((x NEXT/1 ray*) or x-ray* or x-radiation))):ti,ab,kw OR MeSH descriptor: [Radiography] this term only OR ((diagnostic* NEAR/1 (radiolog* or roentgenography or radiograph*))):ti,ab,kw OR MeSH descriptor: [Technology, Radiologic] this term only OR ((radiolog* NEXT/1 technolog*)):ti,ab,kw OR MeSH descriptor: [Lung Injury] this term only OR (((pulmonar* or lung*) NEAR/1 injur*)):ti,ab,kw OR MeSH descriptor: [Acute Lung Injury] this term only OR MeSH descriptor: [Pneumoconiosis] this term only OR (pneumoconios?s):ti,ab,kw OR MeSH descriptor: [Silicosis] explode all trees OR ((((si or quartz or cristobalite or tridymite) NEXT/1 dust) or anthracosilicos?s or silicos?s)):ti,ab,kw OR MeSH descriptor: [Pulmonary Fibrosis] this term only OR (((alveoli* or fibros* or lung* or hamman or pulmonar*) NEAR/1 syndrom*)):ti,ab,kw OR MeSH descriptor: [Tuberculin Test] this term only OR ((tuberculin NEXT/1 test*)):ti,ab,kw OR MeSH descriptor: [Interferon-gamma Release Tests] this term only OR ((((IGRA or T) NEXT/1 spot) or QuantiFERON or PPD or Mantoux or TST or (protein NEXT/1 derivative* NEXT/1 test*) or (Interfer* NEXT/1 gam?a NEAR/ release NEXT/1 (test* or assay*)))):ti,ab,kw OR MeSH descriptor: [Interferon-gamma] this term only OR ((interferon* NEXT/1 (immune* or type ii or gamma) NEXT/1 test*)):ti,ab,kw OR MeSH descriptor: [Enzyme-Linked Immunosorbent Assay] this term only OR ((enzyme NEAR/1 assay) or ELISA)):ti,ab,kw OR ((mine NEXT/1 worker*)):ti,ab,kw OR ((miner? or mining? or (mine NEAR/1 (worker? or labo?r)) or coal or uranium)):ti,ab,kw
Grey source 1: GOOGLE SCHOLAR
Allintitle: silico-tuberculosis

Year limit: 2000-2020
Grey source 2: SCIENCE.GOV
Title search: silico-tuberculosis AND Miner* Year limit: 2000-2020
Grey source 3: WHO GLOBAL INDEX MEDICUS
Title search: silico-tuberculosis Year limit:2000-2020 Language limit: English

SILICO-TUBERCULOSIS AMONG MINERS: PROTOCOL FOR SCOPING REVIEW

Title and abstract screening guide

1. **Is the study design dealing with primary data?**

(*Studies involving randomized clinical trials, non-randomized clinical trials, case-control, cohort and cross-sectional studies, case studies, and qualitative studies)*

☐ NO → Exclude.

☐ Yes, or uncertain → go to the next question.

2. **Does the study population consist of miners?**

(*Studies involving miners with no age restriction within the coal, gold, quartz/cristobalite/tridymite, uranium mines or any mines with silica dust or silica-dust mixtures*)

☐ NO → Exclude.

☐ Yes, or uncertain → go to the next question.

3. **Is the occupational exposure related to silica-dust?**

☐ NO → Exclude.

☐ Yes, or uncertain → go to the next question.

4. **Is the intervention involving diagnostic techniques to screen for silico-tuberculosis?**

☐ NO → Exclude.

☐ Yes, or uncertain → Get full text.

Appendix 3. TITLE AND ABSTRACT SCREENING TOOL

Appendix 4. FULL TEXT SCREENING FORM

SILICO-TUBERCULOSIS AMONG MINERS: PROTOCOL FOR SCOPING REVIEW

Full text screening guide

1. **Is the study design dealing with primary data?**

(*Studies involving randomized clinical trials, non-randomized clinical trials, case-control, cohort and cross-sectional studies, case studies, and qualitative studies)*

☐ NO → Exclude and justify in excel.

☐ Yes or uncertain → go to the next question.

2. **Does the study population consist of miners?**

(*Studies involving miners with* ***no age restriction*** *within the coal, gold, quartz/cristobalite/tridymite, uranium mines or any mines with silica dust or silica-dust mixtures*)

☐ NO → Exclude and justify in excel.

☐ Yes or uncertain → go to the next question.

3. **Is the occupational exposure related to silica-dust?**

☐ NO → Exclude and justify in excel.

☐ Yes, or uncertain → go to the next question.

4. **Is the intervention involving diagnostic techniques to screen for silico-tuberculosis?**

☐ NO → Exclude and justify in excel.

☐ Yes, or uncertain → Get full text.

5. **Is the health outcome of interest silico-tuberculosis?**

☐ NO → Exclude and justify in excel.

☐ Yes, or uncertain → Get full text.

Reason for exclusion (please check):

1. Study design not randomized clinical trials, non-randomized clinical trials, case-control, cohort and cross-sectional studies, case studies, and qualitative studies.

2. Study population not miners.

3. Occupational exposure not related to silica-dust.

4. Study intervention not involving diagnostic techniques that screen for silico-tuberculosis.

5. Study outcome of interest is not silico-tuberculosis.

Appendix 5. Inter-rater agreement and kappa score

Inter-rater agreement			Reviewer2Linda		Total
			1.00	2.00	
Reviewer1Elizabeth	Include	Count	108	2	110
		Expected Count	2.9	107.1	110.0
		% within Reviewer1Elizabeth	98.2%	1.8%	100.0%
		% within Reviewer2Linda	78.3%	0.0%	2.1%
		% of Total	2.1%	0.0%	2.1%
	Exclude	Count	30	5035	5065
		Expected Count	135.1	4929.9	5065.0
		% within Reviewer1Elizabeth	0.6%	99.4%	100.0%
		% within Reviewer2Linda	21.7%	100.0%	97.9%
		% of Total	0.6%	97.3%	97.9%
Total		Count	138	5037	5175
		Expected Count	138.0	5037.0	5175.0
		% within Reviewer1Elizabeth	2.7%	97.3%	100.0%
		% within Reviewer2Linda	100.0%	100.0%	100.0%
		% of Total	2.7%	97.3%	100.0%

Symmetric Measures (Kappa Score)

		Value	Asymptotic Standard Error[a]	Approximate T[b]	Approximate Significance
Measure of Agreement	Kappa	.868	.023	62.852	.000
N of Valid Cases		5175			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

Appendix 6. Data abstraction tables

Table 1: General study characteristics, study population, risk factors and diagnostic techniques for screening silico-tuberculosis

First Author, Year, Country	**Study design**	**Study population 1.Population (sample-size) 2.Mean age 3.Sex 4.Migrant status 5.Insurance sta**	**Significant Risk factors (measure of association, confidence interval, P-value)**	**Non-significant Risk factors (measure of association, confidence interval, P-value)**	**Mine-setting 1.Type 2.Scale 3.Method**	**Exposure Assessed 1.Type 2.Duration (yrs.) 3.Concentratio n**	**Diagnostic test**	**Method of Assessment**	**Differential diagnostics**
Cairncross, 2016, South Africa [1]	Case-study	1.Mixed population (22) 2.NR 3.NR 4.Internal 5.NR	NR	NR	1.Gold/Platinum 2.NR 3.Underground/Roc k drilling/Open cast	1.Dust 2.NR 3.NR	1.Self-reporting	1.In-depth interviews	NR
Carneiro, 2006, Brazil (Carneiro et al., 2006)	Retrospective study	1.Gold miners (140) 2.59.3 3.NR 4.external 5.NR	Cumulative silica exposure I_{EX} [1]OR=1.06, CI=1.01-1.08, P=0.005 [2]OR=1.04, CI=1.01-1.06, P=0.012 Skin color [1]OR= 19.99, CI=3.05-131.16, P=0.002 [2]OR=5.5,1 CI=1.25-24.38, P=0.024	Cumulative silica exposure I_{EX} [3]OR=1.01, CI=0.99-1.03, P=0.338 Skin color [3]OR=1.58 CI=038-6.570, p=0.529	1.Gold 2.NR 3.Underground	1.Dust/ silica 2.6-45 3.NR	1.Chest X Ray 2.Clinical history 3.Spirometry	1. X-ray quality Three independent reader (one experienced and one a B reader) 2. ILO criteria 3. Occupational questionnaire 4. +ve TB cases from history 5. Respiratory symptom questionnaire 6. Brazilian guidelines for spirometry	NR

			Continuity of silica exposure [1]OR=6.42, CI=1.20-34.27, P=0.029 [2]OR=3.85, CI=1.07-13.93, P=0.040 [3]OR=4.61, CI=1.14-18.71, P=0.032						
Charalambous, 2001, South Africa [3]	Case-series	1.Miners (15) 2.NR 3.Male 4.NR 5.NR	NR	NR	1.Gold 2.NR 3.Underground	1.Silica 2.7 3.NR	1.Standardized chest radiograph 2.Sputum smear/culture test	1.Two independent readers ILO criteria 2.Culture +ve for miliary TB cases	NR
Charalambous et al., 2008, South Africa (Charalambous et al., 2008)	Prospective cohort	1.Miners (609) 2.NR 3.Male 4.Not specified 5.NR	HIV [1]HR= 3.0, CI=1.3-7.0 CD4 count/cells/ul 200-500 [2]HR=0.4, CI=0.1-1.1 >500 [2]HR=0.1, CI=0.0-1.1 Employment duration 10-19 yrs. [2]HR= 2.1, CI=0.4-9.9 20-24 yrs. [2]HR=3.0, CI=0.6-14.0 ≥ 25 yrs. [2]HR=4.0, CI=0.9-17.9	Age 35-44 yrs. [1]HR=0.9, CI=0.4-2.1 [2]HR=5.5, CI=0.6-2.1 ≥45 yrs. [1]HR=0.9, CI=0.4-2.1 [2]HR=1.8, CI=0.6-5.9 Employment duration 10-19 yrs. [1]HR=1.1, CI=0.4-3.2 20-24 yrs. [1]HR=1.5, CI=0.5-4.2 ≥ 25 yrs. [1]HR=1.5, CI=0.5-4.4 Silicosis	1.Gold 2.NR 3.Underground	1.NR 2.NR 3.NR	1.Mini chest X Rays 2.IS6110 genotyping analysis	1.Independent experienced reader (single-blinded) ILO criteria 2.Strain differ by > 1 band for reinfection cases Strain differ by only 1 band or are identical	NR

				Early [1]HR=0.8, CI=0.3-2.3 [2]HR=0.9, CI=0.3-3.0 Advanced [1]HR=0.6, CI=0.2-1.9 [2]HR=0.9, CI=0.3-3.0 Drug-resistant TB [1]HR=0.8, CI=0.2-3.4 [2]HR=1.4, CI=0.3-6.1 Post-treatment scarring One zone [1]HR=0.7, CI=0.2-2.9 [2]HR=0.7, CI=0.2-2.8 Two or more zones [1]HR=1.0, CI=0.2-4.4 [2]HR=0.7, CI=0.2-2.6 Cavitation end of treatment [1]HR=1.1, CI=0.5-2.5 [2]HR=0.4, CI=0.1-2.6					

Cheraghvandi et al., 2014, Iran [5]	Case-report	1.Sandblaster (1) 2.29 3.Male 4.NR 5.NR	NR	NR	1.NR 2.NR 3.NR	1.Silica 2.NR 3.NR	1.Medical history 2.High resolution computed tomography (HRCT)	1.Culture +ve for TB 2.Comparisons of previous CT scan	1.Transbronchial lung biopsy specimen differentials for silicosis and multi-drug resistant TB
Churchyard et al., 2000, South Africa (Churchyard, 2000)	Retrospective-cohort	1.Miners (2,236) 2.NR 3.Male 4.NR	HIV [4]OR=15.0, CI=7.4-30.6 Self-presentation [4]OR=5.6, CI=2.6-12.2) [5]OR=4.3, CI=1.9-9.6 Silicosis present [4]OR=3.0, CI=1.4-6.3 [5]OR=2.8, CI=1.2-6.8 CD4 count $\times 10^6$/L <200 [5]OR=28.2, CI=11.5-72.3 Site of disease PTB +EPTB [5]OR=3.1, CI= 1.7–5.6 Sputum -ve [5]OR=0.3, CI=0.1-0.8	Treatment category Retreatment [4]OR=1.5, CI=0.8–2.8 Drug resistance S/R [4]OR=0.9, CI=0.3-3.0 MDR [4]OR=1.2, CI=0.1–13.8 Any [4]OR=1.2, CI=0.5–3.0 Sputum -ve [4]OR=0.9, CI=0.4-2.0 Age in yrs. 0-29 [4]OR=1.1, CI=0.4-3.0 [5]OR=0.9, CI=0.3-2.6 40-49 [4]OR=1.2, CI=0.6-1.9 [5]OR=1.2, CI=0.6-2.3	1.Gold 2.NR 3.NR	1.Silica 2.NR 3.NR	1.Chest radiograph 2.Sputum test	1.ILO classification category 1/1 or greater Two readers (blinded) 2.Smear and/or culture +ve for TB	NR

			Treatment category retreatment [5]OR=1.5, CI=0.8–2.9	>50 [4]OR=1.0, CI=0.4-2.3 [5]OR: 0.5, CI= 0.2-1.4 Extent of disease >3 zones [4]OR=1.1, CI=0.6-1.9 [5]OR=0.97, CI=0.5-1.7 CD4 count $\times 10^6$/L ≥ 500 [5]OR=3.7, CI=0.97-13.4 200-499 [5]OR=5.1, CI=1.8-15.0 Radiological pattern atypical [5]OR=1.4, CI=0.7–2.8					
Corbett et al., 2004, South Africa (Corbett et al., 2004)	Mixed (cross-sectional, retrospective and prospective study)	1.Miners (1,733) 2.NR 3.NR 4.NR 5.NR	Confirmed TB RR=5.1, CI=3.0-9.0 Duration of active TB disease before diagnosis Smear +ve TB DDR=0.16, CI=0.00-0.73 Confirmed TB DDR=0.33, CI=0.14-0.72	Smear +ve TB OR=0.8, CI=0.082-4.2 RR=5.5, CI=2.6-12.2 Culture +ve TB OR=2.1, CI=0.98-4.2 RR=4.4, CI2.2-9.1 Confirmed TB OR=1.7, CI=0.89-3.3 All diagnosed TB OR=1.6, CI=0.83-3.1 RR=5.2, CI=3.2-8.5	1.Gold 2.NR 3.NR	1.Silica 2.NR 3.NR	1.Sputum test 2.Chest radiograph	1.Symptoms questionnaire 2.ILO criteria	NR

Corbett et al., 2000, South Africa (Corbett et al., 2000)	Retrospective cohort	1.Miners (4,022) 2.NR 3.Male 4.NR 5.NR	HIV infection period 1991-1994 IRR=2.8, CI=1.5-5.0 1995-1997 IRR=5.9, CI=4.2-8.2 Silicosis grade Possible IRR=1.4, CI=1.0-2.2 Probable IRR=1.8, CI=1.0-3.0 Early IRR=2.2, CI=1.3-3.7 Advanced IRR=2.5, CI=1.6-4.0 Age 40-49 IRR=1.3, CI=0.9-1.8 >50 IRR=1.3, CI=0.8-2.2 Surface IRR= 0.5, CI=0.3-0.9 Previous TB in yrs. > 5yrs IRR=2.6, CI=1.5-4.4	Employment duration in yrs. 0-4 IRR=1.8, CI=0.9-3.5 10-19 IRR=1.6, CI=1.0-2.5 > 20 IRR, 1.3, CI=0.8-2.3 Previous TB in yrs. 0-5 IRR=1.3, CI=0.6-2.8 Age 18-29 IRR=0.4, CI=0.2-0.7	1.Gold 2.NR 3.Underground	1.Silica 2.NR 3.NR	1.Mini radiograph 2.Sputum test	1.ILO criteria 2.Smear +ve for mycobacterial disease	NR

Dixit, 2007, India [9]	Case-report	1.Stone-driller (1) 2.35 3.Male 4.NR 5.NR	NR	NR	1.NR 2.NR 3.NR	1.Silica 2.NR 3.NR	1. Medical history 2.Respiratory clinical examination 3.Sputum test 4.Mantoux test 5.Skiagram chest test 6.Spirometry	1.NR 2.NR 3.Smear +ve results 4.20mm induration within 72hrs 5.NR 6.NR	NR
Ehrlich, 2011, South Africa [10]	Cross-sectional	1.Miner (520) 2.46.7 3.Male 4.External 5.NR	NR	NR	1.Gold 2.NR 3.Underground	1.Silica/dust 2.21.8 3.Dust of 0.375mg/m^3 Quartz of 0.053mg/m^3	1.Chest radiograph 2.Lung function test	1.ILO classification Two NIOSH trained readers 2.FEV_1 and FVC losses	NR
Farazi, 2015, Iran (Farazi & Jabbariasl, 2015)	Cross-sectional	1.Mixed population (3,121) 2.43.1 3.Male 4.NR 5.NR	Age OR=1.97, CI=1.12-3.46, P=0.02 Smoking OR=3.11, CI=1.30-7.44, P=0.01 Employment duration OR=2.32, CI=1.32-4.10, P=0.004 Exposure duration OR=2.07, CI=1.10-3.88, P=0.03	Nationality OR=0.65, CI=0.27-1.56, P=0.37 Opium addiction OR=0.45, CI=0.12-1.76, P=0.32	1.NR 2.NR 3.NR	1.Silica 2.> 5 3.NR	1.Clinical history 2.Tuberculin skin test (TST) 3.Spirometry 4.Chest radiography 5.Sputum test	1.Questionnaire results 2.+ve TST cases 3.American Thoracic Society criteria 4.Evaluation by specialists WHO criteria ILO classification criteria 5.+ve smear results	NR
Feng et al., 2014, China [12],	Cross-sectional	1.Miners (42) 2.Silico-TB :71.75 PTB: 49.08 3.Male 4.NR 5.NR	NR	NR	1.NR 2.NR 3.NR	1.Silica and dust 2.26.5 3.NR	1.Clinical history 2.Sputum smear/culture microscopy 3.MIRU-VNTR genotyping tool	1.Silica-exposure cases 5-7 readers 2.Radiological features Silico-tuberculosis cases	NR

								3.*M. tuberculosis* isolates	
Franzblau et al., 2018, South Africa [13]	Cross-sectional	1.Miners (132) 2.47.6 3.Male 4.NR 5.NR	NR	NR	1.Gold 2.Large 3.NR	1.Silica 2.22.3 3.NR	1.Digital chest radiograph 2.Film chest radiograph 3.Clinical history	1.Four reader evaluation 2.ILO classification criteria	NR
Girdler-Brown, 2008, South Africa [14]	Cross-sectional	1.Miners (624) 2.49.4 3.NR 4.NR 5.NR	NR	-	1.Gold 2.NR 3.NR	1.Dust/Silica 2.NR 3.NR	1.Clinical history 2.Standard chest radiograph 3.Spirometry	1.Respiratory history questionnaire 2.American Thoracic Society criteria ILO criteria Four reader evaluation 3.GOLD classification	NR
Glynn et al., 2008, South Africa [15]	Retrospective cohort	1.Miners (1,950) 2.Male 3.NR 4.NR 5.NR	NR	-	1.Gold 2.NR 3.NR	1.Silica 2.NR 3.NR	1.Chest radiograph 2.Sputum smear/culture	1.NR 2.+ve culture for TB cases	NR
Hnizdo, 2000, South Africa [16]	Retrospective cohort	1.Miners (27,660) 2.NR 3.NR 4.NR 5.NR	NR	-	1.Gold 2.NR 3.Underground	1.Silica 2.NR 3.NR	1.Pulmonary function test 2.Mass miniature radiograph 3.Standard size chest radiograph 4.Sputum test 5.Clinical history	1.FEV_1 and FVC ILO criteria 2.History of TB cases	NR
Moyo, 2017, Zimbabwe [17]	Case-report	1.Miner (1) 2.68 3.Male 4.NR 5.NR	NR	-	1.Gold/granite 2.NR 3.Rock drilling	1.Silica 2.13 3.NR	1.Chest X Ray 2.Sputum test 3.CT scan 4.Lung function test 5.Occupational history 6.Clinical examination	1.Two reader evaluation +ve sputum case for acid fast bacilli (AAFB) 2.NR 3.NR 4.FEV_1/FVC 5.NR 6.NR	1.Open lung biopsy 2.2nd reader evaluation using CT scan, lung biopsy and occupational history

Murlidhar, 2015, India [18]	Case-report	1.Mixed population (2) 2.NR 3.Female/Child 4.NR 5.NR	NR	-	1.Stone 2.NR 3.NR	1.Silica 2.NR 3.NR	1.Medical history 2.Chest X Ray 3.Sputum test	1.NR 2.ILO classification 3.+ve sputum for acid fast bacilli	NR
Naidoo, 2005, South Africa (Dixit & Dave, 2007)	Cross-sectional	1.Miners (900) 2.42.45 3.NR 4.NR 5.NR	History of TB [6]OR=8.091, CI=3.34-19.61) [7]OR=5.29, CI=2.37–11.78 Ex-smoking status [6]OR: 2.65 CI=1.21-5.81 High CDE [7]OR=4.21, CI=1.31-13.51	Medium CDE [6]OR=1.36, CI= 0.48-3.83 [7]OR=1.43, CI=0.69-2.93 Current smoker [6]OR=1.39, CI=0.68-2.85 [7]OR=1.00, CI=0.68-1.47 Current miner [6]OR=0.65, CI=0.23-1.81 [7]OR=1.35, CI=0.73-2.52 Current miner × high CDE [6]OR=0.51, CI=0.076-3.39 [7]OR=0.21, CI=0.06-0.74 Current miner × medium CDE [6]OR=0.47, CI=0.11-2.01 [7]OR=0.41, CI=0.16-0.98	1.Coal 2.NR 3.Underground & surface	1.Coal/Quartz 2.15.89 3.58.08mg-years/m^3	1.Spirometry 2.Occupational history	1.FEV_1 and FVC results American Thoracic Society standardized criteria Two reader evaluation 2.Interviews	NR
Oni, 2015, South Africa [20]	Case-report	1.Miner (1) 2.59 3.Male 4.Internal 5.NR	NR	-	1.Gold 2.NR 3.Underground	1.Silica 2.11 3.NR	1.Clinical history 2.Chest radiograph 3.Clinical examination 4.HRCT	1.+ve sputum of AAFBs +ve culture of *Mycobacterium Kansasii/NTM* 2.ILO classification 3.+ve TB cases	NR

								4.NR	
Park, 2009, Lesotho (Park et al., 2009)	Prospective cohort	1.Miners (779) 2.NR 3.Male 4.External 5.NR	-	Age OR=1.05, CI=1.01-1.09 HIV OR=0.74, CI=0.38-1.49 Past TB OR=1.45, CI=0.93-2.26 Past TB on medication OR=1.42, CI=0.36-5.59 TB diagnosed OR=3.09, CI=1.42-6.69 Smoking OR=0.83, CI=0.54-1.26 Years mining OR=1.03, CI=0.99-1.07	1.Gold 2.NR 3.NR	1.Silica 2.NR 3.NR	1.Chest radiograph 2.Spirometry 3.Physical examination 4.Medical history	1.American Thoracic Society criteria 2.ILO classification 3.Three readers evaluation FEV_1/FVC 4.Respiratory questionnaire	NR
Qu et al., 2007, China (Qu et al., 2007)	Retrospective/case-control	1.Miners (295) 2.NR 3.Male 4.NR 5.NR	NRAMP1 INT4 Genotypes (TB) G/C OR=2.53, CI=1.21-5.31 G/C + C/C OR=2.66, CI=1.27-5.54 Interaction of TNF-a-308 G/G and NRAMP1 INT4	NRAMP1 INT4 Genotypes (TB) C/C NRAMP1 D543N Genotypes (TB) G/A A/A OR=1.06, CI=0.09-12.74 G/G + A/A OR=1.81, CI=0.84-3.93 TNF-a-308 Genotypes (TB) G/A	1.Iron 2.NR 3.Underground	1.Silica 2.23.1 3.CTE: 242.6 mg a/m^3	1.Chest X Ray 2.Sputum test 3.Patient history/information 4.Polymerase chain reaction-restriction fragment length polymorphism (PCR-RLFP)	1.Chinese pneumoconiosis radiographic diagnostic criteria 2.+ve culture for TB 3.Standardized questionnaire 4.Genome variants	NR

			polymorphisms to PTB NRAMP1 INT4 G/G & G/C+C/C OR=2.38, CI=1.14-4.98, P<0.01 Interaction of NRAMP1 INT4 and D543N G/G polymorphisms to PTB G/G & G/C + C/C OR=3.26, CI=1.47–7.23, P<0.01	OR=0.83 CI=0.34-2.03 A/A G/A + A/A OR=0.81, CI=0.33-1.95 iNOS Ser608Leu Genotypes (TB) C/T OR=1.46, CI=0.69-3.09 T/T OR=3.00, CI=0.17-54.03 C/T +T/T OR=1.50, CI=0.71-3.15 TNF-a-308 Genotypes (Silicosis) G/A OR=1.59, CI=0.80-3.19 A/A OR=1.12, CI=0.16-7.78 G/A + A/A OR=1.52, CI=0.79-2.95 iNOS Ser608Leu Genotypes (Silicosis) C/T OR=0.45, CI=0.27-0.77 T/T OR=0.92, CI=0.16-5.42 C/T + T/T OR=0.47, CI=0.28-0.79					

				Interaction of TNF-a-308 G/A+A/A and NRAMP1 INT4 polymorphisms to PTB NRAMP1 INT4 G/G & G/C + C/C OR=5.71, CI=0.45-73.19 Interaction of TNF-a-308 G/G and NRAMP1 D543N polymorphisms to PTB NRAMP1 D543N G/G & G/A+A/A OR=1.59, CI=0.72-3.50 Interaction of TNF-a-308 G/A + A/A and NRAMP1 D543N polymorphisms to PTB NRAMP1 D543N G/G & G/A+A/A OR=1.25, CI=0.23-6.70 Interaction of NRAMP1 INT4 and D543N G/A+A/A Polymorphisms to PTB NRAMP1 D543N G/G & G/C+C/C OR= 1.23, CI= 0.28–5.45					
Ringshausen et al., 2013, Germany	Observational cohort	1.Miners (118) 2.75	Age ≥ 80 years	COPD [8]OR=1 [9]OR=1	1.Coal 2.NR 3.Underground	1.Silica & dust 2.26	1.Chest imaging/radiography	1.Experienced chest	NR

(Ringshausen et al., 2013)		3.Male 4.External 5.Insured	[8]OR=5.8, CI=2.04–16.26, P <0.001 [9]OR=8.1, CI=2.22–29.21, P= 0.001 Foreign country of birth [8]OR=6.8, CI=1.91–24.0, P= 0.003 [9]OR=4.8, CI=1.26–18.07, P= 0.022 Radiological evidence of prior healed TB [8]OR=5.0, CI=1.69–14.98, P= 0.004	Silicosis [8]OR=1.8, CI=0.75–4.28, P= 0.19 [9]OR=1.5, CI=0.63–3.55, P= 0.36 Smoking [8]OR=3.5, CI=0.92–13.60, P= 0.066 [9]OR=2.6, CI=0.65-10.65, P= 0.18 Radiological evidence of prior healed TB [9]OR=3.0, CI=0.96–9.15, P= 0.059		3.Cumulative respirable dust: 100mg/m^3.	2.Clinical history 3.QFT 4.T-SPOT	physicians/radiologist's evaluation American Thoracic society criteria ILO criteria 2.Structured interview Standardized questionnaire 3.IFN-γ response of TB antigen minus nil control ≥0.35 IU/ml 4. ≥6 SFCs	
Ross, 2010, South Africa (Ross et al., 2010)	Retrospective cohort.	1.Miners (370) 2.44 3.Male 4.Internal 5.NR	Respiratory symptoms Breathlessness OR=2.20, CI=1.18-4.11	Silicosis present OR=1.86, CI=1.03-3.37 History of bronchitis OR 1.51=0.25-9.13 History of asthma OR=3.41, CI=1.22-9.51 History of pneumonia OR=1.36, CI= 0.56 to 3.30	1.Gold 2.NR 3.Underground Surface work	1.Silica 2.22.7 3.NR	1.Medical history 2.Chest radiography	1.History of tuberculosis cases 2.Silicotic profusion of ≥1/0 or large opacities as per ILO classification	NR

				Smoking OR=2.04, CI=1.33-3.12 Respiratory symptoms (adjusted) Cough OR=1.59, CI=0.90-2.83 Phlegm OR=1.45, CI=0.78-2.68 Wheezing OR=1.67, CI=0.92-3.03					
Sonnenberg et al., 2000, Southern Africa (Sonnenberg et al., 2000)	Case-control	1.Miners of (505) 2.40.4 3.Male 4.Internal 5.NR	Previous TB treatment OR=3.61, CI=1.9-6.9, P <0.001 Alcohol Weekends OR=0.91, CI=0.48-1.7, P=0.8 Alcohol daily OR=0.12, CI=0.02-0.93, P=0.04 Silicosis Possible OR=1.4, CI=0.62-3.0, P=0.5 Yes OR=12.6, CI=2.2-71, P=0.004 Years underground 10-19yrs	HIV OR=0.67, CI=0.35-1.3, P=0.2 CD4 (%) 14-28 OR=0.98, CI=0.35-2.8 < 14 OR=0.36, CI=0.04-3.0 Age OR=1.3, CI=0.75-2.4, P=0.3 Home region/neighboring country OR=1.2, CI=0.67-2.2, P=0.5 Primary education OR= 0.76, CI=0.41-1.4 Secondary education	1.Gold 2.NR 3.Underground	1.Silica 2.Duration: 0-9yrs; 10-19yrs; ≥ 20yrs 3.NR	1.Sputum smear examination 2.Chest radiography	1.+ve culture for TB or NTM cases 2.+ve culture for mixed infection of TB and NTM cases Readings by two readers ILO standard guidelines for silicosis Thoracic society criteria used for NTM	NR

			OR=1.1, CI=0.43-2.8, P=0.8 ≥ 2yrs OR=3.2, CI=0.95-10.8, P=0.06	OR=0.46, CI=0.18-1.2 Smoking OR=1.1, CI=0.55-2.3 Chest radiography for cavitation OR=2.1, CI= 1.1-3.8					
teWaterNaude et al., 2006, South Africa [26]	Cross-sectional	1.Miners (520) 2.46.7 3.NR 4.NR 5.NR	Cumulative respirable dust in mg. Years/m^3 [c1]POR=1.45, CI=1.14-1.85 Average intensity respirable dust in ug/m^3 [c1]POR=1.48, CI =1.13-1.95 Cumulative respirable quartz in mg. Years/m^3 [c1]POR=1.47, CI=1.14-1.89 Average intensity respirable quartz in ug/m^3 [c1]POR=1.44, CI=1.11-1.87	Length of service in years [c1]POR=1.31, CI=1.00-1.72	1.Gold 2.NR 3.Underground	1.Dust/Quartz 2.21.8yrs 3.Respirable quartz of 0.053mg/m^3 /Respirable dust of 0.37mg/m^3	1.Self-reported history 2.Chest radiograph	1.Past or present PTB cases 2.Evaluation by two trained NIOSH B readers ILO classification criteria	NR
Tse, 2007, China [27]	Cross-sectional	1.Miners/rock drillers (574) 2.24.6 3.Male 4.NR 5.NR	NR	NR	1.Gold 2.Small scale 3.Underground pit inclusive of rock drilling	1.Dust/silica 2.4-5.9 3.Respirable silica dust of 89.5mg/m^3	1.Chest radiograph 2.Chest X Ray film 3.Occupational history	1.Evaluation by two radiologists 2.Standardized questionnaire used	NR

Tse, 2014, China (Tse, 2014)	Historical cohort	1.Mixed population (3,202) 2.55.3 3.Male 4.Internal 5.NR	-	[1]Smoking [10]OR=1.80, CI=1.20-2.60 [2]Smoking [11]OR=2.54, CI=1.24-5.22	NR	1.Silica 2.24.7 3.NR	1.Medical history	1.Number of tuberculosis cases from history ILO classification criteria	NR

[c1]POR is prevalence odd ratio adjusted for age and smoking; [1]OR is odd ratio for silicosis category 3; [2]OR is odd ratio for coalescence and/or large opacities; [3]OR is odd ratio for tb; [4]OR is odd ratio for all participants; [5]OR is odd ratio for HIV +ve group; [6]OR is odd ratio for $fev_1 < 65\%$; [7]OR is odd ratio for $fev_1 < 65$; [8]OR is odd ratio for +ve qft; [9]OR is odd ration for +ve t-spot; [10]OR is odd ratio for silicosis mortality; [11]OR is odd ratio for TB mortality; [1]HR is hazard ratio for both HIV +ve and -ve participants; [2]HR is hazard ratio for HIV +ve sub-groups; [1]RR is rate ratio for TB incidence; NR is not reported; NTM is Nontuberculous Mycobacterium.

Table 2: Study results of detection of silico-tuberculosis, key finding(s) and limitation(s)

First Author, Year	**Results of Detection of Silico-tuberculosis/silicosis and tuberculosis**	**Follow up.** 1.**Duration** 2.**Results**	**Other Key findings**	**Limitation**
Cairncross, 2016 [1]	•Silico-tuberculosis: Workers were looking for help to obtain proper compensation for their work-related injuries and the lawsuits would help from those neglected by gold mines and end up having silicosis and silico-tuberculosis about twenty-thousands of them represented as ex-miners (*retrenched and disabled gold mine workers*). •TB: "The dust caused chest pains/discomfort and when we went to the mine hospital, we were told we have HIV and TB (several workers).	NR	Several mine workers had chest pains and discomfort they viewed as caused by the dust and were informed they had TB and HIV upon visiting a mine hospital. Workers reported receiving same treatment despite varying symptoms.	NR
Carneiro, 2006 (Carneiro et al., 2006)	•Prevalence of Inactive TB: 24.1% •Inactive TB: n=20 •Silicosis: n=83 •Silicosis category 3: n=19 •Coalescence/large opacities: n=22 •Chronic airflow limitation: 42.2%	NR	Individuals with continued silica exposure are associated with TB and functional severity of silicosis.	Exact onset of silicosis uncertain due to retrospective nature of study.

Charalambous, 2001 [3]	•Military TB: n=15 •Smear +ve TB cases ○HIV -ve: n=3/4 ○HIV +ve: n=6/11 •Bacteriological cure TB: n=8/15 •Nodularity of 3: n=14/15 •Nodularity of 2: n=1/15 N/B: (No attempt made to distinguish changes in nodularity due to miliary TB from that of silicosis. Hence, either TB or silicosis)	1.Two to six months 2.Nodularity cases *(Two months)* •0: n=2/15 •+: n=6/15 •++: n=6/15 •+++: n=1/15 *(Six months)* •0: n=7/15 •+: n=1/15 •+/-: n=1/15 •++: n= 6/15	Nodule profusion increased in military TB cases despite clinical improvement with bacteriological cure of 53% (n=8/15) indicative of silicotic development.	Small number of cases. Lack of long-term follow-up and lung function assessments.
Charalambous et al., 2008 (Charalambous et al., 2008)	•Sputum culture +ve: 75% •>1 +ve culture/smear: 81% •TB reinfection: 68% ○HIV +ve: n=10 ○HIV-ve: n=1 •TB relapse: 31% ○HIV+ ve: n=4 ○HIV-ve: n=1 •Silicosis= n=496 ○Absent in HIV +ve: n=201 ○Absent in HIV-ve: n=107 ○Early in HIV +ve: n=27 ○Early in HIV-ve: n=19 ○Advanced in HIV +ve: n=14 ○Advance in HIV-ve: n=23	NR	HIV infection associated with the strongest risk of TB recurrence.	Fingerprints available for only n= 16/42 culture +ve.
Cheraghvandi et al., 2014 [5]	•+ve TB case: n=1 •+ve sputum smear on hx: n=1 •-ve sputum culture on hx and examination: n=1 •-ve BAL smear on hx and examination: n=1 •-ve PCR on hx: n=1 •Silicosis present on hx: n=1 •Secondary alveolar proteinosis present on hx: n=1 •-ve TB culture on examination: n=1 •Death: n=1	NR	Transbronchial lung biopsy specimen differentials for silicosis and multi-drug resistant TB.	NR
Churchyard et al., 2000 (Churchyard, 2000)	•Sputum +ve for TB ○HIV-ve: 77.6% ○HIV +ve: 76.8% •Silicosis present ○HIV -ve: 12.6% ○HIV +ve: 39% •Zone score ≤ 3 ○HIV-ve: 53.9%	NR	HIV infection, self-presentation compared to detection by the radiological screening program and silicosis were significantly associated with increase case fatality rate.	Diagnosis of silicosis deemed difficult in the presence of TB due to similar radiographic presentations.

	○HIV +ve: 53.5% •Zone score > 3 ○HIV +ve: 46.5% ○HIV -ve: 46.1%			
Corbett, 2004 (Corbett et al., 2004)	*(TB point prevalence cases in HIV +ve vs HIV -ve)* •Smear +ve TB cases ○HIV +ve: 0.44% ○HIV -ve: 0.55% •Culture +ve TB ○HIV +ve: 3.3% ○HIV -ve:1.6% •Confirmed TB ○HIV +ve: 3.8% ○HIV -ve: 2.2% •Diagnosed TB ○HIV +ve: 3.8% ○HIV -ve: 2.3% •Silicosis present ○HIV +ve: 4.65% ○HIV -ve: 2.3 % •No silicosis ○HIV +ve: 3.8% ○HIV -ve: 2.3% *(TB incidence rates in HIV +ve vs HIV -ve cases)* •Smear +ve TB ○HIV +ve: 2.6 ○HIV -ve: 0.48 •Culture +ve TB ○HIV +ve: 2.6 ○HIV -ve: 0.6 •Confirmed TB ○ HIV +ve: 4.7 ○ HIV -ve: 0.91 •Diagnosed TB ○HIV +ve: 6.0 ○HIV -ve: 1.15 •Silicosis present ○HIV +ve: 14.4 ○HIV -ve: 2.8 •No silicosis: ○HIV +ve: 3.7 ○HIV -ve: 0.72	NR	Silicosis and age were significantly associated with TB incidence rates. Disease duration significantly shorter for HIV +ve cases in TB Outcome. Disease duration significantly shorter for silicotic in TB outcome.	NR

Corbett et al., 2000 (Corbett et al., 2000)	*(Silicosis in HIV +ve vs HIV -ve)* •No silicosis ○HIV +ve: 76% ○HIV -ve: 73% •Possible ○HIV +ve: 11% ○HIV -ve: 13% •Probable ○HIV +ve: 4% ○HIV -ve: 6% •Early ○HIV +ve: 4% ○HIV -ve: 4% •Advanced: ○HIV +ve: 5% ○HIV -ve: 5% (Pulmonary TB in HIV +ve vs HIV-ve) •Smear or culture +ve ○HIV +ve: 75% ○HIV -ve: 65% •Smear and culture -ve ○HIV +ve: 7% ○HIV -ve:13% *(Extra-pulmonary TB in HIV +ve vs HIV-ve)* •Smear or culture +ve ○HIV +ve: 4% ○HIV -ve: 8% •Smear and culture -ve ○HIV +ve: 13% ○HIV -ve: 14%	NR	Significant risk factors for TB incidence were silicosis by grading, increasing age, underground job, previous TB, and HIV effect within a time.	Sub-optimal information on seroconversion to HIV +ve among initially HIV -ve men.
Dixit, 2007 [9]	•Smear -ve: n=1 •Reactive Mantoux test: n=1 •Silicosis present: n=1 •Pneumomediastinum: n=1	NR	Pneumomediastinum is an uncommon complication resulting from silico-tuberculosis.	NR
Ehrlich, 2011 [10]	*(Results by reader 1)* •TB: 27.8% •Silicosis: 18.1% •TB + Silicosis: 5.4% •Progressive massive fibrosis (PMF): 0.8% *(results by reader 2)* •TB: 17.5% •Silicosis: 19.9% •TB + Silicosis: 4.5% •Progressive massive fibrosis (PMF): 1.0%	NR	Pulmonary TB is associated with greater FEV_1 than FVC in addition to silicosis and cumulative dust exposure.	Recall bias (10% of recalled TB may in fact be NTM). HIV infection not measured.

	•Past TB: 19.4% •Current TB: 1.7% •TB by any measure (ever reported/active/inactive/read on chest radiograph by either reader): 35.2%			
Farazi, 2015 (Farazi & Jabbariasl, 2015)	•No LTBI/TB ○Silicotic: 38.5 ○Non-silicotic: 48. •LTBI ○Silicotic: 70.2% ○Non-silicotic:35.6 •Active TB ○Silicotic: 0.5% ○Non-silicotic: 0.07% •Past TB ○Silicotic: 0.5% ○Non-silicotic: 0.1% •Silicosis: 7% •Extra-pulmonary TB: n=1 •TB Prevalence (Cases per 100,000) ○Silica exposed/non-silicotic: n=172 ○Silicotic: n=917 •TB incidence (Cases per 100,000) ○Silica exposed/non-silicotic: n=69 ○Silicotic: n=459	NR	Frequency of LTBI/TB was higher in smokers, over thirty-year-old workers, and those employed more than thirty years.	Short-term observation. Lacked the evaluation of type and concentration of silica-particles. Difficulty of diagnosing silico-tuberculosis.
Feng et al., 2014 [12]	•Pneumoconiosis (Referred to as the silicotuberculosis group) ○Stage I: n=4 ○Stage II: n=10 ○Stage III: n=2 •Mycobacterium *tuberculosis* strains ○Resistant strains: 40.48% ○Sensitive strains (anti-tb drugs): 59.52%	NR	Mycobacterium *tuberculosis resistant strains were higher in silico- tuberculosis group than PTB group.*	Limited epidemiological information available on transmission links shown by typing method.
Franzblau et al., 2018 [13]	•Previous TB: 10% •Radiographic results of TB using film vs. soft-copy images ○Film: 38% ○Soft copy: 35% •Parenchymal abnormality (silicosis) using film vs. soft-copy images ○Film: 63% ○Soft copy: 65%	NR	Results from film and soft copy yielded no significant differences in the prevalence of silicosis and tuberculosis. Hard copy imaging showed higher prevalence.	Hard copy digital images were 2/3 the size of film and soft copy images which may contribute to loss of detection accuracy.
Girdler-Brown, 2008 [14]	•Previous TB: 26.4% •+ve microscopy/culture for active TB: 2.9% •Previous or current TB: 16.2% •Silico-tuberculosis: 7.9% •Clinical TB: 2.1% •Airflow obstruction: 5.7%	NR	High prevalence of TB, silicosis, and airflow obstruction.	NR

	•FEV1/FVC ratio results ○<0.7: 13.5% ○<0.75: 26.3% •Gold score results ○Nil: 72.6% ○0: 13.9% ○I: 5.7% ○II: 6.6% ○III: 1.2% ○IV: 0.0% •Silicosis: 12%			
Glynn et al., 2008 [15]	•TB incidence: 10/100 person-years •+ve culture TB case: 85% •Silicosis presence acknowledged but no results included.	NR	Increased TB incidence due to seroconversion overtime.	NR
Hnizdo, 2000 [16]	•Silico-TB: n=185 •Pneumoconiosis (referring to silicosis): 1,349 •TB: 2,599 •Lung function results *(1st episode of TB)* ○FEV_1: 326ml ○FVC: 305ml *(2nd episode of TB)* ○FEV_1: 499ml ○FVC: 495ml *(3rd episode of TB)* ○FEV_1: 583ml ○FVC: 554ml	1.Twelve to > twelve months 2.Lung function test results in 1st, 2nd & 3rd episode in TB participant *(12 months=1st episode of TB)* •FEV_1: 247ml •FVC: 213ml *(12 months=2nd episode of TB)* •FEV_1: 419ml •FVC: 403m *(12 months=3rd episode of TB)* •FEV_1: 503ml •FVC: 462ml *(>12 months=1st episode of TB*	Increase in the number of TB episodes results to chronic impairment of lung function. Subjects with pneumoconiosis and previous TB have increased lung function loss compared to those with only pneumoconiosis.	Non-adjustment for smoking and silica dust exposure. Tuberculosis history assessed retrospectively.

		•FEV_1: 153ml •FVC: 96ml •FEV_1%: 18.4% *(>12 months=2nd episode of TB* •FEV_1: 326ml •FVC: 286ml •FEV_1%: 27.1 *(>12 months=3rd episode of TB* •FEV_1: 410ml •FVC: 345ml •FEV_1%: 35.2%		
Moyo, 2017 [17]	•Lung function test (L) ○FEV_1: 2.24 ○FVC: 3.17 •-ve AAFBs: n=1 •-ve fungal elements: n=1 •Conglomerate nodules in central zone: n=1 •Silicosis with PMF: n=1 •Possible PTB reactivation: n=1	1.Two months 2.+ve AAFBs: n=1	Diagnosis of silicosis with PMF and possible PTB reactivation evaluated upon second reader evaluation.	NR
Murlidhar, 2015 [18]	•TB case: n=2 •Silicosis ○Present: n=1 ○Suspected: n=1	NR	Alleged "child labor" case for secondary silica dust exposure in a child whose mother is a miner but declined taking child to the mines as well.	NR
Naidoo, 2005 (Dixit & Dave, 2007)	•Lung function test results ○FEV_1: 104.43% ○FVC: 103.15%	NR	Dose-related decrease in the lung function respective of silica exposure.	NR
Oni, 2015 [20]	•Previous bilateral nodularity in the upper/mid-zones consistent with silicosis of (q/q, 2/2): n=1 •Current HRCT results of early progressive massive fibrosis: n=1 •Previous +ve sputum for AAFBS: n=1 •Previous +ve culture for *Mycobacterium Kansasii*: n=1 •Current -ve TB on PCR: n=1 •Current lung function test results: n=1 •FEV_1: 1.32L •FVC: 2.24L	1.One year 2.PTB based on no radiological clearing: n=1	Progression of silicosis observed even after cessation to exposure. Silicosis diagnosed after eleven years of exposure (silicosis not reported on previous medical notes).	NR

	•FEV1/FVC ratio of 58% •FEV_1 loss: 47% •FVC loss: 41%	Nodularity with profusion of r/q, 3/2: n=1 Fibrosis: n=1		
Park, 2009 (Park et al., 2009)	•Past TB ○Participants attended Round 1: 24.1% ○Participants attended both rounds: 27.3% •Active TB or on treatment ○Participants attended Round 1: 5.4% ○Participants attended both rounds: 7.2% •Lung function test result (L) ○FEV_1 round 1: 2.99 ○FEV_1 both rounds: 2.92 ○FVC round 1: 3.76 ○FVC round 2: 3.72 ○FEV_1/FVC round 1: 0.79 ○FEV_1/FVC both rounds: 0.78 •Silicosis overall result ○Participants who attended round 1: 15.9% ○Participants who attended both rounds: 26.4% •Silicosis by grading round 1 ○Normal: 65.7% ○Border line: 7.7% ○Grade 1: 13.2% ○Grade 2: 12.2% ○Grade 3: 1.2% ○PMF: 2.4% ○Silicosis ≥ 1/1 with radiological finding of TB/Previous TB: 10.2%	1.One year 2.(*Silicosis by grading round 2)* •Normal: 62.4% •Border line: 10.6% •Grade 1: 10.6% •Grade 2: 14.8% •Grade 3: 1.6% •PMF: 2.5% •Silicosis ≥ 1/1 with radiological finding of TB/Previous TB: 14.8%	Active TB associated with lung function loss.	Mortality rate in the cohort was unknown.
Qu, 2007 (Qu et al., 2007)	•Respiratory symptom results (Silicotic) ○Chest stuffiness: 92.9% ○Chronic cough: 73.9% ○Phlegm production: 62.5% •PTB: n=61 •Silicosis: n=50 •No silicosis: n=11	NR	Risk of PTB highly associated with polymorphism of NRAMPI iNOS Ser608Leu genotype associated with protection against silicosis. No association of iNOS Ser608Leu polymorphism with TB.	NR
Ringshausen, 2013 (Ringshausen et al., 2013)	•Silicosis: 39% •+ve QFT in silicotic: 56.5% •+ve T-SPOT in silicotic: 69.6% •N/B: Whereby + ve QFT & +ve T-SPOT report on latent TB outcome. Hence, indirectly shows silico-tuberculosis results from +ve QFT/T-SPOT in silicotics.	-	No cases of active TB observed during follow-up.	Absence of a GOLD standard for diagnosing latent TB. IGRAs unable to distinguish between MTB and NTM.

Ross, 2010 (Ross et al., 2010)	•Radiological results ○1-3 zones affected: 74.3% ○4-6 zones affected: 25.7% •Sputum/smear results ○Smear +ve: 72.9% ○Smear -ve: 22.7% ○Culture +ve: 77.3% ○Culture -ve: 22.7% • FEV_1 results (TB vs No TB) ○Mean: 3.41 •FVC results ○Participants with TB: 4.11 ○No TB: 4.12 •FEV_1/FVC (%) ○TB mean: 82.87 ○No TB mean: 82.94 ○Lung function loss: NR	1.3 years 7 Months 2.PFT *(Mean FEV_1)* •TB: 2.87 •No TB: 3.07 *(Mean FVC)* •TB: 3.86 •No TB: 4.07 *(Mean FEV_1/FVC %)* •TB: 74.18 •No TB: 75.5 *(Lung function loss)* •FEV_1: 40.3ml/year •FVC: 42.7ml/year	Both TB and non-TB groups experienced excess FEV1 declines due to silica dust exposure and silicosis given low tobacco consumption among miners. However, greater decline in lung function among TB group was due to pulmonary damage caused by TB.	A health survivor effect.
Sonnenberg, 2000 (Sonnenberg et al., 2000)	•TB cases: n=425/505 •Mixed infections: n=7/505 •NTM cases: 73/505 •Silicotic ○No: 394/476 ○Possible: 74/476 ○Yes: 6/476	NR	Both TB and non-TB groups experienced excess FEV_1 declines due to silica dust exposure. Greater decline in lung function among TB group caused by pulmonary damage caused by TB.	Study was restricted only to the working male population. The exclusion of high-risk groups may have led to a "healthy worker effect."
(teWaternaude et al., 2006) [26]	•PTB prevalence ○On history: 19.4% ○On Chest X ray by either reader: 35.2% •Silicosis by either reader: 28.2%	NR	High PTB prevalence was significantly associated with silica and dust exposure even in the absence of silicosis.	Study based on survivor workforce population. Exposure levels measured not representative of the exposures throughout the working lifetime of miners. PTB outcome prior to silica exposure could result to misclassification of "occupational TB."
Tse, 2007 [27]	•Silicosis prevalence: 29.1% •Tuberculosis: 3.7%	NR	High prevalence of accelerated silicosis among those working underground.	Small numbers of unusually exposed workers and too few accelerated silicosis cases.
Tse, 2014 (Tse, 2014)	•Tuberculosis: 49% •Silicosis: 20.3%	NR	Excess risk of death among silicotic due to PTB.	Limited power on study's cohort.

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