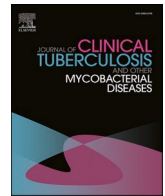




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Mini-review: Silico-tuberculosis

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ABSTRACT

Silicosis continues to be a serious health issue in many countries and its elimination by 2030 (a target set by WHO and the International Labour Organization in 1995) is virtually impossible. The risk to develop pulmonary tuberculosis for silicosis patients is higher than for non-silicosis people, and there is also an increased risk of both pulmonary and extrapulmonary tuberculosis in individuals exposed to silica. HIV coinfection adds further to the risk, and in some countries, such as South Africa, miners living with HIV are a considerable number. The diagnosis of active tuberculosis superimposed on silicosis is often problematic, especially in initial phases, and chest X-ray and smear examination are particularly important for the diagnosis of pulmonary tuberculosis. Treatment is difficult; directly observed therapy is recommended, a duration of at least eight months is probably needed, drug reactions are frequent and the risk of relapse higher than in non-silicosis patients. TB prevention in silicosis patients is essential and include active surveillance of the workers, periodic chest X-rays, tuberculin skin test or interferon-gamma releasing assay testing, and, importantly, adoption of measures to reduce the exposure to silica dust. Chemoprophylaxis is possible with different regimens and needs to be expanded around the world, but efficacy is unfortunately limited. Silico-tuberculosis is still a challenging health problem in many countries and deserves attention worldwide.

1. Introduction

Silicosis is a pneumoconiosis caused by inhalation and deposition in the lungs of particles of free silica and characterized by granulomatous inflammation and pulmonary fibrosis. It is almost exclusively a consequence of occupational exposure and may occur in numerous industrial settings: coal, gold and other minerals mining, quarrying, tunnel building (rails and roads), foundries, cement or glass works, ceramics and porcelain manufacture, marble stone industries, and sand extraction. The workers at highest risk of silicosis are estimated to be 227 million and are largely informal and frequently migrant [1,2]. Of these, 40.5 million artisanal small-scale miners work in over 80 countries worldwide [1]. Non-occupational exposure to silica dust may also occur, but cases are rare (reviewed in Ref. [3]).

In 1995, the WHO and the International Labour Organization started a public campaign of awareness and prevention with the aim to eliminate silicosis from the world by 2030. Even though several low- and middle-income countries established national programmes for the elimination of silicosis [4], the disease continues to constitute an occupational health hazard and the elimination target of 2030 is

virtually impossible to be met.

Among the clinical disorders associated with silicosis, tuberculosis is by far the most prominent, particularly in low and middle-income countries [5], and silicosis is second only to HIV infection as a risk factor for TB disease [6].

This review is based on studies published in English and included in PubMed using the search terms "silico-tuberculosis" and "silicosis".

2. Epidemiology

It is problematic to establish the prevalence of silico-tuberculosis worldwide; the real burden of people exposed to silica dust or affected by silicosis in resource-limited countries is unknown, due to lack of surveillance and poor access to health services [7]. In any case, the rates of silicosis and of silico-tuberculosis are higher in low-income countries because of poor adherence to safety rules, limited preventive equipment and lower education [5]. Few published studies have affected the silico-tuberculosis prevalence, and the literature largely consists of case reports. The relative risk to develop pulmonary tuberculosis for patients with silicosis has been estimated to be 2.8, and extra-pulmonary

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tuberculosis can be up to 3.7 times higher than in individuals without silicosis [8]. The increased risk of both pulmonary and extrapulmonary tuberculosis is linked also to exposition to silica [9], can continue for years even if the exposure ends [10], increases with the severity of silicosis, and is higher in patients with acute and accelerate forms of the disease [11].

Importantly, tuberculosis is transmitted within mines; DNA fingerprinting showed that at least 50% of TB was attributable to ongoing transmission within the mining community, and that in 85% of patients in clusters, transmission was explained by current or past mine employment [12].

Male gender (99% of cases), old age, and pulmonary/pleural TB were significantly associated to cases of silico-tuberculosis in an analysis of all patients notified with tuberculosis between 1999 and 2012 in Portugal [13]. Smear-negative and positive culture sputum were more frequent in silico-tuberculosis; interestingly, a higher risk for extra-pulmonary TB was not confirmed in this study [13]. In a prospective study evaluating 1153 South African gold miners, the annual incidence of tuberculosis was 2.7% in those with silicosis, compared with 0.98% in those without [9], whereas in a study done in Hong Kong and assessing the efficacy of chemoprophylaxis in patients with silicosis, the annual incidence of tuberculosis was 7% in the group receiving placebo [14].

A study including 2255 South African gold miners followed for 24–27 years showed that the risk of developing pulmonary tuberculosis is linked to the intensity of the exposure and the severity of silicosis (where present), and found a mean interval of 7.6 years between the end of exposure to silica dust and the diagnosis of pulmonary TB [10]. The association between crystalline silica exposure and silicosis and pulmonary tuberculosis was clearly confirmed in two other studies [9,15]. In particular, in a US study the cumulative degree of exposure to silica increased the risk to develop silico-tuberculosis with a mean odds ratio of 1.47, that increased to 2.48 in the group with more intense exposure [15]. In another study on 381 gold miners with pulmonary tuberculosis, the risk of TB increased for the miners who had worked for over 10 years, with an OR of 1.9; if exposure had been longer than 15 years, the risk was four times higher than in controls [16].

Silicosis and HIV infection are powerful risk factors for TB and add to each other [17]. HIV infection raises TB incidence by increasing the risk of reactivation of latent *Mycobacterium tuberculosis* infection and favouring more rapid progression from infection to disease. In a prevalence study involving 624 former gold miners from Lesotho, eighteen months after their employment at a South African mine had been terminated, almost 25% had silicosis; 26% of those for whom data was available, had a past history of TB; 1.3% were already on anti-TB drugs; 2.9% had active, undiagnosed TB; and 2.1% were put on anti-TB treatment on clinical grounds [18]. 22.3% of subjects had urine anti-HIV antibodies [18].

3. Pathophysiology

Silica exposure diminishes dendritic cell activation and causes a non-specific impairment in the inflammatory response. Antibacterial mechanisms are affected [19] and susceptibility to bacterial infections, especially *Mycobacterium tuberculosis* and other mycobacteria, increases [20]. Downregulation of Toll-like receptor 2 resulting from silica exposure may increase susceptibility to tuberculosis [21]. Various pathways may cause disease in the presence of silica and *Mycobacterium tuberculosis*, and genetic polymorphism of tumor necrosis factor alpha, natural resistance-associated macrophage protein 1 (NRAMP1), and inducible nitric oxide synthase (iNOS) in macrophages can influence the response to silica exposure and tuberculosis in both South African gold miners [22] and Chinese iron miners [23]. Silica particles increase intracellular replication of *Mycobacterium tuberculosis* and release from macrophages [24]. In rat models, defence against *Mycobacterium tuberculosis* becomes poorer as silicosis progresses [25]. However, silica-induced Th1 responses, with TNF-alpha and IFN-gamma production,

should contribute to resistance to, or elimination of, *Mycobacterium tuberculosis* [26]. The pathophysiological mechanisms are still incompletely identified.

4. Clinical features

Pleural tuberculosis is by far the most common form of extrapulmonary TB [6,9,14,27], followed by pericardial and lymph nodal forms [6,8,9,14]; intracranial, spinal, soft tissue, and disseminated TB are rarer [8]. The presence of typical features of pulmonary TB such as persistent cough, fever, weight loss or haemoptysis can allow to suspect the diagnosis, but the diagnosis of active tuberculosis superimposed on silicosis is often difficult, particularly in initial phases, when clinical manifestations may not be indicative and radiological alterations can be indistinguishable from those due to the pre-existing silicosis. Radiologically, rapid appearance of new opacities, and the finding of pleural effusion or excavations should raise the suspicion. Overall, active disease is not easy to detect on clinical grounds in patients with silicosis. The clinical spectrum of pleural tuberculosis is variable, as the patient may sometimes be asymptomatic and the disease is accidentally discovered through a chest radiography [28]. The symptoms of tuberculous pericarditis are generally nonspecific (fever, weight loss, and night sweats) [29], but a few patients present in late stages with the signs and symptoms of constrictive pericarditis [29,30].

5. Diagnosis

Chest X-ray and smear examination are the backbones of pulmonary tuberculosis diagnosis also in patients with silicosis [31]. The chest X-ray often indicates TB in silicosis patients earlier than the clinical symptoms [4], and regular radiographic screening is perhaps more effective than sputum examination for early TB detection [32]. Comparison of serial films with particular attention to asymmetric nodules or consolidation, effusions, cavities and focal or rapid deterioration should be done [33]. Although cavitation is the strongest indicator of probable silico-tuberculosis, it may also be caused by ischemic changes in a silicosis fibrotic mass [34]. When sputum smear microscopy and chest X-ray leave doubts about the presence of active tuberculosis, chest CT scan can be useful [31]. Nonetheless, cases of silico-tuberculosis in the presence of progressive massive fibrosis remain, for instance, particularly difficult to detect [35] and bronchoscopy with bronchoalveolar lavage should be used, in conjunction with transbronchial biopsy where possible. Silico-tuberculosis is associated with clinically significant lung function impairment, particularly airways obstruction [36]. Spirometry, performed at the time of the diagnosis and at follow-up for the evaluation of possible functional deterioration, can assess the level of lung function impairment after effective treatment of tuberculosis.

6. Treatment

Treatment of tuberculosis in patients with silicosis is difficult [37,38], perhaps due to impairment of macrophage function by free silica and/or poor drug penetration into fibrotic nodules [24,39–41]. Usual anti-tuberculosis drugs with directly observed therapy are recommended but an extended duration of at least eight months is probably needed, to reduce the chances of relapse. In a well conducted, controlled clinical trial in Hong Kong, patients with silico-tuberculosis were randomized to receive 6 months or 8 months of three-times-weekly therapy with isoniazid, rifampicin, pyrazinamide and streptomycin; patients with a history of previous anti-TB therapy received also ethambutol for the first three months [41]. 80% of patients converted to a negative sputum culture in two months, 22% of patients who were treated for six months relapsed during a three-year assessment versus 7% of those who were treated for eight months, and 22% of patients had important adverse drug reactions [41]. In a subsequent South African study, gold miners with pulmonary tuberculosis received isoniazid, rifampicin,

pyrazinamide and streptomycin on weekdays for five months; at the time of diagnosis, chest X-rays were evaluated for the presence of silicosis, and all participants were followed for at least five years after completing treatment [42]. The risk of TB relapse in patients with silicosis was 1.55 times higher than in patients without silicosis. Further studies on the duration and tolerability of anti-TB treatment in patients with silicosis are warranted.

7. Prevention

TB prevention in silicosis patients include active surveillance of the workers, periodic chest X-rays, tuberculin skin test or, where possible, interferon-gamma releasing assay (IGRA) testing [43], and adoption of measures to reduce the exposure to silica dust. In this regard, engineering and work practice control of silica dust exposure [44] are particularly important in communities with high prevalence of tuberculosis. A few studies have evaluated the efficacy and safety of chemoprophylaxis in silica-exposed subjects, with or without silicosis. In a randomized, double-blind, placebo-controlled trial evaluating three chemoprophylaxis regimens (300 mg/day of isoniazid for 24 weeks; 300 mg/day of isoniazid and 600 mg/day of rifampicin for 12 weeks; 600 mg/day of rifampicin for 12 weeks; or placebo for 24 weeks) in 652 silicosis patients who did not have active tuberculosis and had never been treated for TB, the use of any chemoprophylaxis regimen reduced the risk of developing tuberculosis by approximately 50% [14]. However, the proportion of patients who developed tuberculosis was still substantial [14]. In a South African trial where 382 gold miners with silicosis were randomized to receive rifampicin 600 mg, isoniazid 400 mg and pyrazinamide 1.25 g daily as Rifater or placebo, TB was not prevented [45], perhaps due to a high reinfection rate. In a massive, cluster-randomized study conducted in South African gold mines and where isoniazid was dispensed for six months or more, a reduced incidence of tuberculosis during treatment was observed but there was a subsequent rapid loss of protection [46], indicating that mass screening and treatment for latent tuberculosis had no effect on TB control in the mines.

In spite of the above quite discouraging results, in silicosis patients with positive tuberculin skin test (induration ≥ 10 mm), after excluding active TB, chemoprophylaxis should be started, using either isoniazid for six-twelve months, rifampicin for four months, or isoniazid and rifampicin for three months [33].

Long-term adherence to chemoprophylactic regimens and side-effects are major problems. To reduce long-term non-compliance, in a recently published study 513 HIV-uninfected, silicosis adult Chinese patients with or without latent TB infection were given a short-course of three months, directly observed, once weekly rifapentine and isoniazid [47]. The prophylactic regimen was effective in preventing active TB; however, there was a high frequency of adverse events (70.4%), and in particular, 10.8% of the participants experienced flu-like systemic drug reactions, and 2.1% had hepatotoxicity [47].

8. Main research needs

Additional studies are clearly needed on the pathophysiology of silico-tuberculosis. In particular, no research has been done on dendritic cells, neutrophils, NK cells, B cells, and only scant and contradictory data are available on T cells [26].

Silicosis control programs should be integrated with TB control programs at national level, and the effects of the integration studied. The effects of awareness campaigns to sensitize mine workers about their risk of silicosis and of the use of personal protective measures should also be investigated.

Finally, more studies on both TB preventive therapy regimens and on treatment of tuberculosis in patients with silicosis are required.

9. Conclusions

Tuberculosis continues to constitute an important issue in patients with silicosis. Surveillance and reporting of silicosis and TB among former miners must be improved to monitor the effectiveness of control measures. Dust control measures have to be strongly enforced [48] and accompanied by comprehensive TB prevention activities among in-service miners. Serious dust control measures not only may prove impossible to apply in some workplaces, e.g. in low- and middle-income countries gold mines, where deep-level mining happens in constantly changing workplaces, but, somehow surprisingly, are not applied even in high-income countries, such as Australia [48]. In some countries, mining regulations do not have crystalline silica exposure limits, and this problem needs to be corrected as well [49]. A solution to the issue of TB is highly difficult: in many cases, if workers are prohibited from staying in the mines because of their TB status, they will go back to their generally poor communities where it will prove extremely difficult to take a full course of treatment and where TB transmission is likely to occur; if they are allowed to continue their work, spread of TB will increase within the mines. In any case, chemoprophylaxis needs to be expanded around the world to reduce the incidence of pulmonary and extrapulmonary tuberculosis in miners.

Ethical statement

Not applicable.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] Intergovernmental Forum on Mining, Minerals, Metals and Sustainable Development (IGF). Global trends in artisanal and small-scale mining (ASM): a review of key numbers and issues. Winnipeg: IISD; 2018.
- [2] Murie F. Building safety – an international perspective. *Int J Occup Environ Health* 2007;13:5–11. <https://doi.org/10.1179/107735207800244974>.
- [3] Bhagia LJ. Non-occupational exposure to silica dust. *Indian J Occup Environ Med* 2012;16:95–100. <https://doi.org/10.4103/0019-5278.111744>.
- [4] Elimination of silicosis. *GOHNET Newslett* 2007;12:1–19. Geneva: World Health Organization..
- [5] Sharma N, Kundu D, Dhakeda S, Das A. Silicosis and silicotuberculosis in India. *Bull World Health Organ* 2016;94:777–8. <https://doi.org/10.2471/BLT.15.163550>.
- [6] Dheda K, Barry CE, Maartens G. Tuberculosis. *Lancet* 2016;387:1211–26. [https://doi.org/10.1016/S0140-6736\(15\)00151-8](https://doi.org/10.1016/S0140-6736(15)00151-8).
- [7] Farazi A, Jabbariasl M. Silico-tuberculosis and associated risk factors in central province of Iran. *Pan Afr Med J* 2015;20:333. <https://doi.org/10.11604/pamj.2015.20.333.4993>.
- [8] Cowie RL. The epidemiology of tuberculosis in gold miners with silicosis. *Am J Respir Crit Care Med* 1994;150(5 Pt 1):1460–2. <https://doi.org/10.1164/ajrccm.150.5.7952577>.
- [9] teWaterNaude JM, Ehrlich RI, Churchyard GJ, Pemba L, Dekker K, Vermeis M, et al. Tuberculosis and silica exposure in South African gold miners. *Occup Environ Med* 2006;63:187–92. <https://doi.org/10.1136/oem.2004.018614>.
- [10] Hnizdo E, Murray J. Risk of pulmonary tuberculosis relativeto silicosis and exposure to silica dust in South African goldminers. *Occup Environ Med* 1998;55:496–502. <https://doi.org/10.1136/oem.55.7.496>.
- [11] American Thoracic Society Committee of the Scientific Assembly on Environmental and Occupational Health. Adverse effects of crystalline silicaexposure. *Am J RespirCrit Care Med* 1997;155:761–8. <https://doi.org/10.1164/ajrccm.155.2.9032226>.
- [12] Godfrey-Faussett P, Sonnenberg P, Shearer SC, Bruce MC, Mee C, Morris L, et al. Tuberculosis control and molecular epidemiology in a South African gold-mining community. *Lancet* 2000;356:1066–71. [https://doi.org/10.1016/S0140-6736\(00\)02730-6](https://doi.org/10.1016/S0140-6736(00)02730-6).
- [13] Melo V, Baia L, Rita Gaio A, Duarte R. Silicosis, tuberculosis timebomb? *Rev Port Pneumol* 2016;22:355–7. <https://doi.org/10.1016/j.rppnen.2016.07.005>.
- [14] Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong

- Kong. *Am Rev Respir Dis* 1992;145:36–41. <https://doi.org/10.1164/ajrccm/145.1.36>.
- [15] Calvert GM, Rice FL, Boiano JM, Sheehy JW, Sanderson WT. Occupational silica exposure and risk of various diseases: an analysis using death certificates from 27 states of the United States. *Occup Environ Med* 2003;60:122–9. <https://doi.org/10.1136/oem.60.2.122>.
- [16] Corbett EL, Churchyard GJ, Clayton T, Herselman P, Williams B, Hayes R, et al. Risk factors for pulmonary mycobacterial disease in South African gold miners. A case-control study. *Am J Respir Crit Care Med* 1999;159:94–9. <https://doi.org/10.1164/ajrccm.159.1.9803048>.
- [17] Corbett EL, Churchyard GJ, Clayton TC, Williams BG, Mulder D, Hayes RJ, et al. HIV infection and silicosis: the impact of two potent risk factors on incidence of mycobacterial disease in South African miners. *AIDS* 2000;14:2759–68. <https://doi.org/10.1097/00002030-200012010-00016>.
- [18] Girdler-Brown BV, White NW, Ehrlich RI, Churchyard GJ. The burden of silicosis, pulmonary tuberculosis and COPD among former Basotho goldminers. *Am J Ind Med* 2008;51:640–7. <https://doi.org/10.1002/ajim.20602>.
- [19] Beamer CA, Holian A. Silica suppresses Toll-like receptor ligand induced dendritic cell activation. *FASEB J* 2008;22:2053–63. <https://doi.org/10.1096/fj.07-095299>.
- [20] Blanco Pérez JJ, Pérez González A, Morano Amado LE, Guerra Vales L, Vázquez Gallardo R, Salgado Barreira Á, et al. Clinical significance of environmental mycobacteria isolated from respiratory specimens of patients with and without silicosis. *Arch Bronconeumol* 2016;52:145–50. <https://doi.org/10.1016/j.arbres.2015.07.007>.
- [21] Beamer GL, Seaver BP, Jessop F, Shepherd DM, Beamer CA. Acute exposure to crystalline silica reduces macrophage activation in response to bacterial lipoproteins. *Front Immunol* 2016;7:49. <https://doi.org/10.3389/fimmu.2016.00049>.
- [22] Corbett EL, Mozzato-Chamay N, Butterworth AE, De Cock KM, Williams BG, Churchyard GJ, et al. Polymorphisms in the tumor necrosis factor- α gene promoter may predispose to severe silicosis in black South African miners. *Am J Respir Crit Care Med* 2002;165:690–3. <https://doi.org/10.1164/ajrccm.165.5.2010050>.
- [23] Qu Y, Tang Y, Cao D, Wu F, Liu J, Lu G, et al. Genetic polymorphisms in alveolar macrophage response-related genes, and risk of silicosis and pulmonary tuberculosis in Chinese iron miners. *Int J Hyg Environ Health* 2007;210:679–89. <https://doi.org/10.1016/j.ijheh.2006.11.010>.
- [24] Snider Jr DE. The relationship between tuberculosis and silicosis. *Am Rev Respir Dis* 1978;118:455–60. <https://doi.org/10.1164/arrd.1978.118.3.455>.
- [25] Dong H, Jing W, Yabo Y, Xiaokang Y, Wan W, Min M, et al. Establishment of rat model of silicotuberculosis and its pathological characteristic. *Pathog Glob Health* 2014;108:312–6. <https://doi.org/10.1179/2047773214Y.0000000157>.
- [26] Konecny P, Ehrlich R, Gulumian M, Jacobs M. Immunity to the dual threat of silica exposure and Mycobacterium tuberculosis. *Front Immunol* 2019;9:3069. <https://doi.org/10.3389/fimmu.2018.03069>.
- [27] Barboza CE, Winter DH, Seiscento M, Santos Ude P, Terra Filho M. Tuberculosis and silicosis: epidemiology, diagnosis and chemoprophylaxis. *J Bras Pneumol* 2008;34:959–66. <https://doi.org/10.1590/s1806-37132008001100012>.
- [28] Udawadia ZF, Sen T. Pleural tuberculosis: an update. *Curr Opin Pulm Med* 2010;16:399–406. <https://doi.org/10.1097/MCP.0b013e328339cf6e>.
- [29] Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med* 2000;161:1376–95. doi: 10.1164/ajrccm.161.4.16141.
- [30] Ortals DW, Avioli LV. Tuberculous pericarditis. *Arch Intern Med* 1979;139:231–4.
- [31] Ryu YJ. Diagnosis of pulmonary tuberculosis: recent advances and diagnostic algorithms. *Tuberc Respir Dis (Seoul)* 2015;78:64–71. <https://doi.org/10.4046/trd.2015.78.2.64>.
- [32] Solomon A. Silicosis and tuberculosis: Part 2. A radiographic presentation of nodular tuberculosis and silicosis. *Int J Occup Environ Health* 2001;7:54–7. <https://doi.org/10.1179/107735201800339605>.
- [33] Leung CC, Yu IT, Chen W. Silicosis. *Lancet* 2012;379:2008–18. [https://doi.org/10.1016/S0140-6736\(12\)60235-9](https://doi.org/10.1016/S0140-6736(12)60235-9).
- [34] Chong S, Lee KS, Chung MJ, Han J, Kwon OJ, Kim TS. Pneumoconiosis: comparison of imaging and pathologic findings. *Radiographics* 2006;26:59–77. <https://doi.org/10.1148/rg.261055070>.
- [35] Moyo D, Kgalamono S. Diagnostic challenges of silico-tuberculosis in a case with progressive massive fibrosis – a Zimbabwe case report. *Occup Health Southern Afr* 2017;23:11–3.
- [36] Ehrlich RI, Myers JE, te Water Naude JM, Thompson ML, Churchyard GJ. Lung function loss in relation to silica dust exposure in South African gold miners. *Occup Environ Med* 2011;68:96–101. <https://doi.org/10.1136/oem.2009.048827>.
- [37] Medical Research Council/Miners' Chest Diseases Treatment Centre. Chemotherapy of pulmonary tuberculosis with pneumoconiosis. Second report to the Medical Research Council from the Joint Investigators. *Tubercle* 1967;48:1–10.
- [38] Morgan EJ. Silicosis and tuberculosis. *Chest* 1979;75:202–3. <https://doi.org/10.1378/chest.75.2.202>.
- [39] Allison AC, Harington JS, Burbeck M. An examination of the cytotoxic effects of silica on macrophages. *J Exp Med* 1966;124:141–61. <https://doi.org/10.1084/jem.124.2.141>.
- [40] Lowrie DB. What goes wrong with the macrophage in silicosis? *Eur J Respir Dis* 1982;63:180–2.
- [41] Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A controlled clinical comparison of 6 and 8 months of antituberculosis chemotherapy in the treatment of patients with silicotuberculosis in Hong Kong. *Am Rev Respir Dis* 1991;143:262–7. <https://doi.org/10.1164/ajrccm/143.2.262>.
- [42] Cowie RL. Silicotuberculosis: long-term outcome after short course chemotherapy. *Tuber Lung Dis* 1995;76:39–42. [https://doi.org/10.1016/0962-8479\(95\)90578-2](https://doi.org/10.1016/0962-8479(95)90578-2).
- [43] Leung CC, Yam WC, Yew WW, Ho PL, Tam CM, Law WS, et al. T-Spot.TB outperforms tuberculin skin test in predicting tuberculosis disease. *Am J Respir Crit Care Med* 2010;182:834–40. <https://doi.org/10.1164/rccm.200912-1875OC>.
- [44] Lahiri S, Levenstein C, Nelson DI, Rosenberg BJ. The cost effectiveness of occupational health interventions: prevention of silicosis. *Am J Ind Med* 2005;48:503–14. <https://doi.org/10.1002/ajim.20222>.
- [45] Cowie RL. Short course chemoprophylaxis with rifampicin, isoniazid and pyrazinamide for tuberculosis evaluated in gold miners with chronic silicosis: a double-blind placebo-controlled trial. *Tuber Lung Dis* 1996;77:239–43. [https://doi.org/10.1016/s0962-8479\(96\)90007-6](https://doi.org/10.1016/s0962-8479(96)90007-6).
- [46] Churchyard GJ, Fielding KL, Lewis JJ, Coetzee L, Corbett EL, Godfrey-Faussett P, et al. Thibela TB Study Team. A trial of mass isoniazid preventive therapy for tuberculosis control. *N Engl J Med* 2014;370:301–10. <https://doi.org/10.1056/NEJMoa1214289>.
- [47] Ruan QL, Huang XT, Yang QL, Liu XF, Wu J, Pan KC, et al. Efficacy and safety of weekly rifampentine and isoniazid for tuberculosis prevention in Chinese silicosis patients: a randomized controlled trial. *Clin Microbiol Infect* 2020. <https://doi.org/10.1016/j.cmi.2020.06.008> [S1198-743X(20)30348-7 E-published ahead of print].
- [48] Editorial. The world is failing on silicosis. *Lancet Respir Med* 2019;7:283. [https://doi.org/10.1016/S2213-2600\(19\)30078-5](https://doi.org/10.1016/S2213-2600(19)30078-5).
- [49] Hayumbu P, Robins TG, Key-Schwartz R. Cross-sectional silica exposure measurements at two Zambian copper mines of Nkana and Mufulira. *Int J Environ Res Public Health* 2008;5:86–90. <https://doi.org/10.3390/ijerph5020086>.