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Evaluation of a Tuberculosis screening strategy directed to quarry workers in a high-incidence area

Ana Sofia da Silva Carvalho Pereira de Sousa

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INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR

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EVALUATION OF A TUBERCULOSIS SCREENING STRATEGY DIRECTED TO QUARRY WORKERS IN A HIGH-INCIDENCE AREA

Tese de Candidatura ao grau de Doutora em Ciências Médicas submetida ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto

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To my mother and my father.

To my brothers.

To my husband and my kids.

To my family and my friends.

I am thankful, of course, to God. For each story, each idea, each word, each day.

Isaac Bashevis Singer

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Nothing is softer or more flexible than water, yet nothing can resist it.

Lao Tzu

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Acronyms

ACF: Active Case Finding

aOR: Adjusted Odds Ratio

ARI: Annual rate of infection

CI: Confidence Interval

CXR: Chest X-ray

HIV: Human Immunodeficiency Virus

ICER: Incremental Cost-Effectiveness Ratio

IGRA: Interferon-Gamma Release Assays

ILO: International Labor Organization

NHS: National Health Service

NNS: Number needed to screen

NTP: National Tuberculosis Program

SDG: Sustainable Development Goals

TB: Tuberculosis

TPT: Tuberculosis preventive treatment

TST: Tuberculin Skin Test

WHO: World Health Organization

Publications

1. Sousa S, Rocha D, Silva JC, Ribeiro AI, Gonçalves G, Almeida Á, Correia AM, Duarte R, Carvalho C. Comparing the cost-effectiveness of two screening strategies for latent tuberculosis infection in Portugal. Pulmonology. 2021 Nov-Dec;27(6):493-499. doi: 10.1016/j.pulmoe.2021.04.002. Epub 2021 May 27. PMID: 34053903.
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Abstract

Tuberculosis (TB) is one of the leading causes of morbidity and mortality from an infectious agent worldwide. Portugal, a medium-incidence country, has consistently seen TB notification rates decline for the last two decades. However, two municipalities in Northern Portugal are considered TB high-incidence areas, with close to fourfold the national rate. On their borders, a mining community is present along the *Tâmega* River. This area is noteworthy in the Portuguese TB epidemiological context due to the presence of a significant share of the country's quarry workers. Their higher risk is mainly due to silicosis and exposure to silica, but other common risk factors may occur.

Aligned with the End TB Strategy, a strategy consisting of annual TB disease and infection screening directed to *Penafiel* and *Marco de Canaveses* quarry worker*s* was implemented in 2018 by the local Public Health units and the regional and national TB Program teams. This thesis aimed to measure the effect of that strategy.

IGRA was used as a more cost-effective strategy for TB infection screening. Through molecular epidemiology, active transmission of TB was documented, with several outbreaks between quarry workers occurring simultaneously. Among 997 workers screened during a four-year period, with an average of 2.06 screenings per worker, three cases of TB disease were diagnosed, and a prevalence of TB infection of 19.8% was found. Radiological findings compatible with silicosis were identified in 25% of workers. The overall rate of TB infection was 3.2 per 100 person-year, with silicosis, diabetes, and older age being significant risk factors for TB infection. From 2018 to 2022, the annual rate of infection decreased in the group of quarry workers regularly screened for TB; the decline was about three times larger than the one observed in the TB notification rate observed in the *Penafiel* and *Marco de Canaveses* communities. The economic evaluation of the screening program suggested that it cost less than the monetary benefit return in the perspective of society; companies and workers saved most of the predicted costs of inaction.

The results support the effectiveness and cost-effectiveness of regular TB screening in quarry workers from high-incidence areas in reducing their overall risk of infection. Although screening directed at vulnerable groups is a mandatory strategy to eliminate TB and contributed to the faster decrease in the rate of infection among quarry workers, the burden of TB in communities where ongoing active transmission occurs can continuously put most vulnerable groups at risk if no other community measures are implemented. Genotyping all *Mycobacterium tuberculosis* strains in the communities, together with public health authorities' routine epidemiological investigations, could reduce active transmission. The screening strategy directed at quarry workers, which consists of a symptom questionnaire, chest-X ray, and IGRA, should be maintained and aligned with the End TB strategy.

Furthermore, the systematic TB infection screening for patients with silicosis should be ensured independently of their working status. The development of innovative technologies to address TB infection, specifically tests that are better predictors of progression to TB, could increase the screening effectiveness and decrease overall and National Health Service-related costs. Ending silicosis, a preventable and highly disabling condition, would contribute to achieving End TB. Finally, gathering a high-risk group's TB screening strategy with an enhanced case detection strategy in high-incidence communities could lead the way to control (or eliminate) TB.

Resumo

A tuberculose (TB) é uma das principais causas de morbimortalidade por agente infecioso em todo o mundo. Portugal é considerado um país de média incidência, onde o declínio da incidência tem diminuído consistentemente nas últimas décadas. No entanto, dois municípios do Norte de Portugal são considerados áreas de elevada incidência de TB, com cerca de quatro vezes a taxa de notificação nacional. Na fronteira entre ambos existem freguesias, nas margens do rio Tâmega, onde a indústria de extração e transformação da pedra representa uma importante atividade económica. Os trabalhadores das pedreiras são importantes no contexto epidemiológico português da TB, sobretudo nesta área onde existem em grande número. O seu maior risco deve-se principalmente à silicose e à exposição à sílica, mas podem ocorrer outros fatores de risco comuns.

Alinhada com a Estratégia *End TB*, as Unidades de Saúde Pública e as equipas regional e nacional do Programa Nacional para a Tuberculose implementaram em 2018 uma estratégia de rastreio de TB doença e infeção dirigida a trabalhadores da indústria da pedra de Penafiel e Marco de Canaveses. Esta tese teve como objetivo medir o efeito dessa estratégia.

Para o rastreio de TB infeção, foi utilizada uma estratégia que consiste na realização de um teste IGRA, que foi a mais custo-efetiva. Através da epidemiologia molecular, foi documentada transmissão ativa de TB, com vários surtos simultâneos entre trabalhadores da indústria da pedra. Foram rastreados 997 trabalhadores durante um período de quatro anos, com uma média de 2,06 rastreios por trabalhador; foram diagnosticados três casos de TB doença e foi encontrada uma prevalência de TB infeção de 19,8%. Foram encontradas evidências radiológicas compatíveis com silicose em 25% dos trabalhadores. A taxa de infeção foi de 3,2 por 100 pessoas-ano, tendo a silicose, diabetes e idade avançada sido identificados como fatores de risco significativos para TB infeção. De 2018 a 2022, a taxa anual de infeção diminuiu no grupo de trabalhadores regularmente rastreados para TB; esta diminuição foi cerca de três vezes superior à observada na taxa de notificação de TB em Penafiel e Marco de Canaveses. A avaliação económica do programa de rastreio sugeriu que este custou menos do que o retorno monetário obtido pela prevenção de casos de TB doença na perspetiva da sociedade; as empresas e os trabalhadores pouparam a maior parte dos custos previstos de inação.

Os resultados desta tese apoiam a efetividade e custo-efetividade do rastreio regular de TB em trabalhadores da indústria da pedra em áreas de elevada incidência. Embora o rastreio dirigido a grupos vulneráveis seja considerado uma estratégia fundamental para

eliminar a TB e tenha contribuído para a diminuição mais rápida da taxa de infeção entre os trabalhadores da indústria da pedra, a carga de TB nas comunidades onde ocorre transmissão ativa pode colocar os grupos mais vulneráveis continuamente em risco, se não forem implementadas outras medidas. A genotipagem de todas as estirpes de *Mycobacterium tuberculosis* isoladas na área de alta incidência, juntamente com a investigação epidemiológica realizada por rotina pelas autoridades de saúde, poderia reduzir a transmissão ativa. A estratégia de rastreio composta por questionário de sintomas, radiografia de tórax e IGRA deve ser mantida, alinhada com a estratégia *End TB*. Além disso, o rastreio sistemático de TB infeção em pessoas com silicose deve ser garantido, quer estejam a trabalhar ou não. O desenvolvimento de tecnologias inovadoras para abordar a TB infeção, especificamente testes que sejam melhores indicadores da progressão para TB doença, poderia aumentar a efetividade do rastreio e diminuir os custos totais e especialmente os custos suportados pelo Serviço Nacional de Saúde. Eliminar a silicose, uma doença evitável e altamente incapacitante, contribuiria também para eliminar a TB. Em conclusão, garantir o rastreio de TB aos grupos de risco identificados e aumentar a deteção precoce de casos infeciosos nas comunidades de elevada incidência poderá contribuir para o controlo (ou eliminação) da TB.

1. Introduction

1.1 **End TB strategy**

In the scope of the transition from the 2015 Millennium Development Goals to the Sustainable Development Goals (SDG) for 2030, the world community launched a dramatically accelerated fight against tuberculosis (TB) at the 2014 World Health Assembly (World Health Organization, 2015d). “Ending the TB epidemic” was set as a target within the health-related SDG 3 by the United Nations General Assembly in September 2015 (World Health Organization, 2015b). The World Health Organization’s (WHO) End TB Strategy, aligned with the United Nations SDG, emphasised the role of communities and civil society in ending the TB epidemic (World Health Organization, 2023b).

The End TB Strategy was based on three pillars: 1) integrated, patient-centred care and prevention; 2) bold policies and supportive systems; and 3) intensified research and innovation (World Health Organization, 2015b).

The first pillar implies early diagnosis of TB, including universal drug-susceptibility testing and systematic screening of contacts and high-risk groups; treatment of all people with TB, including drug-resistant TB and patient support; collaborative TB/HIV activities and management of co-morbidities; and preventive treatment of persons at high risk and vaccination against TB (World Health Organization, 2015b).

The second requires political commitment with adequate resources for TB care and prevention; engagement of communities, civil society organisations, and public and private care providers; universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control; social protection, poverty alleviation and actions on other determinants of TB (World Health Organization, 2015b).

The final one can be realised through discovery, development, and rapid uptake of new tools, interventions, and strategies, as well as by researching ways to optimise implementation and impact while promoting innovations (World Health Organization, 2015b).

These pillars were built upon four fundamental principles to be respected by all countries adopting the Strategy: 1) government stewardship and accountability, with monitoring and evaluation; 2) building a strong coalition with civil society and communities; 3) protecting and promoting human rights, ethics, and equity; and 4) adapting the strategy and targets at country level, with global collaboration (World Health Organization, 2015b).

Strategy targets and milestones were defined based on projections of what could be achieved in two phases. Key elements of the first phase (2016-2025) included optimum use

of existing interventions, achievement of universal health coverage for essential prevention, treatment, and care interventions, and efforts to address the social determinants and consequences of TB. The second phase (2026-2035) will also require the availability and wide use of new tools, including vaccines, point-of-care diagnostic tests for infection and disease, and shorter treatment regimens for TB disease and TB infection (World Health Organization, 2015b).

For 2035, a 95% reduction in TB deaths and a 90% reduction in TB incidence rate, both compared with 2015, and zero TB-affected families facing catastrophic costs due to TB were set as the main targets (World Health Organization, 2015d).

A paradigm shift was set from TB control to TB elimination. The TB elimination strategy broadened the concept of TB control to identify and treat the pool of latently infected individuals from which future TB cases will be generated (Matteelli *et al.*, 2018). Hence, ending TB can be achieved by combining the effective treatment of active TB — early case detection and high cure rates to interrupt transmission — with methods to prevent new infections and neutralise existing latent infections. Vigorous implementation of the WHO's former strategy (Stop TB Strategy) is needed to achieve the first, facilitated by the effective supply of and demand for health services. The latter calls for new technology, including biomarkers of TB risk, diagnostics, drugs, and vaccines (Dye *et al.*, 2013). TB elimination, defined as less than one TB case per million population, a scenario where TB is not eradicated but instead kept at such a low level that it no longer constitutes a public health problem (Matteelli *et al.*, 2018), can be reached only by combining rapid diagnosis and effective treatment of both TB disease and TB infection cases (Dye *et al.*, 2013). Systematic diagnosis and treatment of TB infection is vital to the TB elimination strategy (World Health Organization, 2014). Preventing TB infection and stopping the progression from infection to disease is critical to reducing TB incidence (World Health Organization, 2022b).

TB infection is considered the reservoir for most emerging TB disease cases in low-incidence countries. TB preventive treatment has been a core strategy for TB control in many low-prevalence settings for decades (Fox *et al.*, 2021). The management of TB infection first entered WHO recommendations with the End TB Strategy as a mainstay of its first pillar and a key element to pursue elimination. In 2019, the Guideline Development Group that produced the *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* decided to consider implementation considerations instead of restricting the recommendations based upon a TB incidence threshold (World Health Organization, 2020); thus, screening for TB infection was also considered for high-incidence settings.

Multisectoral collaboration and accountability were considered key to the successful implementation of the End TB Strategy. The required mix of biomedical, public health, and socioeconomic interventions, combined with research and innovation, is far beyond the remit of National Tuberculosis Programs (NTP) (World Health Organization, 2022b).

Preventive treatment among populations at increased risk of TB is essential for TB control and elimination (Yang *et al.*, 2020). Populations at the highest risk of progression from TB infection to TB disease can be identified, and diagnostic tests and risk stratification can be used to select those individuals most likely to benefit from preventive therapy (Rangaka *et al.*, 2015). Widespread treatment of high-risk populations could have a measurable impact on TB incidence (Havumaki *et al.*, 2021).

A human-rights-based response to TB was set in action, particularly towards the rights of those who are most affected by it: the most vulnerable, marginalised, and hard-to-reach populations (Raviglione and Krech, 2011; Stop TB Partnership, 2019; Litvinjenko *et al.*, 2023). Several studies have reported a strong geographic correlation between social deprivation and TB (Raina MacIntyre *et al.*, 1997; Lönnroth *et al.*, 2009; Whiting, Unwin and Roglic, 2010; Apolinário *et al.*, 2017). The greater risk of TB among people from more disadvantaged socioeconomic groups is partially explained by greater exposure to risk factors. For example, smoking and alcohol abuse follow the socioeconomic gradient (MN *et al.*, 2007; Lönnroth *et al.*, 2009; Imtiaz *et al.*, 2017).

The End TB strategy fostered socioeconomic interventions to reduce poverty, increase social protection, and ensure universal access. Ending extreme poverty could result in a reduction in the global incidence of TB of 33.4%, and expanding social protection coverage could result in a reduction in incidence of 76.1% by 2035; both pathways could reduce TB incidence in 84.3% (54.7–94.9) (Carter *et al.*, 2018). To tackle socioeconomic determinants just as vigorously as the remaining technical elements (active case-finding, effective diagnosis and treatment of infectious cases, and management of TB infection) was considered mandatory to eliminate TB worldwide (Migliori and Garcia-Basteiro, 2018).

Vulnerable groups are those whose socioeconomic conditions or lifestyle make it difficult to recognise the clinical onset of TB, access diagnostic and treatment services, self-administer treatment and attend regular healthcare appointments (European Centre for Disease Prevention and Control, 2016). People within key population groups have a higher risk of TB because of increased exposure, limited access to quality-assured TB services, or biological or behavioural factors, and are often hard to reach and marginalised (European Centre for Disease Prevention and Control, 2016; Stop TB Partnership, 2019; National Institute for Public Health and the Environment, 2022). The burden of TB is substantially higher among vulnerable groups than general populations, suggesting a need for improved

integration of these groups, including dedicated efforts for their identification, targeted screening and prevention measures, as well as treatment support (Litvinjenko *et al.*, 2023). Commit to systematic screening of relevant risk groups for TB disease and TB infection, as identified in WHO guidance documents, was highlighted in the End TB strategy (United Nations, 2018). The provision of universal access to TB care and prevention with greater attention on vulnerable and hard-to-reach populations was highlighted in Pilar 1 (World Health Organization, 2015d). Intensifying TB screening in the identified subpopulations was proposed as an important strategy in Portugal (Sentís *et al.*, 2021).

1.2 **Epidemiology of TB in Portugal**

Tuberculosis (TB) continues to be an important cause of morbidity and mortality worldwide. World Health Organization (WHO) estimated that, in 2022, 10.6 million people had TB, and 1.3 million died from the disease (World Health Organization, 2023a). The global gap between the estimated number of people developing TB (incident cases) and the reported number of people newly diagnosed with TB (notified cases) had grown in 2020 and 2021 as a consequence of the COVID-19 pandemic and narrowed to a best estimate of 3.1 million in 2022 (similar to the pre-pandemic level of 2019). The estimated TB incidence rate was 133 per 100,000 population in 2022 globally. The net reduction from 2015 to 2022 was 8.7%, far from the WHO End TB Strategy milestone of 50% (World Health Organization, 2023a). The net reduction in the global number of deaths caused by TB from 2015 to 2022 was 19%, far from the WHO End TB Strategy milestone of a 75% reduction by 2025 (World Health Organization, 2023a).

The COVID-19 pandemic adversely affected access to TB services and financing and intensified key social determinants of TB (Falzon *et al.*, 2023). With adequate funding, leadership and action to facilitate the affordable and equitable provision of TB services, social protection measures and effective interventions, the TB epidemic could be brought to an end (Millington *et al.*, 2024).

TB notification rate has consistently declined in Portugal for the last two decades. It was inferior to 20 cases per 100,000 population-year for the first time in 2016; in 2022, it was 14.5 cases per 100,000 population (Direção-Geral da Saúde, 2024). From 2015 to 2022, the net reduction in TB incidence was 30.7%, and in deaths from TB was 43.5% (Direção-Geral da Saúde, 2024).

Similar to what happens around the world, the distribution of TB is not geographically homogeneous in Portugal: most cases happen in urban areas from the districts of *Porto*, *Lisbon* and *Setúbal* (Nunes, 2007; Oliveira *et al.*, 2020; Dias *et al.*, 2023). TB is more

frequent in socioeconomically disadvantaged areas (Oliveira *et al.*, 2022) and areas with a higher incidence of HIV (Couceiro, Santana and Nunes, 2011).

In two municipalities in Northern Portugal (*Penafiel* and *Marco de Canaveses*), the highest TB notification rate in the country is found - 67.5 cases per 100,000 population-year in 2015-2019 (first published data at the municipality level) (Direção-Geral da Saúde, 2020). It has stayed high and was 56.6 cases per 100,000 population in 2018-2022 (Direção-Geral da Saúde, 2024), i.e., >40 cases per 100,000 population-year, defined as the cut-off of TB high-incidence (UK Health Security Agency, 2020).

The *Tâmega* sub-region, where both *Penafiel* and *Marco de Canaveses* are located, is the area with the greatest deprivation in the Northern region in areas such as income, health and disability, education, housing, environment and access to goods and services (Luís Alves Sousa, 2014). Based on the Primary Health Care information system, the proportion of individuals with alcohol abuse in both genders and smoking in men was higher in this sub-region than in the rest of the North region in 2017 (Administração Regional de Saúde do Norte, 2020).

The economic activity of extracting and transforming stone in these two municipalities is relevant. In 2018, 184 extraction and processing companies had been registered (Sousa *et al.*, 2024). The companies were predominantly based in the parishes on the banks of the *Tâmega* River, which are also the parishes with the highest risk of TB (Unidade de Saúde Pública Vale do Sousa Sul, 2018).

In 2022, under a specific contract with the European Centre for Disease Prevention and Control, quarry workers were highlighted as a vulnerable group for TB in the Portuguese epidemiological context; a need to expand on and strengthen existing comprehensive TB service delivery was considered mandatory (National Institute for Public Health and the Environment, 2022). Quarry workers are frequently exposed to various conditions that place them at increased risk of disease onset and transmission besides silicosis, such as alcohol use, smoking, precarious employment, poor living and working conditions (Rosenman and Hall, 1996; Coutinho, D; Sousa, P; Oliveira, O; Gaio, R; Duarte, 2016; Francisco *et al.*, 2017). An estimated 30% of TB cases from those communities occurred in individuals who were quarry workers (Sousa *et al.*, 2019).

Active miners working in formal and informal settings are considered a vulnerable group for TB (Litvinjenko *et al.*, 2023). Mining communities often have the highest reported incidence of TB (Gottesfeld, Reid and Goosby, 2018). The burden of silicosis is found to be one of the main determinants of deaths, Years of Life Lost, and Years of Life with Disability due to TB (Albadrani, 2023). When TB and silicosis coexist, it increases the risk of death and makes

TB treatment less effective, so silicosis should be acknowledged as a major comorbidity of TB and should be included as one of the key risk factors in the differentiated TB care approach (Rupani, 2023c). The differential diagnosis between silicosis and TB is complex and contributes to delays in diagnosis and consequently to cases being more infectious (Cabral Melo Pereira *et al.*, 2016; Khemakhem *et al.*, 2022) – which leads to the emergence and amplification of TB outbreaks in the community.

The risk of TB increases with silicosis (Konečný *et al.*, 2019), as a relative risk of TB for people with silicosis compared to people without silicosis between 1.4 and 4.0 was pointed out in several studies (Ehrlich, 2018; Shafiei *et al.*, 2019; Ehrlich *et al.*, 2021; Yang *et al.*, 2022; Jamshidi *et al.*, 2023; Rupani, 2023a). Exposure to silica dust, even without silicosis, was also associated with a higher risk of progression to TB (Ehrlich *et al.*, 2021; Jamshidi *et al.*, 2023).

1.3 **TB infection**

TB infection is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest TB disease (WHO, 2018). It has been recognised that TB infection is not a stable condition but rather a spectrum of infections (e.g., intermittent, transient or progressive) which may lead to incipient, then subclinical, and finally active TB disease (Zellweger *et al.*, 2020).

Current laboratory tests are imperfect means to distinguish tuberculous immunoreactivity and tuberculous infection (Behr *et al.*, 2021). TB immunoreactivity cannot distinguish those who have cleared the infection from those with persistent infection, emphasising the urgent need for tests that can identify people with asymptomatic infections (Behr, Edelstein and Ramakrishnan, 2019).

Tuberculin skin test (TST) and interferon-gamma release assays (IGRA) are the main diagnostic tools for TB infection, although no gold standard test exists so far (WHO, 2022). Available tests evaluate the adaptive cellular immune response to mycobacterial antigens, not distinguishing active, latent, or past infection. Either the TST or IGRA can be used to test for TB infection according to WHO 2022 guidelines (WHO, 2022).

New *Mycobacterium tuberculosis* antigen-based skin tests may also be used to test for TB infection (WHO, 2022), but they still cannot reliably identify those at risk of progression to active disease. All available tests lack accuracy in identifying the progressors from infection to TB disease (Goletti *et al.*, 2022).

Around a quarter of the world population is estimated to be infected with *Mycobacterium tuberculosis* (World Health Organization, 2022a). In Portugal, data from 2002-2009

estimated that the prevalence of TB infection in the general population was 15% (Lopes *et al.*, 2014), and it is expected that it has decreased further over time (Ding *et al.*, 2022). It is considered that an individual from the general population with TB infection has a 10% chance of developing TB disease throughout life and a 5% chance in the first two years after exposure (Centers for Disease Control and Prevention, 2013; World Health Organization, 2015a, 2015c), making it a presumable reservoir of infection and an obstacle to eliminating the disease.

Preventive treatment is an essential component of the management of TB infection, designed to prevent the progression of TB infection to clinically active TB disease (Goletti et al., 2022). It reduces the risk of developing TB disease by 65-75% (Ai *et al.*, 2016). Identification and treatment of TB infection can greatly reduce the likelihood of developing TB disease and can potentially protect individuals and the population by reducing the number of potential future sources of infection.

2. Objectives

This work intends to assess the effectiveness and the cost-effectiveness of an annual TB screening strategy directed to quarry workers from a TB high-incidence area.

This thesis addresses the following specific objectives:

- Compare the cost-effectiveness of two TB infection screening strategies (two-step Tuberculin Skin Test (TST) plus Interferon-Gamma Release Assay (IGRA) with the IGRA-only screening strategy) in immunocompetent contacts of TB respiratory cases (**Publication 3.1**).
- To identify factors associated with being part of a cluster of TB cases among quarry workers in a TB high-incidence area (**Publications 3.2 and 3.3**).
- Identify subgroups of quarry workers with higher TB infection incidence rates (**Publication 3.4**).
- Compare the TB infection rate trends among quarry workers annually screened with the community TB notification rate trends during the screening period (**Publication 3.5**).
- Compare the TB infection screening program costs with its benefits measured in monetary units (**Publication 3.6**).

A detailed description of the methods is provided in each article, addressing the specific objectives.

3. Publications

3.1 Comparing the cost-effectiveness of two screening strategies for latent tuberculosis infection in Portugal

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ORIGINAL ARTICLE

Comparing the cost-effectiveness of two screening strategies for latent tuberculosis infection in Portugal

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KEY WORDS
Tuberculin Skin Test;
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Abstract
Introduction and objectives: Screening for latent tuberculosis infection (LTBI) in close contacts of infectious TB cases might include Tuberculin Skin Test (TST) and Interferon-Gamma Release Assays (IGRA), in combination or as single-tests. In Portugal, the screening strategy changed from TST followed by IGRA to IGRA-only testing in 2016. Our objective was to compare the cost-effectiveness of two-step TST/IGRA with the current IGRA-only screening strategy in immuno-competent individuals exposed to individuals with respiratory TB.
Materials and Methods: We reviewed clinical records of individuals exposed to infectious TB cases diagnosed in 2015 and 2016, in two TB outpatient centers in the district of Porto. We estimated medical, non-medical and indirect costs for each screening strategy, taking into account costs of tests and health care personnel, travel distance from place of residence to screening site and employment status. We calculated the incremental cost-effectiveness ratio (ICER) as

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the cost difference between the two screening strategies with the difference number of LTBI diagnosis as a measure of cost-effectiveness, assuming that treating LTBI is a cost-effective intervention. We also calculated adjusted odds-ratios to test the association between diagnosis of LTBI and screening strategy and estimated the total cost for averting a potential TB case.
Results: We compared 499 contacts TST/IGRA screened with 547 IGRA-only. IGRA-only strategy yielded a higher screening effectiveness for diagnosing latent tuberculosis infection (aOR 2.12, 95%CI: 1.53 - 2.94). ICER was €106 per LTBI diagnosis, representing increased effectiveness with a slightly increased cost of IGRA-only screening strategy.
Conclusions: Our data suggests that in Portugal LTBI screening with IGRA-only is more cost-effective than the two-step TST/IGRA testing strategy, preventing a higher number of cases of TB cases.

Introduction

Systematic diagnosis and treatment of latent tuberculosis infection (LTBI) is a key part of the TB elimination strategy in low-incidence countries.[1] Screening strategies in individuals with close contact with infectious cases of TB include the tuberculin skin test (TST) followed by the interferon-gamma-release assay (IGRA) in individuals with positive TST results (two-step strategy); single-step IGRA testing; and single-step TST testing.[2]

IGRA tests have specificity greater than 95% in the diagnosis of LTBI.[3] The TST specificity is similar (97%) in populations not vaccinated with Bacillus Calmette-Guérin (BCG), but is considerably lower (60%) in those vaccinated.[3] Sensitivity of the two tests is roughly the same: 80-90% for IGRA; 80% for TST.[3,4] Some studies have shown that the progression rate (likelihood that a person with a positive test will develop active TB) is higher in IGRA-positive individuals.[5,6,7]

A cost-effectiveness study in the United Kingdom estimated that two-step TST/IGRA screening strategy is less costly than single-step IGRA testing (£162,387 *vs.* £ 203,983 per 1000 contacts).[2] However, this study only considered medical costs. In France, a decision analysis model, considering only direct medical costs, showed that in almost all scenarios QuantiFERON (QFT) was more effective and cost-effective than TST in detecting LTBI.[8]

One study in Brazil, though, showed that the most cost-effective strategy was TST (US$ 16,021/averted case) and that the incremental cost-effectiveness ratio was US$ 227,977/averted TB case for QFT-GIT.[9] Another study of individuals entering the Dallas County Jail (Texas, United States) reported a substantially higher positivity rate of IGRA than TST: these authors suggested that sensitivity of TST screening was lower, and that IGRA was more time-efficient and associated with four-fold lower indirect costs. The overall cost per LTBI case detected was nearly three-times higher for the TST than the IGRA.[10]

A recent report of the European Centre for Disease Prevention and Control used a deterministic TB transmission model to predict the impact of different LTBI screening and treatment strategies for several risk-groups, including contacts of TB cases. They concluded that from the healthcare perspective, LTBI screening is most cost-effective when done using the two-step approach (TST first and, if positive, followed by IGRA).[11,12]

Given the heterogeneous results of different studies, the World Health Organization advised more research in this field.[13]

The Portuguese National Health Service maintains TB outpatient centers that are responsible for TB and ITBL diagnosis, treatment, and screening across the country, under technical guidance from the National Tuberculosis Programme. In the Northern Region, TB outpatient centers switched from the two-step TST/IGRA to the single-step IGRA-only screening strategy, after shortages in tuberculin supply. Before this switch, TST was performed to exposed contacts immediately after diagnosis of TB in index case and repeated 8-10 weeks after the last exposure of risk, followed by IGRA testing (QuantiFERON Gold Plus ®) whenever TST was positive. After 2016, IGRA-only (QuantiFERON Gold Plus ®) was performed only once, 8-10 weeks after the last exposure to index case of TB. The IGRA assay available during the study period in the Northern Region was the QFT-Plus assay.[14,15]

The objective of this study was to compare the cost-effectiveness of the two strategies described above, in terms of medical costs (for the healthcare system) and direct and indirect non-medical costs related to LTBI screening (excluding treatment costs), for LTBI screening in close contacts of confirmed cases of respiratory TB.

Material and Methods

Patient Selection

We examined clinical records of all individuals screened for TB and LTBI in two TB outpatient centres from the Northern Health Region: Penafiel (180,000 inhabitants, annual TB incidence rate of $47.7/10^5$ in 2012-16) and Vila Nova de Gaia (330,000 inhabitants, annual TB incidence rate of $26.0/10^5$ in 2012-16).[16] Only individuals exposed to an infectious TB patient, diagnosed from 1 January 2015 to 31 December 2016, were included. Exclusion criteria were those described in Figure 1.

We extracted socio-demographic information (sex, age, parish of residence, employment status), clinical information (history of TB/LTBI, immunosuppression, diagnosis of TB during screening), LTBI screening test information (screening strategy, date[s], result[s], diagnosis, initiation of

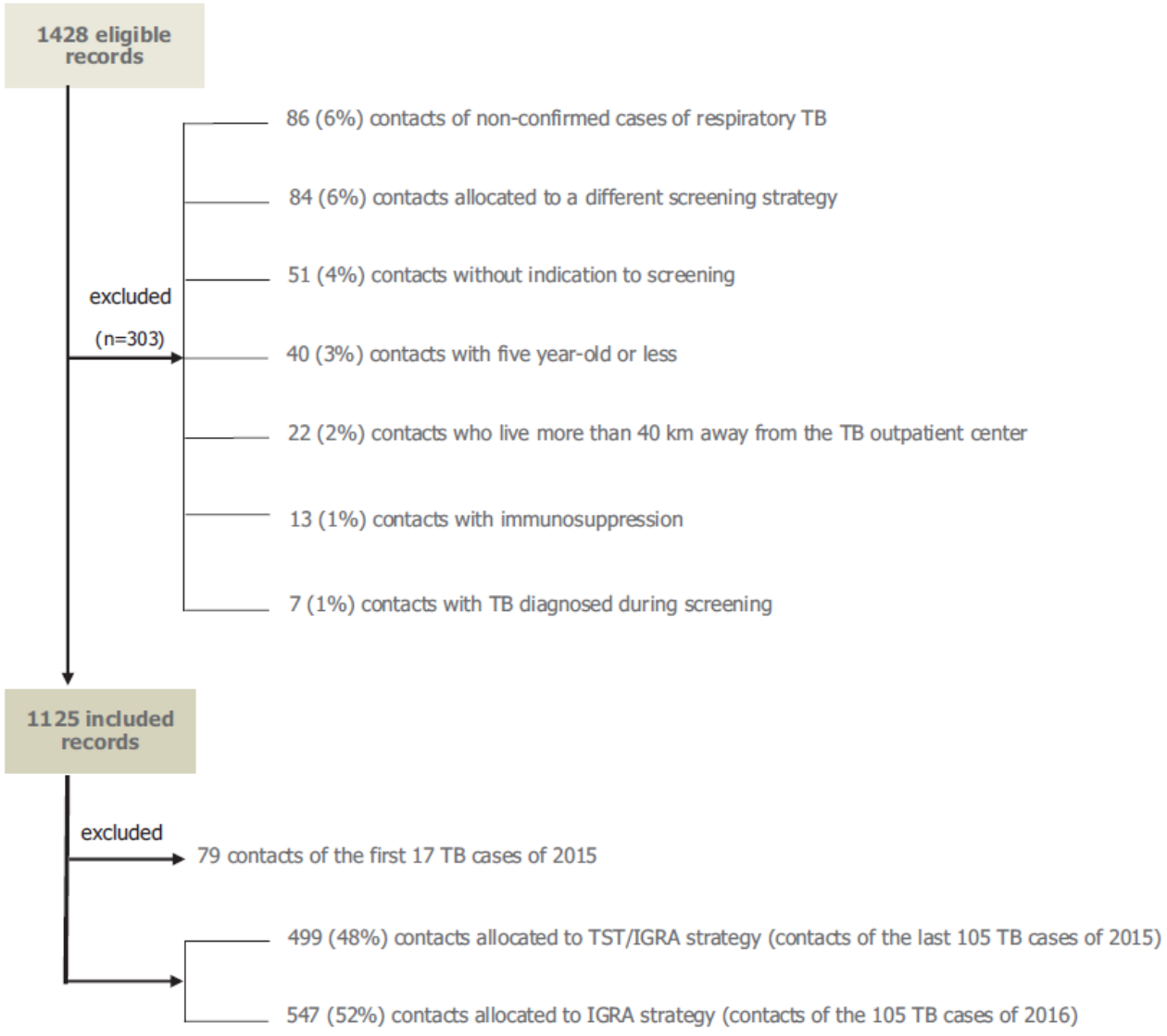

Figure 1 Eligible and included records, with reference to exclusion criteria.

treatment), and information on the index TB cases (diagnosis date, sputum smear results).

Cost Effectiveness

Cost-effectiveness was expressed as an incremental cost-effectiveness ratio (ICER), which was calculated by dividing the cost difference between the two screening strategies with the difference number of LTBI diagnosis.[11,17] We assumed that treating LTBI is a cost-effective intervention and focused only in the differences between strategies until the moment of LTBI diagnosis.

The median costs in the TST/IGRA and TST-only groups were compared using Mann-Whitney test. The proportion of individuals diagnosed with LTBI, number of visits to the TB outpatient center, and adherence to screening were also compared for these two groups using the Chi-squared test or Fisher's exact test, as appropriate. Adjusted odds-ratios (aORs) and 95% confidence intervals (95% CIs) for each screening strategy and diagnosis of LTBI were calculated using logistic regression. Screening strategy, sex, age, place of residence, professional status (employed/unemployed), TB outpatient center, index case sputum smear positivity, infectious period, and site of disease in the index case were included in the initial regression models. In this procedure, a backward stepwise approach was used, and at each step, the least significant variable that was not a substantial confounder (whose removal would lead to a change of more than 20% in the OR of one or more parameters remaining in the model) was removed. Sex and index case sputum smear positivity were retained regardless of *p*-value.

Direct individual medical costs were calculated as the sum of estimated costs from the screening test(s), specimen transportation to the testing laboratory, and the work of healthcare professionals (collection and testing of specimens) – data provided by the Northern Regional Health Administration for 2014-2016. IGRA (QuantiFERON-TB Gold Plus) cost was €37.66 (including ELISA kit, antigen, and mitogen) and the TST cost was €1.00 (including tuberculin). Disposable material costs were estimated using online prices (including laboratory materials, blood collection materials, tuberculin needles and syringes, gloves, compresses), and were calculated as €0.31 for one TST and €0.57 for one IGRA.

Direct non-medical costs were estimated per screened individual by multiplying the number of visits to the health center by the distance traveled (calculated taking into account patient's address), with an estimated cost of €0.10 per km. To assess the impact of this estimate on final results, a sensitivity analysis was also performed using an estimated cost of €0.35 per km, the reference value used by the Portuguese Government. This cost was adjusted considering that contacts of the same index case could share their mean of transport if they went to the TB outpatient center on the same day.

Indirect costs per screened individual were calculated by multiplying the number of visits to the health center by the half-daily average income (from *Instituto Nacional de Estatística*, Statistics Portugal) for working individuals. Half-daily income was used in order to not overestimate indirect costs, considering that TB is associated with socio-economic deprivation.[18,19] A sensitivity analysis was also performed using daily average income. The number of potentially averted TB cases was estimated based on the number of individuals who started LTBI treatment, a 10% lifetime risk of developing TB, and a 70% efficacy of treatment (assuming that all patients who began LTBI treatment finished their treatment).[20]

Definitions

The following definitions were used in this study:

- Adherence to screening: proportion of individuals who showed up for screening that completed all recommended screening steps;[21]
- Confirmed respiratory TB patient: person with a positive respiratory TB diagnosis (tracheal, laryngeal, bronchial, pulmonary, and/or pleural), confirmed by a positive culture for *Mycobacterium tuberculosis complex* (MTC) or a positive smear plus MTC nucleic acid detection in sputum or bronchoalveolar lavage;[22]
- Close contact: person who had close contact with a patient who had respiratory TB for a cumulative time of at least 8 h if sputum smear-positive, or 40 h if sputum smear-negative (National Tuberculosis Programme recommendation);[23]
- Immunosuppressed individual: individual receiving chemotherapy, radiotherapy, an immunosuppressive drug, or infected with HIV;[21]
- Period of infectiousness: time interval during which MTC may be transferred between individuals, estimated as the number of days between onset of symptoms and TB diagnosis;[24]
- Latent tuberculosis infection: positive IGRA test in an individual who does not have active TB;[24]
- Medical direct costs: healthcare-related costs (screening tests, specimen transportation to the testing laboratory, and work of healthcare professional);[21]
- Non-medical direct costs: costs related to the transportation of an individual to a TB outpatient center for screening;[21]
- Indirect costs: productivity loss from an individual's absence from work because of travel to the TB outpatient center for screening.[21]

Stata® IC 15.0 (Student version) was used for statistical analysis. Ethical approval for this study was obtained from the Ethics Boards of the Institute of Public Health of the University of Porto (CE17061) and the Northern Regional Health Administration (39/2017).

Results

From 1428 eligible close contacts of infectious cases of TB, 303 (21%) met the exclusion criteria and were rejected from the analysis (Figure 1). From the remaining 1125 individuals, 578 (51%) had been screened in 2015 using the TST/IGRA strategy and 574 (49%) were screened in 2016 using the IGRA-only strategy. In order to assure that we were comparing the costs of screening contacts of the same number of TB cases, we included all 2016 TB cases and the same number of cases diagnosed in 2015 starting from the end of the year

(79 contacts screened with TST/IGRA in January/February 2015 were excluded).

Baseline Comparison of Groups

The median age of screened individuals was 38 years-old (interquartile range [IQR]: 25.0-51.0), 54% were women, and 58% (n = 641) were employed. Their places of residencies were a median of 11 km (IQR 6.5-15.5) and 14 min (IQR 8.5-19.4) away from the visited TB outpatient center. The two groups had no significant differences in terms of age, sex, employment status, and distance to the visited TB center (Table 1). However, the IGRA-only group had a significantly higher proportion of individuals who were exposed to highly infectious TB patients (positive sputum smears) (Table 1). The proportion of contacts diagnosed with LTBI and the adherence to screening were also greater in the IGRA-only group.

Multivariable Analysis

After adjusting for sex, age, TB outpatient center, index case sputum smear results, and period of infectiousness, the IGRA-only group had an increased risk for diagnosis of LTBI (aOR = 2.12, 95% CI: 1.48−2.93) (Table 2).

Total average costs were €42.71 per screened individual in the TST/IGRA group and €55.21 in the IGRA-only group; the corresponding median values were €43.71 and €60.23, respectively (Table 3). Medical direct costs were higher in the IGRA group, but non-medical direct costs and indirect costs were higher in the TST/IGRA group (Table 3). The cost per LTBI diagnosis was €280.42 in the TST/IGRA group (76 per 499 screened individuals) and €205.44 in the IGRA group (147 per 547 screened individuals). The estimated number of potentially averted cases of TB was 5 in the TST/IGRA group and 8 in the IGRA-only group. Thus, the cost per potentially averted TB case was €4412.48 in the TST/IGRA group (€21,312.29/4.83) and €3719.20 in the IGRA group (€30,199.87/8.12).

Sensitivity Analysis

After changing the previous assumptions regarding travel (cost/km of €0.35 instead of €0.10, and average daily income instead of average half-daily income), total costs were €64.48 per screened individual in the TST/IGRA group and €65.63 per individual in the IGRA-only group (median €72.20 and €71.12, respectively) (Table 3). The cost per LTBI diagnosis was €423.36 in the TST/IGRA group (76 in 499 individuals) and €244.22 in the IGRA group (147 in 547 individuals). The cost per potentially averted TB case was €6661.60 in the TST/IGRA group (€32,175.52/4.83) and €4421.13 in the IGRA group (€35,899.61/8.12). Medical direct costs were greater in the IGRA group, but non-medical direct costs and indirect costs were greater in the TST/IGRA group.

Incremental cost-effectiveness ratio (ICER)

The calculated ICER was €106 per LTBI diagnosis, representing increased effectiveness with a slightly increased cost of IGRA-only screening strategy.

Discussion

Our comparison of two groups of close contacts of TB cases who followed different LTBI screening strategies showed that, when compared to the TST/IGRA group, the IGRA-only group had increased odds of having LTBI diagnosed (aOR = 2.12, 95% CI = 1.53−2.94) . Adherence to screening was also higher in the IGRA-only group, probably because this strategy requires fewer visits to the TB outpatient centers. From a societal perspective, the IGRA-only strategy appears to be more cost-effective than TST/IGRA strategy, because it has a lower cost per diagnosed LTBI case (€205.44 *vs.* €280.42) and a lower cost per potentially averted case of TB (€3,719.20 *vs.* €4,412.48).

Table 1 Characteristics of screened contacts by strategy used.

	TST/IGRA strategy n=499	IGRA strategy n=547	p-value
Median age	37	39	0.108
Proportion of male individuals	49%	44%	0.118
Proportion of working individuals	59%	57%	0.689
Median distance from place of residence to TB outpatient center in kilometers	11	10	0.148
Median time needed to travel from place of residence to TB outpatient center in minutes	15	13	0.014
Average number of contacts per index case	5	6	
Proportion of contacts of a TB case with positive sputum-smear	66%	80%	<0.001
Median infectious time of TB cases	56 days	67 days	0.370
Proportion of contacts who were exposed to a pulmonary TB case (not pleural)	97%	99%	0.118
Proportion of diagnosed LTBI	15%	27%	<0.001
Median number of visits to the TB outpatient center	4	2	<0.001
Adherence to screening	81%	86%	0.038
First step screening concluded	98%		

LTBI: latent tuberculosis infection.

Table 2 Logistic regression model for diagnosis of LTBI (final model).

Variables	Reference group	Other categories	Odds Ratio	95% confidence interval
Screening strategy	TST/IGRA strategy	IGRA strategy	2.12	1.53 - 2.94
Sex	Female	Male	1.11	0.81 - 1.51
Age group	5-10 years	11-17 years	2.89	0.76 - 10.89
		18-29 years	2.88	0.83 - 10.01
		30-39 years	2.43	0.69 - 8.55
		40-49 years	2.11	0.60 - 7.42
		50-59 years	3.25	0.92 - 11.51
		≥60 years	3.92	1.10 - 13.94
TB Outpatient Center	Gaia TB outpatient center	Penafiel TB outpatient center	1.09	0.79 - 1.49
Infectious characteristics of index case	Negative sputum smear	Positive sputum smear	0.97	0.67 - 1.41
Index case infectious period	≤30 days	30-59 days	0.93	0.57 - 1.54
		60-89 days	1.40	0.90 – 2.21
		90-119 days	1.58	0.92 – 2.68
		>120 days	1.83	1.17 – 2.86
Constant	0.05			0.01- 0.17

LTBI: latent tuberculosis infection.

The odds ratio for LTBI diagnosis was greater in the IGRA-only group than in the TST/IGRA group in Penafiel (high TB-incidence) than in Vila Nova de Gaia (medium TB-incidence). There is evidence that the TST and IGRA have similar sensitivity[3,4] but the increased specificity of two-step strategies comes with a lower sensitivity. Previous studies showed that increasing age and immunosuppression are associated with false negative results, especially with TST.[25] Other preconditions, like inflammatory diseases, might be associated with IGRA false negative results.[26] Nevertheless, we used data from healthy individuals, >5 years old, without HIV infection, diabetes or pharmacological immunosuppression (table 1). We expect very few false positive results with the IGRA-only screening strategy, because of its high specificity, but no gold-standard test is available for confirmation.

Previous cost-effectiveness studies suggested that two-step screening was less effective averting active TB cases, but more cost-effective than IGRA-only screening.[2] The present study also considered the effect of societal costs, and included not only medical costs but also non-medical direct and indirect costs. Our results suggests that the IGRA-only strategy is more cost-effective, mainly because of its higher effectiveness in diagnosing LTBI (and potentially averting TB cases) and decreased indirect costs (less productivity lost by individuals and society). As expected, the IGRA-only strategy represents increased costs for health services, because of the unit cost of the IGRA test itself and associated laboratory work. The incremental cost-effectiveness ratio of € 103 per LTBI diagnosis represents the amount of money spent for the outcome of interest. We considered effectiveness only for LTBI diagnosis, and not for treating LTBI (this was studied elsewhere[11]).

This may have led to an overestimation of the number of potentially averted cases of TB in both groups. A selection bias in the IGRA-only group may have occurred, because individuals in this group were exposed to more infectious TB cases (80% of index cases were sputum-smear positive in the IGRA-only group, but only 68% were sputum-smear positive in the TST/IGRA group). This might have occurred because the criteria used to identify eligible contacts were stricter for the more expensive screening strategy. However, including infectiousness in our regression model should have eliminated this bias.

Table 3 Screening costs by screening strategy (median [IQR], in EUR)

	Assumptions 1 (cost/km €0.10; half-average income)			Assumptions 2 (cost/km €0.35; average income)		
	TST/IGRA	IGRA-only	p-value	TST/IGRA	IGRA-only	p-value
Medical direct	€12.83 [12.83 – 12.83]	€49.74 [49.74 – 50.95]	<0.001	€12.83 [12.83 – 12.83]	€49.74 [49.74 – 50.95]	<0.001
Non medical direct	€3.23 [1.33 – 4.56]	€0.91 [0.36 – 1.51]	<0.001	€11.31 [4.64 – 15.98]	€1.80 [0.50 – 3.05]	<0.001
Indirect	€17.50 [0.00 – 28.49]	€8.75 [0.00 – 14.25]	<0.001	€34.99 [0.00 – 56.99]	€17.50 [0.00 – 28.50]	<0.001
Total	€43.71 [16.14 – 52.37]	€60.23 [50.64 – 66.64]	0.006	€72.20 [24.44 – 86.34]	€71.12 [50.64 – 84.65]	0.2116

LTBI: latent tuberculosis infection. IQR: interquartile range.

Conclusion

From a societal perspective, IGRA-only screening appears to be more cost-effective than TST/IGRA screening for LTBI, with a lower cost per LTBI diagnosis and a lower cost per potentially averted TB case. These results indicate an increased effectiveness of IGRA-only screening, at an only slightly increased cost.

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3.2 Coffee shops, a hub for TB clusters?

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LETTER TO THE EDITOR

Coffee shops, a hub for TB clusters?

Stone quarry workers account for about 30% of the tuberculosis (TB) cases[1] in *Penafiel* and Marco de *Canaveses*, two municipalities in the northern region of Portugal that have the highest TB notification rates of the country.[2]

In high incidence areas, only a small number of reliable epidemiologically linked cases are identified using conventional contact investigations.[3] Whole-genome sequencing (WGS) is increasingly used to study transmission dynamics.

We conducted a retrospective study including all notified cases of TB in stone quarry workers from the municipalities of *Penafiel* and *Marco de Canaveses* from 1 January 2012 to 31 December 2019. First, we analysed classical epidemiological data from the stone quarry workers with TB diagnosed during 2012–2014. Secondly, all the available strains of *M. tuberculosis* isolated from 2015 to 2019 were sent for WGS in the National Reference Laboratory using a single nucleotide polymorphisms (SNP)-based approach.[4] Then we compared clustered and non-clustered cases using the Chi-squared test or Fisher's exact test.

According to local public health services' records, 11 stone quarry workers with confirmed TB were notified between 2012 and 2014. Work-related exposure led to universal screening initiatives in workplaces: 135 co-workers of the same companies were screened. TB disease screening included chest-X ray and symptom questionnaire (96.3% adherence; one case found in 130 screened) and TB infection screening was performed through Tuberculin Skin Test (36.3% adherence; 30 cases found in 49 screened; two initiated preventive treatment). During 2016–2017, eight new cases were found among those previously screened individuals, i.e., 5.9% of the co-workers developed TB disease in a period of three years. The results of their screening were not screened (one), incompletely screened (four), not treated TB infection (two), previous negative screen (one). TB infection screening was not performed in more than 60% of the contacts, which may have contributed to the high proportion of screened workers that developed TB. However, we hypothesize whether this could reflect that transmission occurred in other settings besides workplaces (namely social or familiar).

A total of 76 current or former stone quarry workers diagnosed with TB in the 2015–2019 period were found, i.e., 18.8% of the notified cases of TB in 2015–2019.[2] Three of those were excluded (not confirmed TB). Of the 73 included cases, 35 (47.9%) had available specimens. Genotyped and non-genotyped cases of TB had similar characteristics regarding the considered risk factors (Table 1).

All the cases were male, born in Portugal, with an average age of 50-years-old (median 51, interquartile range (IQR) 43–56), and had pulmonary TB. The main risk factors included tobacco use, silicosis and alcohol dependence (Table 1). No cases of HIV were found (six had not registered HIV status). Two of the genotyped TB strains were polyresistant to isoniazid and streptomycin, and 33 were susceptible to all first line drugs. The delay between onset of symptoms and diagnosis was on average of 78 days (median 63 days; IQR: 34.0–88.0).

A high molecular diversity of *M. tuberculosis* was found (Fig. 1). Clusters included cases from 2015 to 2019, suggesting ongoing active transmission. As we did not genotype all the strains of M. tuberculosis from the community, we could be missing the remaining strains from other clusters.

Median (IQR) time between successive cases in clustered cases was 205 (95.5–308.3) days. Clustered cases were more prone to have alcohol dependence and smoking habits, which could be associated with attending coffee shops regularly (Table 1). Likewise, being professionally inactive, having a previous episode of TB and a positive sputum smear were also more common among clustered cases. As positive sputum smear indicates higher infectiousness, that is expected. In a study that analysed MIRU-VNTR molecular clustering data from 7458 patients, cases in large molecular clusters were also more likely to have multiple social risk factors.[5]

Using a logistic regression analysis, none of the transmission settings was a significant predictor of clusters but attending public places was the better predictor (OR 1.8, 95% CI 0.254–12.449). Social contacts in community public places such as coffee shops seem to contribute to the maintenance of ongoing active transmission of TB. In other study, workers that converted from IGRA negative to positive had no co-workers with active TB and were not identified as close contacts, suggesting they could have been infected in social settings.[6]

In our opinion, the high molecular diversity found in a small sample of stone quarry workers cases suggests a complex scenario of transmission between them and the high-risk communities in which they live and work. Stone quarry workers are not only more prone to transmit TB to other people of the community; they are also more susceptible to

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Table 1 Characteristics of clustered and non-clustered TB cases.

	Non-genotyped cases ($n = 38$)	Genotyped cases ($n = 35$)	p value	Not clustered ($n = 7$)	Clustered cases ($n = 28$)	p value
Age groups years			$p = 0.706$			$p = 0.517$
21–44	8 (21.1%)	9 (25.7%)		1 (14.3%)	8 (28.6%)	
45–64	26 (68.4%)	24 (68.6%)		6 (85.7%)	18 (64.3%)	
≥65	4 (10.5%)	2 (5.7%)		0	2 (7.1%)	
Employment status						$p = 0.166$
Active	25 (65.8%)	27 (77.1%)	$p = 0.284$	7 (100.0%)	20 (71.4%)	
Inactive	13 (34.2%)	8 (22.9%)		0	8 (28.6%)	
Silicosis						$p = 1.000$
Yes		18 (51.4%)		4 (57.1%)	15 (53.6%)	
No		16 (45.7%)		3 (42.9%)	13 (46.4%)	
Alcohol dependence						$p = 0.220$
Yes		13 (37.1%)		1 (14.3%)	12 (42.9%)	
No		22 (62.9%)		6 (85.7%)	16 (57.1%)	
Tobacco use						p=0.652
Yes		24 (68.6%)		4 (57.1%)	20 (71.4%)	
No		11 (31.4%)		3 (42.9%)	8 (28.6%)	
Previous treatment of TB						$p = 0.084$
Yes		10 (28.6%)		0	10 (35.7%)	
No		25 (71.4%)		7 (100.0%)	18 (64.3%)	
Sputum smear						$p = 0.155$
Positive		25 (71.4%)		3 (42.9%)	22 (78.6%)	
Negative		10 (28.6%)		4 (57.1%)	6 (21.4%)	
Number of days between symptoms and diagnosis						$p = 0.935$
3–30		6 (17.1%)		1 (14.2%)	5 (17.9%)	
31–65		13 (37.1%)		3 (42.9%)	10 (35.7%)	
≥66		16 (45.7%)		3 (42.9%)	13 (46.4%)	
Attended public places						$p = 0.401$
Yes	21 (55.3%)	21 (60.0%)	$p = 0.683$	3 (42.9%)	18 (64.3%)	
No	17 (44.7%)	14 (40.0%)		4 (57.1%)	10 (35.7%)	
Close contact with relatives with TB						$p = 1.000$
Yes	3 (7.9%)	5 (14.3%)	$p = 0.468$	1 (14.3%)	4 (14.3%)	
No	35 (92.1%)	30 (85.7%)		6 (85.7%)	24 (85.7%)	

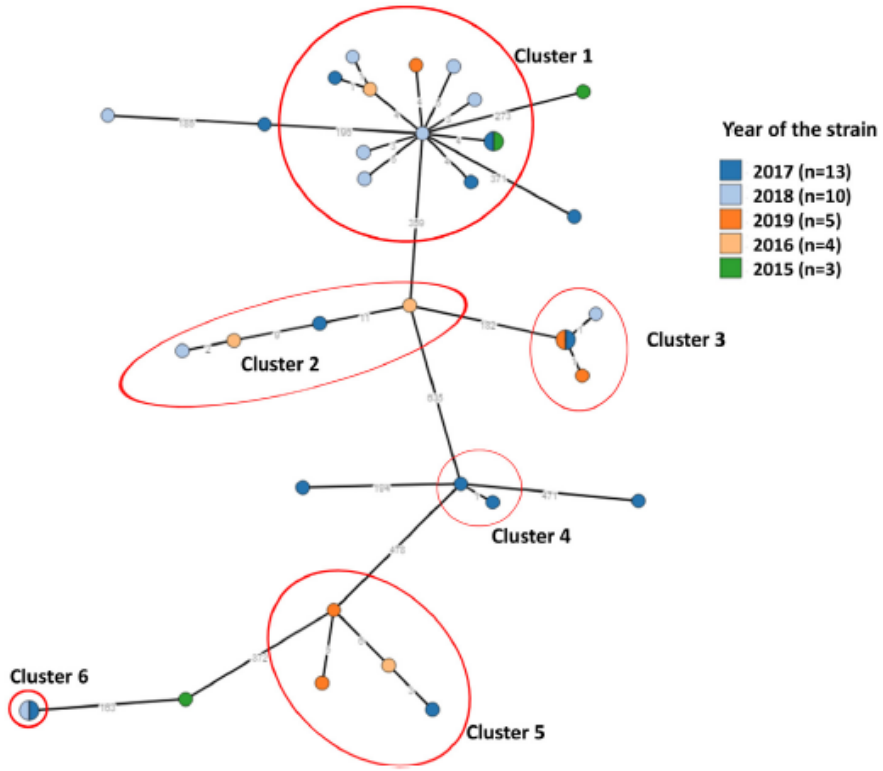

Fig. 1 Network of 35 *Mycobacterium tuberculosis* (MTB) isolates. Phylogeny of MTB isolates was determined based on a core single nucleotide polymorphisms (SNP) approach. Each node corresponds to a single or multiple isolates (i.e., nodes with slices). Nodes are coloured by year of strain isolation and genetic clusters of closely related isolates were defined whenever the strains had less than six SNP difference and are highlighted in red circles. Clades representing determined lineages from the global *M. tuberculosis* tree are indicated [cluster_1: lineage4.3.4.2 (100.0%, *n* = 12); cluster_2: lineage4.3.2 (100.0%, *n* = 4); cluster_3: lineage4.3.2 (100.0%, *n* = 3); cluster_4: lineage4.1.2.1 (100.0%, *n* = 2); cluster_5: lineage4.1.1.1 (100.0%, *n* = 4); cluster_6: lineage4.1.1.3 (100.0%, *n* = 2)].

infection and re-infection by *M. tuberculosis*, given their common and multiple risk factors, especially in places where epidemiological links are difficult to establish. WGS could routinely contribute to identifying public places that are hotspots of TB transmission.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

We would like to acknowledge Miguel Pinto (Genomics and Bioinformatics Unit, Department of Infectious Diseases, National Institute of Health, Portugal) for his collaboration with the analysis of the genomic data, and the laboratory staff of the Innovation and Technology Unit (National Institute of Health, Portugal) for the M. tuberculosis genomes sequencing. We also would like to acknowledge the professionals of the Public Health Units of Vale do Sousa Sul (Penafiel) and Baixo Tâmega (Marco de Canaveses) who performed epidemiological enquiry to all the notified cases of TB during the 2015-2019.

Ethical approval

Ethical approval for this study was obtained (Ethics Boards of the Northern Regional Health Administration, 134/2022).

No funding was obtained for this study.

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3.3 An investigation of TB infection and reinfection among stone quarry workers

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LETTER TO THE EDITOR

An investigation of TB infection and reinfection among stone quarry workers

Stone quarry workers are considered at increased risk from tuberculosis (TB) mainly because of their prolonged exposure to silica.[1] They are considered a vulnerable population group for TB in Portugal, especially in the municipalities of *Penafiel* and *Marco de Canaveses*.[2,3]

Understanding transmission patterns is essential for developing prevention strategies and prioritising resources.[4] Whole-genome sequencing (WGS) is an important tool to identify clusters.[5,6]

Data from all cases of TB in stone quarry workers from 2015 to 2019, for whom *M. tuberculosis* (MTB)-positive specimens were available for complementary laboratory testing (n = 35, 47.9% of the eligible sample) was analysed. The data was collected by the local public health services during their routine surveillance and public health authority duties. TB clusters were identified using WGS (single nucleotide polymorphism [SNP]-based approach[7]), and the largest cluster identified was investigated to distinguish potential exposure settings and propose strategies to reduce transmission.

Six clusters were found. The largest cluster included 12 MTB isolates from 2015 to 2019. Five of the 12 cases (41.7%) had already had at least one previous episode of TB, six (50.0%) had silicosis and alcohol dependence, and eight (66.7%) were smokers (Fig. 1). Out of the 12 cases, who lived in seven different parishes of the *Penafiel* and *Marco de Canaveses* municipalities, nine (75.0%) were employed in seven companies, and nine (75.0%) reported frequently attending seven different coffee shops (Fig. 2).

Cases C1.2 and C1.5 were identified as close contacts of a co-worker from the same company that had had active TB in 2014 (a non-genotyped case that was considered the primary case for this cluster - X). The three worked in the central region of Portugal during the week and returned to three different parishes for the weekend. C1.2 shared the same room, and C1.5 shared transport and meals with the primary case. C1.2 had active TB in 2015, diagnosed during screening; C1.5 only had active TB in 2017 (a reinfection, previous treatment in 1999). C1.5 was identified for screening but the follow-up cannot be traced, and the screening result is not known. Failure to attend or incomplete screening was previously reported in this population,[2] with active TB cases identified late among those considered close contacts.

Case C1.5, who also had silicosis and was a smoker, had a cough for three months before the diagnosis (Fig. 1); he was the suspected primary case of a community outbreak that included another six cases of TB in the first six months of 2017 in the parish where he lives. None of the other six cases were genotyped.

The primary case of this genotyped cluster (X) was considered cured in 2015 but had a second episode of active TB in 2017 at 33 years old. The new strain was genotyped and found to be associated with a different cluster suggesting that X was re-infected two years after his cure.

Case C1.9 was working abroad at the time of diagnosis and reported attending a bar also attended by C1.12 and two previous non-genotyped cases (Fig. 2).

These 12 stone quarry workers had identical strains of *Mycobacterium tuberculosis* (with less than six differences in SNP), which suggests that they belong to the same chain of transmission. Nevertheless, it is probable that missing intermediary cases exist both in the general community and in other non-genotyped cases among stone quarry workers. The importance of household contact was not assessed in this study, but the epidemiological enquiry did not find any relatives who previously had TB.

Based on epidemiological investigation data, only close contacts in the workplace were identified. Social connections such as those occurring in coffee shops and not identified by the case, are difficult to find. However, these social contacts seem to be important in maintaining the ongoing active transmission in this high-risk population.

Active transmission of TB among stone quarry workers in this cluster was driven by multiple factors, including those related to occupation, but also those related to social habits. We highlight that this outbreak probably spread to different regions of the country and possibly to other countries. Stone quarry workers' vulnerability, mainly due to silicosis, probably makes them more prone to TB infection and reinfection.

To better understand TB transmission dynamics in this high-risk population and the community, it would be beneficial if all the cases occurring in the country or region were genotyped. That would allow us to understand the transmission chains and different exposure settings better.

It is paramount that the local public health services explore all possible exposure settings during the epidemiological investigation whenever a new case is notified. Strategies to protect the most vulnerable should be enhanced: not

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Case	Silicosis	Tobacco	Alcohol	Previous TB
C1.1	Yes	Yes	No	Yes
C1.2	No	No	Yes	No
C1.3	Yes	Yes	Yes	Yes
C1.4	No	Yes	Yes	Yes
C1.5	Yes	Yes	No	Yes
C1.6	Yes	No	No	Yes
C1.7	No	No	No	No
C1.8	No	Yes	No	No
C1.9	No	Yes	Yes	No
C1.10	Yes	No	No	No
C1.11	No	Yes	Yes	No
C1.12	Yes	Yes	Yes	No

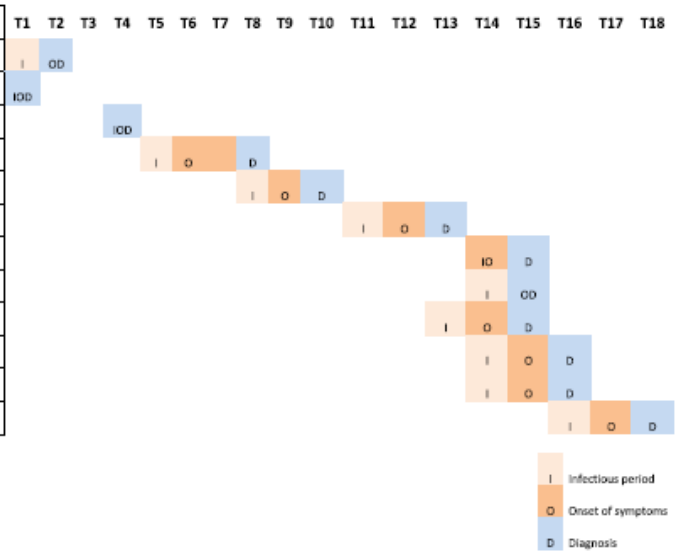

Fig. 1 Detailed analysis of the 12 cases of Cluster 1 by trimester (T) regarding risk factors and time of diagnosis. Infectious period was considered for three months before symptoms onset if positive sputum smear or for one month before symptoms onset if negative sputum smear.

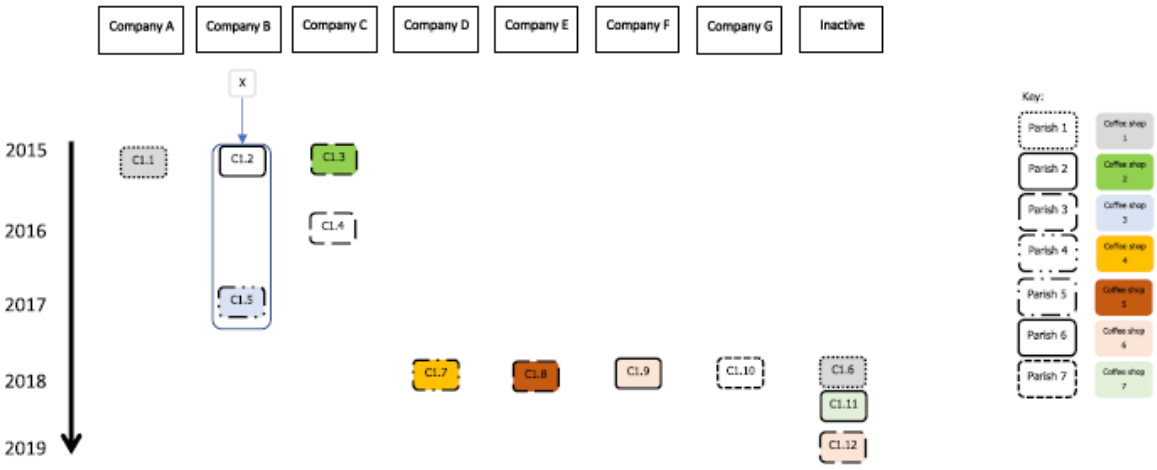

Fig. 2 Detailed analysis of the 12 cases of Cluster 1.

only strategies addressing individuals such as promoting screening and health literacy to recognize symptoms and decrease diagnosis delay, but also environmental level strategies such as improving the ventilation conditions of the sites at which exposure occurs.

Ethical approval for this study was obtained (Ethics Boards of the Northern Regional Health Administration, 134/2022).

No funding was obtained for this study.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

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3.4 Enhancing Tuberculosis Surveillance in Quarry Workers: Identifying Vulnerable Subgroups

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ORIGINAL ARTICLE

Enhancing tuberculosis surveillance in quarry workers: identifying vulnerable subgroups

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Abstract

Background Stone quarry workers and others exposed to silica are especially vulnerable to tuberculosis (TB). Silicosis is a known risk factor for TB disease, but other common comorbidities and habits such as diabetes and alcohol and tobacco consumption may increase risk. We aimed to estimate the risk of TB infection among stone quarry workers and to identify associated factors.

Methods An annual TB infection screening strategy using interferon-gamma release assay (IGRA) was implemented in 2018 for quarry workers in two high-incidence municipalities in Portugal. Workers with a first negative IGRA test were followed up and stratified by age group, preconditions including silicosis, diabetes and hypertension, and alcohol and tobacco abuse. Incidence rates and adjusted risks for TB infection were quantified using Cox regression hazard rates.

Result From 2018 to 2022, 997 stone quarry workers were screened for TB. Of those, 347 were negative in their first and performed at least one additional IGRA test, being included in the analysis. The overall rate of infection was 3.2 per 100 person-year. Silicosis, diabetes, and age above 45 years were independent risk factors for TB infection [adjusted hazard ratio (aHR) 2.9 (95% CI: 1.4–5.9), 2.9 (1.1–7.7), and 2.73 (1.1–6.6) respectively].

Conclusions Silicosis and diabetes seem to be independent risk factors for TB infection and should be targeted to reduce the burden of TB further. We suggest periodic screening of TB infection in people with silicosis, but more broadly in all those exposed to silica, especially if they also have other comorbidities such as diabetes.

Keywords Tuberculosis · Infection · Incidence · Silicosis · Diabetes

Background

The tuberculosis (TB) infection rates in a community depend on the local epidemiology and the presence of specific risk factors (European Centre for Disease Prevention and Control et al. 2018). Mining communities often have the highest reported incidence of TB (Gottesfeld et al. 2018). That is the case in Penafiel and Marco de Canaveses, two Northern Portugal municipalities where the country's highest tuberculosis (TB) notification rates are observed (Programa Nacional para a Tuberculose 2021). In 2021, the pooled TB notification rate in Penafiel and Marco de Canaveses was 55.2 cases per 100,000 population — which was close to fourfold the national rate (14.6 cases per 100,000 population (Direção-Geral da Saúde 2023)).

Silicosis is associated with an increased risk of progression to TB disease, depending on the severity of silicosis (Rupani 2023; Yang et al. 2022). Even in the absence of

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silicosis, exposure to silica dust is by itself also associated with an increase in the risk of TB (Ehrlich et al. 2021; Jamshidi et al. 2023). The duration of silica exposure is an important factor responsible for the increased TB risk (Yarahmadi et al. 2013).

The exact mechanisms of silica's involvement in the pathological processes during mycobacterial infection are not fully understood (Konečný et al. 2019). However, the presence of silica particles in the lung may facilitate infection, progression, and deterioration of the clinical course and outcome of TB (Konečný et al. 2019).

Screening of occupational diseases should be considered the employer's responsibility; many countries have occupational health and safety legislation addressing it (World Health Organization 2021a). Prolonged silica exposure justifies silicosis and TB screening (Jamshidi et al. 2023); the World Health Organization (WHO) recommends that current and former workers with silica exposure should be systematically screened for TB disease (strong recommendation, low certainty of evidence) (World Health Organization 2021a). A chest X-ray (CXR)-based screening approach, together with an assessment of symptoms suggestive of TB, is recommended for miners exposed to silica, given their high risk of lung disease (including TB) and lung damage from silicosis (World Health Organization 2021b). The screening interval should be no longer than 12 months (World Health Organization 2021a).

Preventive treatment in populations at increased risk is essential for TB control and elimination (Yang et al. 2020). Although many patients with TB infection do not progress to have TB disease (Chen et al. 2023), preventive therapy in patients with silicosis is especially beneficial (Yew et al. 2019). WHO recommends that people who have silicosis should be systematically tested and treated for TB infection (World Health Organization 2020), but some authors suggest that preventive treatment for TB infection should be considered for any workers with prolonged silica exposure (whether or not silicosis has developed), especially in geographical regions with a high prevalence of TB (Yew et al. 2019).

Globally, alcohol abuse, smoking, and diabetes are among the top five risk factors for TB (World Health Organization 2022), taking into consideration not only the relative risk but also the great number of exposed individuals. As in the general population, these common problems also affect stone quarry workers.

In this study, we aimed at (1) Estimating the TB infection rates among stone quarry workers, and (2) Identifying factors associated with an increased risk of TB infection among stone quarry workers to characterise those that would benefit the most from routine TB infection screening.

Methods

Study population and study design

A prospective cohort was set up for the study from 2018 to 2022, including workers from TB-high-risk stone quarries (where at least two cases of TB had been reported in the previous 5 years), located in the Penafiel and Marco de Canaveses municipalities.

Screening methodology

Stone quarries' occupational health services performed the screening activities as part of workers' annual health surveillance, in collaboration with public health local services, local TB outpatient centres, and the Northern regional TB laboratory (Fig. 1) (Sofia Sousa et al. 2019). Screening activities included a health questionnaire and chest X-ray (CXR). The standardised questionnaire was applied by occupational nurses or doctors, according to the national standard of care guidelines (Programa Nacional para a Tuberculose 2020). The questionnaire included age, sex, current symptoms, previous history of TB disease or infection, self-reported symptoms, current habits (alcohol, tobacco, and other drug use) and comorbidities (silicosis, diabetes, hypertension, cancer, kidney failure, HIV, hepatitis B and C). It also included self-reported contact with someone with TB and attendance at coffee shops, as public places seem important in maintaining transmission between quarry workers (Sousa et al. 2024). An initial assessment of silicosis was performed from CXR results.

After the exclusion of TB disease, the QuantiFERON® TB Gold In-Tube interferon-gamma release assay (IGRA) was offered to individuals with no previous history of TB to test for TB infection. According to standard procedure, the assay result was considered positive, negative, or indeterminate (Nishimura et al. 2020). Indeterminate results were excluded from the analysis.

Diagnosis

The diagnosis of TB infection was based on a positive IGRA result without any pulmonary or extra-pulmonary findings compatible with TB on the symptom questionnaire, CXR or microbiological sputum examination. The IGRA test was performed annually from 2018 to 2022 for workers without a history of TB disease or infection.

The diagnosis of silicosis was based on compatible CXR findings performed in 2018 or 2019.

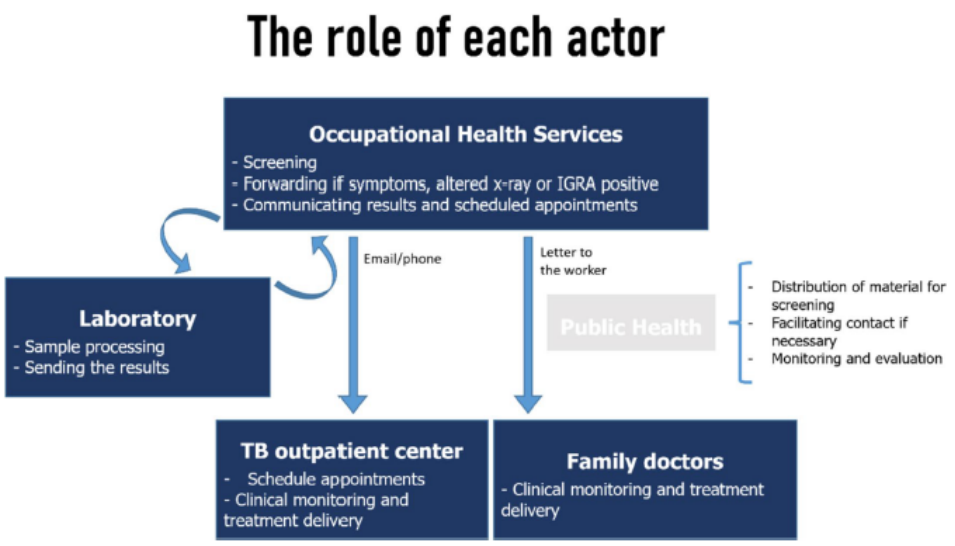

Fig. 1 The role of each actor

Other clinical diagnoses, such as diabetes, arterial hypertension, HIV, hepatitis B, and hepatitis C, were self-reported to a health professional.

Exclusion criteria (Fig. 2)

- Workers diagnosed with TB disease;
- Workers with previous diagnosis of TB disease or TB infection;
- Workers who had a positive result in their first IGRA test;
- Workers with only one IGRA test or none performed.

Definitions

Infected workers: workers who converted from negative IGRA in their first assessment to positive IGRA in different years, during the study period (2018–2022).

Non-infected workers: workers who did not convert—all IGRA negative, at least two IGRA tests done in different years, during the study period (2018–2022).

Prevalence of latent TB: number of workers with a positive result in their first IGRA test, divided by the number of workers tested during the study period.

To calculate prevalence, workers with TB disease diagnosis, those with previous TB disease or TB infection, and those who did not perform IGRA tests were excluded.

Time of follow-up: number of days between the first negative IGRA test and the last IGRA test performed (negative or positive).

Infection rate: number of new cases of infected workers divided by the days of follow-up (summarised as person-year).

Descriptive and statistical analysis

Proportions were calculated for independent variables. Proportions of infected and non-infected workers were compared using the appropriate Chi-squared or Fisher's exact test.

A Cox regression model assessed whether any risk factors could predict IGRA conversion/TB infection. For each exposure, a hazard ratio (HR) was calculated for the two groups (infected workers vs non-infected workers), with non-infected workers representing the comparison group. A backward stepwise approach using the variables included in Table 1 was used, with the least significant variables being progressively removed until the final and best-fitting regression model was achieved. Interactions were tested, and included only if they significantly improved the model's fit.

All the variables used had less than 20% missing values. Missing values were eliminated from the analysis (Dong and Peng 2013).

SPSS® and Stata 15 were used for statistical analysis.

Ethical considerations

Ethical approval for this study was granted by the Ethics Boards of the Northern Regional Health Administration

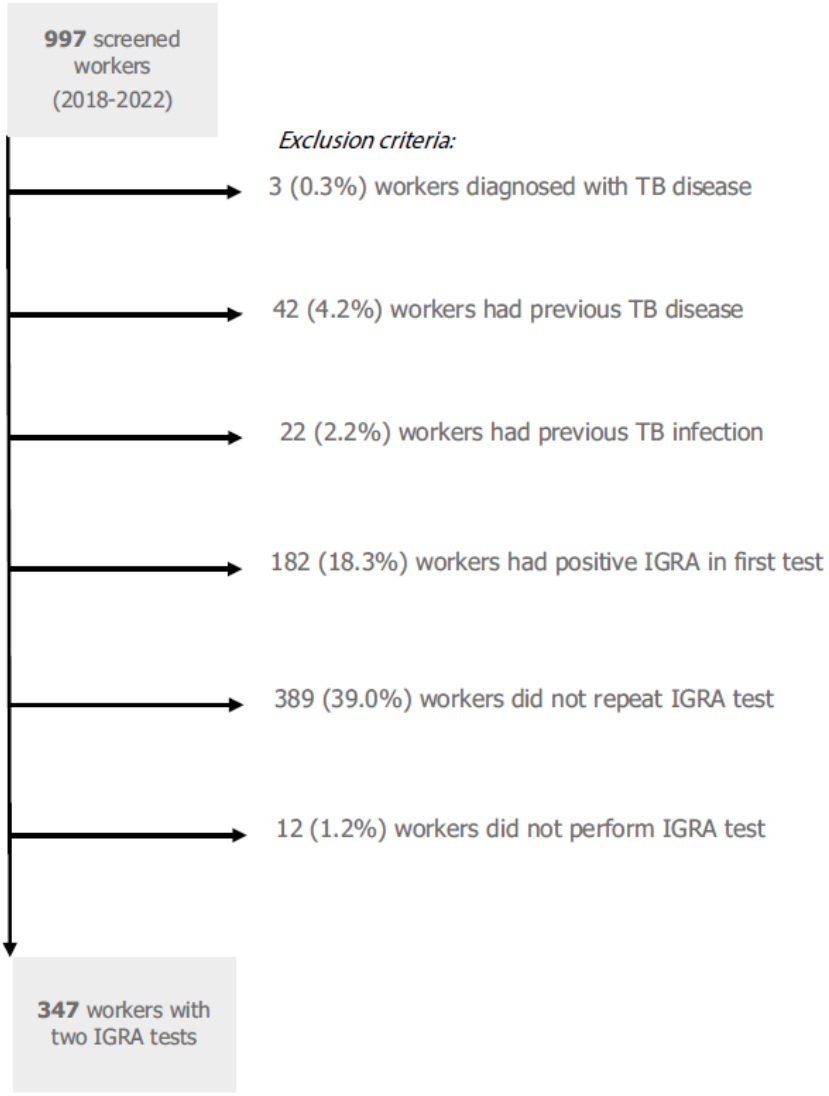

Fig. 2 Description of the exclusion criteria which were used

(41/2018). Participants gave consent for their data to be used in the research.

Results

A total of 997 workers were screened between 2018 and 2022, of which 918 performed a first IGRA test. The prevalence of TB infection was 19.8% (182/918). Three workers were diagnosed with active TB disease and referred to treatment.

A total of 347 workers working in 11 different stone quarries of the municipalities of Penafiel and Marco de Canaveses were included in the analysis (Fig. 2). Workers excluded from the analysis did not significantly differ from those included in terms of age and sex distribution ($p=0.42$ and $p=0.11$ respectively).

Infected workers were all men, older than non-infected workers (Table 1) and had more silicosis than non-infected (43.8% vs 18.5%, $p<0.01$). The diagnosis of silicosis was based on radiological findings in 259 out of 311 observations (83.2%). The proportion of tobacco users was not different between groups (21.9% vs 23.8%, $p=0.83$). Daily alcohol use and reporting close contact with TB cases were frequent (72.1% and 60.3% respectively) and not different between groups. Infected workers had diabetes (15.6% vs

Table 1 Comparing infected and non-infected workers regarding baseline exposures

	Infected workers (negative to positive) ($n=33$)	Non-infected workers (negative to negative) ($n=314$)	Total ($n=347$)	*P* value
Age groups				
18–44 years	24.2% (8/33)	58.3% (183/314)	55.0% (191/347)	<0.001*
45–65 years	75.8% (25/33)	41.7% (131/314)	45.0% (156/347)	
Sex				
Female	0.0% (0/33)	8.3% (26/314)	7.5% (26/347)	0.154
Male	100.0% (33/33)	91.7% (288/314)	92.5% (321/347)	
Silicosis (radiological findings)				
Yes	43.8% (14/32)	18.5% (42/227)	21.6% (56/259)	0.002*
No	56.2% (18/32)	81.5% (185/227)	78.4% (203/259)	
Silicosis (radiological findings + self-reported)				
Yes	43.8% (14/32)	16.1% (45/279)	19.0% (59/311)	<0.001*
No	56.2% (18/32)	83.9% (234/279)	81.0% (252/311)	
Alcohol use				
Yes	68.8% (22/32)	72.5% (198/273)	72.1% (220/305)	0.679
No	31.2% (10/32)	27.5% (75/273)	27.9% (85/305)	
Tobacco use				
Yes	21.9% (7/32)	23.8% (65/273)	23.6% (72/305)	0.833
No	78.1% (25/32)	76.2% (208/273)	76.4% (233/305)	
Other drugs use				
Yes	0.0% (0/32)	0.4% (1/273)	0.3% (1/305)	–
No	100.0% (32/32)	99.6% (272/273)	99.7% (304/305)	
Diabetes mellitus				
Yes	15.6% (5/32)	4.8% (13/273)	5.9% (18/305)	0.029*
No	84.4% (27/32)	95.2% (260/273)	94.1% (287/305)	
Hypertension				
Yes	28.1% (9/32)	11.7% (32/273)	13.4% (41/305)	0.023*
No	71.9% (23/32)	88.3% (241/273)	86.2% (263/305)	
Dislipidemia				
Yes	3.1% (1/32)	1.8% (5/273)	2.0% (6/305)	0.489
No	96.9% (31/32)	98.2% (268/273)	98.0% (299/305)	
Mental health problem				
Yes	0.0% (0/32)	4.0% (11/273)	3.6% (11/305)	0.613
No	100.0% (32/32)	96.0% (262/273)	96.4% (294/305)	
HIV, Hepatitis B or C				
Yes	0.0% (0/32)	0.0% (0/273)	0.0% (0/305)	–
No	100.0% (32/32)	100.0% (273/273)	100.0% (305/305)	
Report symptoms				
Yes	31.2% (10/32)	22.7% (62/273)	23.6% (72/305)	0.378
No	68.8% (22/32)	77.3% (211/273)	76.4% (233/305)	
Report attending to coffee shops				
Yes	50.0% (16/32)	42.6% (116/273)	43.3% (132/305)	0.561
No	50.0% (16/32)	57.5% (157/273)	56.7% (173/305)	
Report contact with TB				
Yes	68.8% (22/32)	59.3% (162/273)	60.3% (184/305)	0.344
No	31.2% (10/32)	40.7% (111/273)	39.7% (121/305)	

* indicates statistical significance

4.8%, $p=0.03$) and hypertension (28.1% vs 11.7%, $p=0.02$) more frequently than non-infected (Table 1).

The median number of days of follow-up was 1292 days per person [interquartile range (IQR) 474–1781]. The median age was 43 years old (IQR 35–51) and 92.5% were male. The overall incidence rate of infection was 8.7 per 100,000 person-days [or 3.2 per 100 person-year (PY)]. The rate of infection was 7.95 per 100 PY among workers with silicosis, 5.36 per 100 PY among workers with diabetes, and 5.13 per 100 PY among older workers (Table 2).

Table 2 Incidence rate per main risk factors

	Silicosis		Diabetes		Age group	
	Exposed	Unexposed	Exposed	Unexposed	45–65 years	18–44 years
Infected workers (new infections)	14	18	2	16	25	8
Time of follow up (days)	64,273	298,356	13,609	278,805	177,858	201,737
Incidence rate (per 100 000 person-day)	21.78	6.03	14.70	5.74	14.06	3.97
Incidence rate (per 100 000 person-year)	7949.70	2200.95	5365.50	2095.10	5131.90	1449.05
Incidence rate (per 100 person-year)	7.95	2.20	5.36	2.09	5.13	1.45

In the multivariable analysis, having silicosis, diabetes, and age above 45 were found to be independent risk factors for TB infection [adjusted hazard ratio (aHR) = 2.9, 95% CI: 1.4–5.9, aHR = 2. 9, CI 95% 1.7–7.8, and aHR = 2.7, 95% CI: 1.1–6.6 respectively) (Fig. 3).

Discussion

We found that silicosis is independently associated with an increased risk of TB infection (aHR 2.9, CI 95% 1.4–5.9). A 2023 meta-analysis estimated the pooled relative risk of progression to TB disease among individuals exposed to silica or with silicosis to be 1.4 (95% CI 1.2–1.5); studies focused on TB infection were excluded from analysis (Jamshidi et al. 2023). To the best of our knowledge, estimates of the relative risk that silicosis represents for TB infection are not provided elsewhere in the literature. However, biological changes caused by silica particles in the lung tissue presumably contribute to TB infection among silica-exposed individuals and not only to the progression to TB disease (Konečný et al. 2019).

We compared workers with radiological silicosis with workers without radiological silicosis, all working in a high-incidence area of TB and occupationally exposed to silica dust. Undiagnosed sub-radiological silicosis, defined as an early stage of silicosis that is not detectable by radiology but detectable by pathological examination (Sarkar et al. 2023), was not considered. Considering this, our relative risk estimate is probably underestimated compared to the same estimate comparing quarry workers with the general population. Considering the absolute risk estimate, we found a TB incidence rate among workers with silicosis [7.95 per 100 person-years (PY)], which is comparable to the TB incidence found in HIV patients in Ethiopia (8.6 per 100 PY) (Ahmed et al. 2018), a high-incidence country for TB (132 per 100,000 population in 2021 (Ahmed et al. 2018)).

Older workers had an increased adjusted risk of developing TB infection, as supported by the literature (Kawatsu et al. 2021). However, the incidence rate of TB infection in younger workers was estimated to be 1,45 per 100 PY, e.g., similar to that found in a risk population of health workers (da Silva et al. 2022).

Diabetes was also independent and significantly associated with an increased risk of TB infection (aHR 2.89, CI 95% 1.08–7.69). In the published literature, diabetes has been associated with a two- to four-fold increased risk of TB disease (Al-Rifai et al. 2017; Krishna and Jacob 2000). In

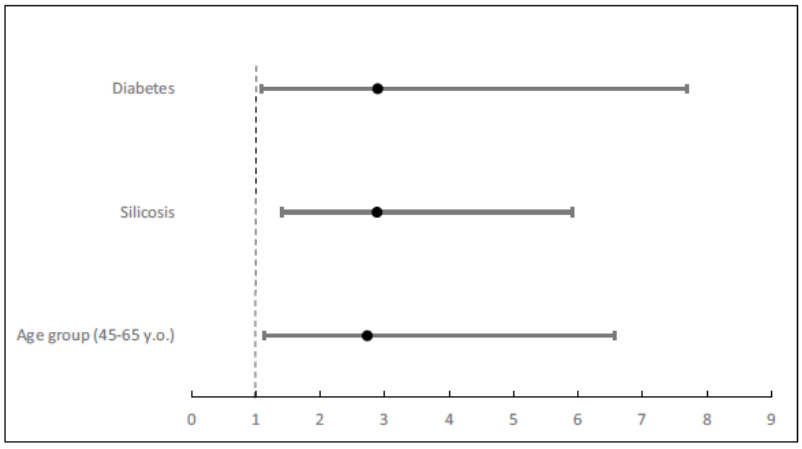

Fig. 3 Representation of adjusted hazard ratios for TB infection per risk factor (Cox regression final model for IGRA conversion)

a 2017 meta-analysis, diabetes was associated with a small but statistically significant increased risk for TB infection (Lee et al. 2017). The World Health Organization (WHO) does not recommend systematic testing for TB infection in people with diabetes unless they also belong to other risk groups (World Health Organization 2020), which include people with silicosis, but not people exposed to silica dust. This recommendation was based on a very low quality of evidence. Our results suggest that systematic TB infection screening could be considered for people with diabetes exposed to silica, even without silicosis.

In a 2022 meta-analysis, the pooled incidence of pulmonary TB among patients with type 2 diabetes mellitus was 130 per 100,000 PY (Wu et al. 2022). Considering our data, even if only 10% of the cases progress to TB disease (Chen et al. 2023), that would correspond to a TB disease incidence rate of 537 per 100,000 PY in diabetic patients exposed to silica, e.g., more than four times higher than the one found in diabetic patients non-exposed to silica.

The association between hypertension and TB infection is less well documented. A 2017 systematic review found no evidence to support an association between TB disease and hypertension; however, a lack of adequately designed studies was reported (Seegert et al. 2017). In a 2020 study, TB infection was associated with a significantly elevated incidence of hypertension after multivariable adjustment (Mandieka et al. 2020).

Our study design allowed us to conclude that hypertension diagnosis, such as the remaining studied exposures, preceded TB infection. Nevertheless, the adjusted results did not show hypertension as an independent risk factor for TB infection.

Although we adjusted for silicosis, our study did not control for the dose of exposure to silica, either cumulative or present, which could confound the results. Alcohol and tobacco consumption were also not quantified, and there is a known association between these risk factors and cardiovascular diseases such as hypertension (Nagao et al. 2021). Socioeconomic factors, referred to as "the causes of causes", also play an important role in TB infection (Duarte et al. 2018; Qin et al. 2022).

In our study, comorbidities were self-reported, which could have led to an information bias. However, the diagnosis was based on radiological findings in most cases for silicosis. In Portugal, clinical follow-ups of diabetes and hypertension are part of family medicine practice and are frequently screened and monitored (Raposo et al. 2017), so misclassification also should not be a major problem.

Although current laboratory tests are an imperfect means to distinguish tuberculous immunoreactivity and tuberculous infection (Behr et al. 2021), our study design allows us to conclude that IGRA conversion occurred during the study period and, therefore, we could assume recent TB infection in an area with ongoing transmission (Sousa et al. 2024). The community risk of having TB was steady during the study period.

In this study, an active case-finding strategy allowed the early diagnosis of TB disease cases, contributing to the decrease of infectious time in the community, presumably saving the occurrence of other new infections and future cases.

The prevalence of TB infection among stone quarry workers was 19.8%, higher than the prevalence in the general population of the country (estimated to be 15% in a study using data from 2002–2009) (Lopes et al. 2014), and it is expected that it will decrease further over time (Ding et al. 2022).

The risk of infection should not be the only factor considered when deciding which stone quarry workers should be screened and treated for TB infection — the intervention's effectiveness should also be considered. A 9-month course of community-wide isoniazid preventive therapy did not improve TB control in South African gold mines, measured as TB incidence 12 months after the intervention (Churchyard et al. 2014). The authors suggested that the high rates of ongoing transmission and the rapid waning of individual protection contributed to these findings (Churchyard et al. 2014). Moreover, TB screening should be combined with screening for other diseases, such as silicosis, and with health-promotion activities aiming at reducing occupational exposure to silica (World Health Organization 2021a).

In conclusion, silicosis, diabetes, and older age were found to be risk factors for TB infection in stone-quarry workers. Silicosis is a work-related preventable disease, and diabetes is also preventable. Efforts should be made to prevent silicosis and control diabetes, contributing to achieving global TB goals. We consider that systematic TB infection screening should be maintained in patients with silicosis, as recommended by the WHO. In addition, regular TB infection screening should be considered for people exposed to silica dust in TB high-incidence areas, especially in those that accumulate other risk factors such as older age and diabetes.

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Authors' contributions Sofia Sousa and Raquel Duarte conceived the study. Sofia Sousa, Catarina Magalhães Alves, and Sofia Santos collected the data. Sofia Sousa and Carlos Carvalho performed the statistical analysis. Sofia Sousa wrote the first draft of the manuscript. Sofia Sousa, Carlos Carvalho, Catarina Magalhães Alves, Guilherme Gonçalves, and Raquel Duarte reviewed and edited the manuscript. All authors approved the final manuscript before submission.

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Availability of data and materials This is not applicable because individual privacy could be compromised.

Declarations

Ethics approval and consent to participate Ethical approval for this study was granted by the Ethics Boards of the Northern Regional Health Administration (41/2018). Participants have given consent for their data to be used in the research.

Consent for publication Not applicable.

Competing interests The authors have no conflicts of interest to declare.

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3.5 Impact of Annual TB Screening on Stone Quarry Workers in High-Incidence Portuguese Municipalities in 2018-2022

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Impact of annual TB screening on stone quarry workers in high-incidence Portuguese municipalities

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SUMMARY

SETTING: The Portuguese municipalities of Penafiel and Marco de Canaveses are high TB incidence areas, where stone quarry workers represent comprise a vulnerable population.

OBJECTIVE: To assess the annual rate of TB infection (ARI) in stone quarry workers and to compare it with the TB notification rate in the general community.

DESIGN: An annual TB infection screening strategy using interferon-gamma release assay (IGRA) was implemented in 2018 for workers from high-risk stone quarries. A prospective cohort was enrolled and workers screened in periods of 2 years were included. IGRA-positive workers were referred for preventive treatment. ARI was calculated as the proportion of workers with IGRA conversion.

RESULTS: Of the 232 IGRA-negative workers in 2018, 20 tested positive in 2019 (8.6% ARI). Of 171 IGRA-negative workers in 2019, eight tested positive in 2021 (4.7% in 2 years). Two of the 150 IGRA-negative workers in 2021 tested positive in 2022 (1.3% ARI). ARI decreased by 84.9% between 2019 and 2022. In the two municipalities, the TB notification rate declined 23.9% between 2018 and 2021.

CONCLUSION: A more pronounced reduction in ARI was observed among stone quarry workers regularly screened for TB infection compared to the notification rate among the general population in high-incidence municipalities. A screening strategy for high-risk populations, together with enforced community measures, could foster risk reduction in the community.

KEY WORDS: tuberculosis; infection rate; screening; epidemiology

The Portuguese municipalities of Penafiel and Marco de Canaveses were high TB incidence areas during the 2017–2021 period, with annual notification rates of respectively 55.9 and 57.1 cases/100,000 population.[1] Stone quarry workers in these municipalities are particularly vulnerable to TB.[2,3] Silicosis is associated with an increased risk of TB infection and progression to TB disease.[4–7] A meta-analysis of silicosis as a risk factor for TB yielded a pooled relative risk of 4.01 (95% confidence interval [CI] 2.88–5.58).[8] A strategy consisting of an annual TB screening of stone quarry workers from high-risk companies was implemented by the public health services in these municipalities in 2018. After excluding TB disease, an interferon-gamma release assay (IGRA) was used for TB infection screening.[9] The annual rate of TB infection (ARI) is commonly used to measure the effectiveness of TB control programmes.[10] To calculate ARI, studies often use the prevalence of TB infection in children to infer the extent of transmission in a community.[11,12]

Available tests are not gold-standard for diagnosing TB infection.[13] Nevertheless, the test used for TB infection screening is often IGRA, as it is recommended by the regional guidelines, and the fact that tuberculin skin testing (TST) has lower specificity for TB infection in bacille Calmette-Guérin (BCG) vaccinated populations.[14] The prevalence of TB infection may be overestimated in countries with a high BCG coverage, such as the adult population of Portugal.[15]

In two Japanese studies, the estimation of ARI was based on age-specific IGRA positivity in healthcare workers[11] or close contacts of TB cases;[16] the authors used the middle of the year of infection (year of the IGRA test minus the mean age of each age group) to estimate when the conversion to a positive result occurred.[11,16] In the Tokyo area, ARI was steady over approximately two decades (0.1% to 0.2% between 1986 and 2004). A study in adolescents from Tanzania showed that ARI was 1.3% in a 12-year-old cohort and 1.6% in the 16-year-old.[17] Another study from Kenya reported an ARI of 2.6% in adolescents aged 12–18 years, a value higher than previous estimates with children.[10] A 2016 study modelled the incidence of infection with *Mycobacterium tuberculosis* among adults using data on infection incidence in children, disease prevalence in adults and social contact patterns. They estimated that in high-incidence countries, ARI in adults was 1.5–6 times higher (2.5–10% per year) than in children.[18] In healthcare workers from

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low and middle-income countries, the estimated ARI was 18%.[19]

A TB incidence exceeding 100 cases/100,000 has been linked to an ARI increase of approximately 1%.[20] However, ARI estimates in most high-burden countries might underestimate "true" risk among adults in high-burden settings, which is probably closer to 5–10%.[13] There is a strong relationship between TB incidence rates and prevalence of TB infection,[21] and ARI is also expected to be greater in high-incidence countries, as shown by the reported studies. The risk of progressing from infection to disease could be increased following multiple exposures.[22] A 2023 study highlighted the fact that ARI may often be a substantial underestimate of the actual force of infection in a community,[21] where many members are already infected with M. tuberculosis.[23] The authors suggest that reinfections are concentrated in high-prevalence populations, and older persons who have escaped infection are less likely to be exposed and infected. In contrast, those already infected are more likely to be re-exposed and reinfected.[23]

In this study, we aimed 1) to assess ARI trends from 2018 to 2022 in stone quarry workers routinely screened for TB disease and TB infection; and 2) to compare ARI trends among stone quarry workers to the decline in TB notification rates in the municipalities of Penafiel and Marco de Canaveses.

METHODS

Study population and study design

Workers from stone quarries located in Penafiel and Marco de Canaveses were the target population. We estimated the number of workers using a Management System of Local Units available at the Department of Public Health of Northern Regional Health Administration, Porto, Portugal. An annual TB screening strategy was implemented in the two municipalities. A prospective cohort was enrolled from 2018 to 2022.

Inclusion criteria: The inclusion criterion was being a worker from a high-risk company (with at least two cases of TB in the previous 5 years) (Figure 1).

Exclusion criteria: Exclusion criteria were 1) workers with previous TB disease or TB infection; 2) workers who did not undergo IGRA testing; and 3) workers with indeterminate IGRA results (Figure 2).

Screening methodology

Occupational health services were responsible for performing the screening activities as part of the annual health surveillance for workers, in collaboration with local public health services, local TB outpatient centres and a regional laboratory. Screening activities included a symptom questionnaire, chest X-ray (CXR) and sputum examination (if workers presented with productive cough), and IGRA to diagnose TB infection. The Northern Regional Health Administration covered the costs related to laboratory tests. CXR was performed at the quarry (if a mobile X-ray device was available) or in nearby clinics as part of the workers' health surveillance, with costs covered by the employers.[24]

Workers with symptoms and/or CXR findings were referred to the family doctor or medical appointment at the TB outpatient centre, as required. IGRA-positive workers were offered preventive treatment and followed up at the local TB outpatient centre closer to their residence, according to the national standard of care.[25] Screening activities were paused from March 2020 until March 2021 due to the COVID-19 pandemic.

IGRA

Occupational health nurses performed IGRA at the workplace, according to the procedures discussed in an annual training session. The QuantiFERON® TB Gold In-Tube (QTF; Qiagen, Hilden, Germany) test was used. IGRA tubes were transported to the laboratory in a maximum of 6 h, and then processed according to the manufacturer's instructions. According to standard procedure, the assay result was considered indeterminate, negative or positive.[11,26]

Diagnosis of TB infection

The diagnosis of TB infection was based on a positive IGRA result without any findings suggestive of active pulmonary or extrapulmonary TB on the symptom questionnaire, CXR and microbiological sputum examination.

Descriptive and statistical analysis

In consecutive years from 2018 to 2022 (except 2020), ARI was calculated as the proportion of workers with IGRA conversion (negative to positive). The TB notification rate from the two municipalities was calculated based on National Tuberculosis Programme data from 2018 to 2021 (the most recent data available). The TB notification rate among stone quarry workers was calculated for 2015–2019. We relied on the count of active workers with TB disease during that period, as documented in another study.[27] We used the total of stone quarry workers registered in 2018 as the denominator. We calculated the percentage decrease in TB notification and TB infection rates. We recorded the characteristics of workers who joined and left the companies in 2018–2019. Data from other years were not included due to a high percentage of missing values. However, according to occupational health professionals' reports, the population dynamics of the companies were similar during the remaining study years. We performed a sensitivity analysis: we recalculated ARI excluding workers who remained in the screening programme since 2018, as it has been suggested in the literature that participants who drop out tend to accumulate risk factors.[28,29]

Proportions of workers who dropped out and workers who joined the companies were compared

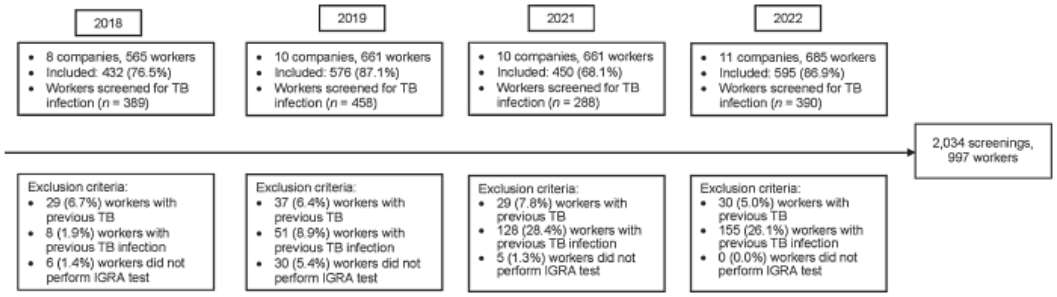

Figure 1. Selected companies and eligible workers, included sample and exclusion criteria.

using the χ^2 or Fisher's Exact test, as appropriate. We only dealt with variables (proportion of workers with silicosis, alcohol and tobacco use and those with reported symptoms), with less than 20% missing values. Missing values were eliminated from the analysis.[30] SPSS® v28.0.1.1 (IBM Corp, Armonk, NY, USA) was used for statistical analysis.

Ethical considerations

Ethical approval for this study was granted by the Ethics Boards of the Northern Regional Health Administration, Porto, Portugal (41/2018).

RESULTS

A total of 2,403 registered active workers in Penafiel and Marco de Canaveses were found in 2018. Considering this denominator and 52 active stone quarry workers who were diagnosed with TB in 2015–2019 in the two municipalities, the TB notification rate among active stone quarry workers was 540 cases/100,000 population-year for the same period. A total of 11 companies with two or more cases of TB in the previous 5 years were selected from 2018 to 2022 (Figure 1). A total of 997 individuals were recruited during the study period; on average, each worker was screened two times.

Workers screened in the 2-year periods, comprising three cohorts (2018–2019, 2019–2021 and 2021–2022) were included in the study (Figure 2). Of the 232 IGRA-negative workers in 2018, 20 tested positive in 2019 (8.6% ARI). Of 172 IGRA-negative workers in 2019, eight tested positive in 2021 (4.7% ARI). Two of 151 IGRA-negative workers in 2021 tested positive in 2022 (1.3% ARI). The infection rate decreased by 84.9% between 2019 and 2022.

From 2018 to 2019, of the seven companies that performed screening activities in both years, 121 workers (28.0%) left, and 86 workers (28.7%) joined the companies (Table 1). From 2021 to 2022, 78 of the 151 workers screened for TB infection had been screened since 2018. Two of 73 IGRA-negative workers in 2021 tested positive in 2022 (2.7% ARI). The infection rate thus decreased by 68.6% between 2019 and 2022.

The TB notification rate in Penafiel and Marco de Canaveses was 72.6 cases/100,000 in 2018, 63.5 cases/100,000 in 2019, 32.2 cases/100,000 in 2020 and 55.2 cases/100,000 in 2021. The notification rate decreased by 23.9% between 2018 and 2021 (Figure 3).

DISCUSSION

The ARI decreased in a group of stone quarry workers regularly screened for TB in a high-risk area in Northern Portugal. The combined effect of screening, promoting treatment and preventive treatment of a vulnerable population and the community measures implemented for the pandemic probably contributed to these results. ARI in stone quarry workers decreased 2.9 to 3.6 times faster

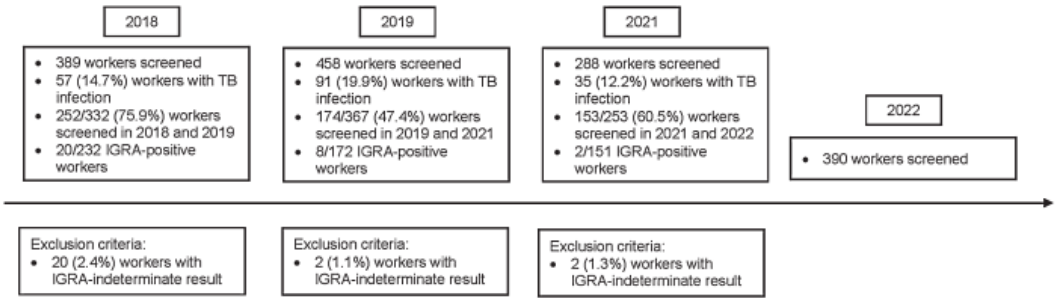

Figure 2. Three cohorts of workers screened for TB infection. IGRA = interferon-gamma release assay.

Table. Comparing follow-up losses and workers who entered the screening programme in terms of main risk factors.

	Left the programme, 2019 (n = 121) n/N (%)	Remained in the programme, 2019 (n = 311) n/N (%)	Joined the programme in 2019 (n = 124) n/N (%)	P value (drop/join)
Age groups, years				<0.001
18-44	41 (33.9)	144 (46.3)	73 (58.9)	
45-65	80 (66.1)	167 (53.7)	51 (41.1)	
Silicosis				0.624
Yes	32/97 (33.0)	56/251 (22.3)	22/75 (29.3)	
No	65/97 (67.0)	195/251 (77.7)	53/75 (70.7)	
TB disease diagnosis	0	0	1	—
TB infection prevalence (excluding undetermined)	34/106 (32.1)	23/271 (8.5)	37/98 (37.8)	0.462
Adherence to preventive treatment	21/34 (61.8)	12/23 (52.2)	27/37 (73.0)	0.447
Alcohol use				0.886
Yes	82/120 (68.3)	236/310 (76.1)	68/102 (66.7)	
No	38/120 (31.7)	73/310 (23.5)	34/102 (33.3)	
Tobacco use				0.399
Yes	39/120 (32.5)	81/310 (26.1)	39/102 (38.2)	
No	81/120 (67.5)	228/310 (73.5)	63/102 (61.7)	
Previous TB/TBI				0.342
Yes	13/121 (10.7)	25/311 (8.0)	17/124 (13.7)	
No	108/121 (83.3)	286/311 (92.0)	107/124 (86.3)	
Report symptoms				0.327
Yes	29/117 (24.8)	74/311 (23.8)	19/102 (18.6)	
No	88/117 (75.2)	237/311 (76.2)	83/102 (81.4)	

TBI = TB infection.

when compared to the TB notification rate in the general population. Given that the TB notification rate among stone quarry workers was 7.5 times higher than the notification rate in the general population, this screening strategy likely led to the reduction of TB risk among this vulnerable population. TB notification rate decreased in 2020 and was steady at a pre-pandemic level in 2021; this may have been due to under-notification mainly at the beginning of the COVID-19 pandemic.[31,32] In the light of our analysis, this suggests that the decrease could be lower and the difference in ARI decline could be greater.

As reported by previous studies, ARI in the adult population in high-incidence countries is estimated to be 5–10%.[12] We found an ARI of 8.6% in the first year of the screening programme, which is consistent with this finding. Determining changes in the risk of infection is an informative indicator for changes in transmission patterns of *M. tuberculosis* in a community.[12] The literature suggests that ARI substantially underestimates the true force of infection in a community, as traditionally measured based on measurements of point prevalence of TB infection in children.[13] In this study, we directly measured the

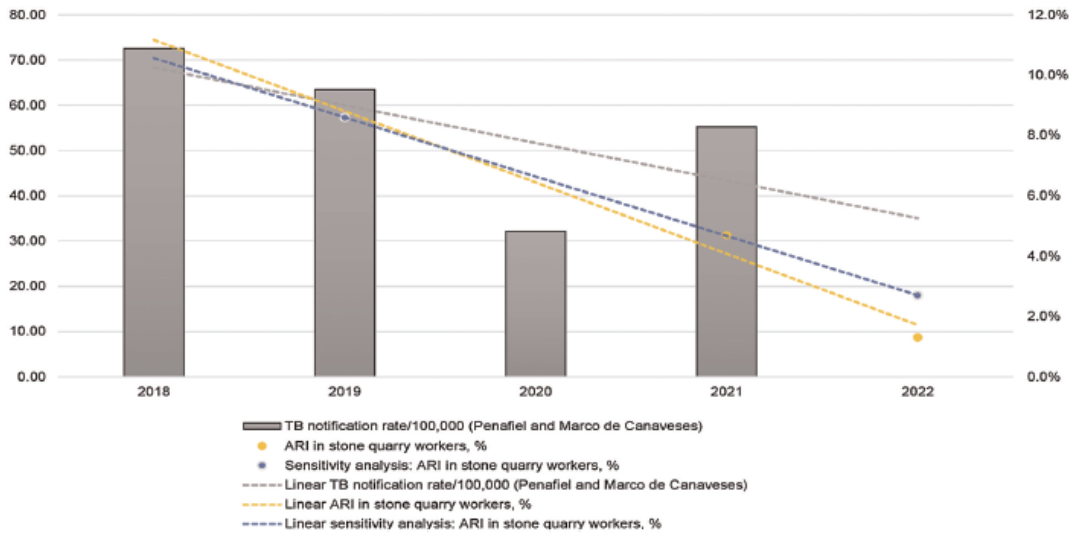

Figure 3. Comparing the decline of TB notification rate and ARI during the screening period. ARI = annual rate of infection.

conversion from IGRA-negative to IGRA-positive in a high-risk population.

Precarious employment, which includes employment instability,[33] is a significant determinant of population health inequities.[34] Workers who left and those who joined the companies are frequently in precarious employment. In our study, workers could have dropped out from the screening programme because of short-term contracts, moving from one company to another, retirement or unemployment. They had more silicosis and TB infection than those who remained; however, workers who left the companies were not statistically different from those recruited for our risk factor analysis, except in terms of age (recruited workers were younger). Although the follow-up losses are a limitation, we were able to obtain data on their main characteristics and perform a sensitivity analysis accordingly. We calculated an ARI of 2.7% from 2021 to 2022, instead of 1.3%. Nevertheless, the decline in ARI in these "mobile workers" was 2.9 times higher than the decrease in the TB notification rate observed in the general population.

From 2018 to 2022, 997 workers were screened at least once, representing 41.5% of the number of estimated active stone quarry workers in the two municipalities. TB exposure among stone quarry workers is not only work-related.[27] Unemployed and retired workers, who tend to be older and more likely to have (severe) silicosis, are, in theory, at increased risk of being TB-infected (or -reinfected) in social places in their free time. This screening programme focused on active workers, but a substantial burden of TB infection may be found in inactive workers. Given our study design, included workers had a greater chance of being infected than workers from other stone quarries at lower TB risk., We therefore contend that the computed ARI might be an overestimation of the TB risk among active stone quarry workers. Nonetheless, inactive workers likely accrued additional risk factors and susceptibility to TB.

Reinfection and the heterogeneous distribution of reinfection are important drivers of transmission;[23] these are not measured by the ARI. Modelling studies suggest that 60–80% of TB infections result from reinfection of previously infected persons.[23] ARI may not accurately reflect the real risk of infection among previously infected workers, as reinfection tends to be more frequent among previously infected individuals (and these were excluded from our analysis). On the other hand, the TB notification rate is based on reinfections, as it includes not only new cases of TB but also relapses and reinfections. The fact that ARI in a high-risk population decreased more than the TB notification rate in the general community therefore suggests that the TB screening strategy in stone quarries had an impact that will be reflected in a steeper decline in TB incidence, first in this high-risk population, and then in the general population. Not only was the screening programme maintained when anti-COVID community measures were in force (2021 and 2022), but it was also used to foster awareness and engagement among TB stakeholders.

As the risk of reinfection of previously treated persons is high, and infection treatment might fail to provide durable protection, we suggest that community measures should be prioritised. To ensure TB risk reduction, active case-finding was recently found to dramatically affect transmission reduction, especially if high-risk subpopulations can be targeted.[35]

In conclusion, ARI decreased in a group of stone quarry workers who were regularly screened for TB infection in two high-incidence municipalities of Northern Portugal from 2018 to 2022. The decline was bigger than the one observed in the TB notification rate in the general community. Therefore, we recommend that the screening strategy consisting of a symptoms questionnaire, CXR and IGRA is maintained in this high-risk population, together with an active case-finding strategy directed towards the general population of these high-incidence communities.

Conflicts of interest: none declared.

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3.6 Is it worth screening quarry workers for TB infection in high-incidence areas? A cost-benefit analysis

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Original Research

Is it worth screening quarry workers for TB infection in high-incidence areas? A cost-benefit analysis

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ABSTRACT

Background: Tuberculosis (TB) infection screening of high-risk groups is an important strategy for achieving End TB targets. A TB infection screening program was implemented for quarry workers from a Portuguese high-incidence area in 2018–2022. We aimed to calculate the cost-benefit of the screening program from the societal perspective.

Methods: We calculated medical and non-medical direct and indirect screening costs and compared them with the cost savings from averted cases of TB disease. We estimated the number of potentially averted TB disease cases based on the risk of progression of TB infection to TB disease found in the literature.

Results: During the screening program, 997 workers were screened. TB infection was diagnosed in 215 workers, 150 of those initiated preventive treatment. Screening program total costs were €136,295. Twenty-nine TB cases were potentially prevented, what would have costed €152,386. Savings of €16,091 were obtained (€4516, €40898, and -€29322 from the workers, employers, and NHS, respectively).

Conclusions: The monetary benefit of a TB infection screening program directed to quarry workers in a high-incidence area was greater than its cost. Companies and workers saved substantially more money. TB infection tests that are better predictors of progression to TB disease could reduce NHS costs.

1. Introduction

Screening of high-risk groups for Tuberculosis (TB) is considered paramount for TB elimination, with management of TB infection being crucial to achieving End TB global targets.

Some studies compared the cost-effectiveness of TB disease screening strategies directed to groups such as migrants, persons living with HIV, and contacts, measuring it as cost per TB case detected or cost per disability-adjusted life year averted [1,2]. Regarding TB infection, formerly known as latent TB infection, some modelling studies were designed to find cost-effective screening strategies for migrants [3–5]. In a 2023 systematic review, authors did not find studies that directly evaluated the benefits and harms of TB infection screening programs compared with no screening [6]. As programmatic costs greatly impact cost-effectiveness, research should provide both fixed and variable costs of screening interventions [2]. There is a need for clearer guidance on which specific tools and screening algorithms or strategies are cost-effective, essentially highlighting the knowledge gap that still exists despite the World Health Organization's endorsement of systematic screening [2].

The cost-effectiveness of a screening strategy is linked to the prevalence of TB infection in a population. When the prevalence is higher, the more likely testing will be cost-effective [2,7]. In a 2020 Italian study, the annual TB infection screening of healthcare workers during a period of five years resulted in a high financial burden (€38,902.90 per seroconversion). Applying a more restrictive screening strategy (only in

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high-risk workers), only one seroconversion would have been missed, with a relevant drop in the costs: €6756.40 per seroconversion, which was considered cost-effective [8].

The TB notification rate in *Penafiel* and *Marco de Canaveses*, two municipalities of Northern Portugal, was 55.2 cases per 100,000 population in 2021 – which was close to fourfold the national rate (14.6 cases per 100,000 population [9]). Social health disparities, a higher proportion of workers exposed to silica or with silicosis and the presence of other common risk factors such as tobacco and alcohol use, make this a hot spot for TB [10–13]. From 2018 to 2022, a screening program directed to quarry workers was implemented. Occupational health services performed the screening activities as part of workers' annual health surveillance, in collaboration with public health local services, local TB outpatient centres, and the Northern regional TB laboratory [11].

In this study, we aimed to 1) Evaluate the screening program's direct and indirect costs from the perspective of society (including health services, companies, and individuals); 2) Compare the program costs with its effectiveness measured as the number of TB averted cases converted in monetary units.

2. Methods

2.1. Study population and study design

A TB disease and infection screening program was implemented from 2018 to 2022. It was directed to workers from high-risk stone quarries (where at least two cases of TB had occurred in the previous five years) located in two Portuguese high-incidence municipalities. Until 2018, symptom-based passive screening for TB disease was implemented, either for risk workers or the general population. Additionally, as part of the NTP surveillance strategy, every time a TB case was notified, an epidemiological investigation was performed to identify close contacts to screening before or after 2018.

We aimed to find the cost-benefit of the TB infection screening program. We compared costs of the screening program and costs saved by the number of averted TB disease cases.

2.2. Screening program costs

Screening activities included a health questionnaire and chest X-ray (CXR) to exclude TB disease. The standardized questionnaire was applied by occupational nurses, according to the national standard of care guidelines [14], during work hours at the workplace. After the exclusion of TB disease, the QuantiFERON® TB Gold In-Tube interferon-gamma release assay (IGRA) was indicated to be performed on individuals with no previous history of TB. We considered the number of IGRA tests performed according to data from the laboratory, which included tests carried out without indication (waste). We estimated the total number of CXR performed during the program according to adherence data to CXR from 2018 to 2019.

Direct medical costs were calculated as the sum of estimated costs from the screening test(s), and the work of healthcare professionals. We considered the cost opportunity of healthcare professionals reported by Northern Health Administration in another Portuguese study [15] (Table 1). Specimen transportation to the testing laboratory was not considered because the health services provided the usual transport used to transport other products.

Direct non-medical costs were not considered because screening tests were performed during work and at the workplace.

Indirect costs were calculated by multiplying the estimated time by the average income (from *Instituto Nacional de Estatística*, Statistics Portugal) (Table 1).

Table 1
Direct and indirect costs used to calculate TB screening program costs.

What	How much	Who pays
Direct individual medical costs		
Chest X-ray	5.00€	*Company*
QuantiFERON-TB Gold Plus (including ELISA kit, antigen, and mitogen)	€37.66	*Health Administration*
Disposable material (laboratory materials, blood collection materials, syringes, gloves, compresses)	€0.57	*Health Administration*
Occupational health nurse • Interview/health questionnaire • Time to fill in forms and collect blood (IGRA test)	*9.7€/hour, 30 min/worker*	*Company*
Occupational health doctor • Diagnosing and refering workers	*25€/hour, 2 min/worker*	*Company*
Administrative • Receive and register samples	*5€/hour*	*Health Administration*
Laboratory technician • Process samples and give results	*18€/hour* *5,5 h per 22 tests*	*Health Administration*
Indirect costs		
Amount of time to perform: • Symptom questionnaire: 10 min • IGRA: 20 min • Chest X-ray: 15 min	*€1056 (average salary)* *⇔ €8.4/hour (1056*14/220/8)*	*Company*

2.3. Preventive treatment costs

A medical appointment in a TB outpatient centre was scheduled for all workers with a positive IGRA test result, and preventive treatment was offered accordingly. We used data from the screening program to estimate costs related to the diagnosis and treatment of TB infection, namely: the number of workers diagnosed with TB infection (and among them the number of workers with silicosis and the number of workers with diabetes) and adherence to preventive treatment.

Regarding direct medical costs, we used the median costs of TB drugs as described in a 2023 European study [16]. We assumed a scheme of daily isoniazid and rifampicin for three months, a medical follow-up with three medical appointments and three blood tests (analysis of liver enzymes *ALT* and *AST* and total bilirubin) according to the standard care [14]. We used 2022 exams' cost as published by the Portuguese Central Administration of Health System [17]. We estimated the costs of a medical appointment of 15 min each, at a medical professional cost per hour described (Table 1).

Regarding direct non-medical costs, we considered those attributed to the individual who had to pay for transportation to and from the TB outpatient centre and analysis centre. An estimated cost of €0.10 per km and a median distance of 10 km per trip was assumed.

Regarding indirect costs, we considered that three working days were lost per individual who adhered because of the need to do blood tests and medical appointments.

2.4. Measure of effectiveness

The number of potentially averted TB cases was estimated based on the number of individuals who started preventive treatment, a 10 % lifetime risk of developing TB [18,19], and a 70 % efficacy of preventive treatment [20,21]. Considering that quarry workers are a vulnerable group to TB, the general population's lifetime risk should be underestimated for this group. Then, we considered the risk per year among individuals with silicosis and with diabetes as reported in a 2020 systematic review [22].

We used the average life expectancy in the sub-region of *Tâmega e Sousa*, where the municipalities of *Penafiel* and *Marco de Canaveses* are located, as reported by Statistics Portugal. We calculated the expected years to live based on the median age of the quarry workers screened during the program.

2.5. TB disease costs

We estimated the costs that would have been incurred with the number of potentially averted TB cases. Regarding direct medical costs, we used the median costs of TB drugs as described in a European study from 2023 [16]. We assumed a TB-sensitive scheme of 56 doses of isoniazid, rifampicin, pyrazinamide, and ethambutol in the intensive phase and 126 doses of isoniazid and rifampicin in the maintenance phase.

We considered that 29 % of TB patients in Portugal are treated as inpatients as reported in a 2019 Portuguese study [23]. We estimated direct costs of hospitalization based on a Portuguese study using 2009 data [24]; we applied a 35 % cumulative inflation rate to the value to have a 2022 estimate.

According to the standard care, eight medical appointments, eight blood tests (including analysis of liver enzymes *ALT* and *AST* and total bilirubin), eight samples of mycobacterial exams (direct and culture), one antimicrobial susceptible test and three CXR are the minimal requirement according to the standard care [14]. We used 2022 exams' costs [17]. We estimated the costs of a medical appointment of 20 min each, at a medical professional cost per hour described. We also considered the cost of Directly Observed Therapy (DOT) as a 5-min nurse consultation to each one of the required 182 doses.

We estimated screening costs that occur whenever a new TB case is found based on an average cost of €55.21 per screened individual and an average number of six contacts per index case as reported in another Portuguese study [15].

Regarding direct non-medical costs, we considered the same as described in Preventive treatment costs.

Regarding indirect costs, we considered that two months of work were lost per individual, plus the number of days needed for medical appointments and exams.

2.6. Social discount rate

As the risk of TB disease in an individual with TB infection is estimated to be half in the first two years and half in the remaining lifetime, we assume that the prevented costs are not all saved immediately. Even so, as we performed an analysis at constant prices, inflation rate was not considered for future savings.

We assumed a social discount rate of 0.0 % because the real interest rate on Portuguese debt was negative in 2022 (inflation of 7.8 % and interest rate on Portuguese debt 2.2 %) [25].

2.7. Ethical considerations

Ethical approval for this study was granted by the Ethics Boards of the Northern Regional Health Administration (41/2018). Informed consent was obtained.

3. Results

Among 184 quarries identified in the municipalities, 11 met the inclusion criteria and were included in the study. A total of 997 workers (41.5 % of the total of registered active workers found in the 184 of quarries) were enrolled in the four-year TB screening program; their median age was 43 years old (Interquartile range [IQR] 34–50). Each worker was screened 2.06 times on average (n = 2053 screenings). 97.1 % (968 out of 997) of workers were Portuguese-born. Adherence to chest X-ray (CXR) was 70 % (690 CXR/988 screenings in 2018–2019); it was 96 % when a radiologic mobile unit was used. According to data from the laboratory, 1493 IGRA tests were performed during the four-year program; 86 of those (5.7 %) were performed on individuals with a history of TB exposure and were considered wasted.

The program's total cost was €91,980.53 according to a whole society perspective (Table 2). The companies paid €27,935.80 (30 %) and the National Health Service (NHS) paid €64,044.72 (70 %). The median cost per screening was €44.80.

Table 2
Total direct and indirect costs 2018–2022.

Exam/Work	Total cost
Chest X-ray (n = 1434)	€7168.88
IGRA tests (n = 1493)	€56,226.38
Disposable material (n = 1493)	€851.01
Occupational health nurses	*€6939.54*
Occupational health doctors	*€1710.83*
Administratives' work	*€248.83*
Laboratory technician work	*€6718.50*
Quarry workers' work time lost	*€9020.43*
Total costs	*€91,980.53*

During the screening program, there were three diagnosis of TB disease and 215 diagnosis of TB infection. Among 347 workers who did at least two IGRA tests during the study period, 33 workers converted from IGRA negative to IGRA positive (9.5 %). The average cost per TB infection diagnosis was €427.82. Among the diagnosis of TB infection, 94 were made in workers with silicosis (43.8 %) and 33 in workers with diabetes (15.6 %), which were the two main comorbidities identified. 70 % of the workers with TB infection initiated preventive treatment. Preventive treatment and follow-up added €294.45 per TB infection case that initiated preventive treatment (Table 3). A total of €44,314.73 were added to the screening program, e.g., the four-year screening program costed €136,295.26 to the whole society.

The number of potentially averted TB cases was estimated based on the number of individuals who started preventive treatment. Considering that 66 workers with silicosis were diagnosed with TB infection and initiated preventive treatment, with a risk of 3.7 % per year of developing TB disease, during a life expectancy of 18.92 years (half-life expectancy than that of the general population at 43 years old), 23 TB cases were averted. Among 23 workers with diabetes who were diagnosed with TB infection and initiated preventive treatment, considering a risk of 0.76 % per year, during a life expectancy of 18.92 years, 2 TB cases were averted. Among the remaining 88 workers diagnosed with TB infection and initiated preventive treatment, considering a lifetime risk of 10 %, 4 cases were averted. In total, 29 cases were averted (half during the first two years and the remaining in the following 16.92 years).

We estimated a cost per TB disease case of €5254.70 (Table 4). Total costs prevented were €152,386.60; half was saved in the first two years and the remaining value was saved in the next 16 years.

Comparing the costs of the screening program with the costs of the TB disease cases averted yields total savings of €16,091.34 (€4516.00, €40,898.80, and -€29,322.45 from the workers, employers, and NHS, respectively).

Companies and workers saved respectively 48 % and 71 % of costs they would incur if no screening program had been implemented (predicted costs of inaction). On the other hand, the NHS paid 48 % higher costs for the screening program (Fig. 1).

4. Discussion

The monetary benefit of a TB infection screening program directed to

Table 3
Total costs per individual under preventive treatment.

Exam/Work	Total cost	Who pays
TB drugs cost (3HR - daily)	€130.50	Health system
Liver analysis (AST/ALT/total bilirrubin)	€14.10	Health system
Medical appointments direct costs	€18.75	Health system
Transportation to medical appointments and analysis	€12.00	Worker
Indirect costs (lost working days)	€105.60	Company
Total costs	*€294.45*	

Table 4
Total costs per TB disease case.

Exam/Work	Total cost	Who pays
TB drugs cost (2HRZE; 4HR)	€346.78	Health system
Liver analysis (AST/ALT/total bilirrubin)	€37.60	Health system
Hospitalization costs (29 % patients)	€3654.45	Health system
Mycobacterial laboratory costs (TSA/culture/direct)	€85.15	Health system
Chest X-ray	€15.00	Health system
Medical appointments direct costs	€66.67	Health system
Laboratory work	€27.00	Health system
DOTS cost	€147.12	Health system
Screening costs	€330.00	Health system
Transportation to medical appointments and analysis	€218.00	Worker
Indirect costs (lost working days)	€2921.60	Company
Total costs	*€5254.70*	

quarry workers in a high-incidence area was greater than its cost from the perspective of the whole society. We considered medical and non-medical costs but not the monetized value of health improvements, namely improvements in quality of life or prevented disability, which would increase prevented costs. Additionally, the transmission of *Mycobacteria tuberculosis* to others could have been avoided and secondary cases of TB infection and disease could have been averted [26], but related costs were not included, which also underestimated NHS prevented costs.

Catastrophic costs due to TB are an important issue for individuals and families [28]. We estimated that workers saved 70 % of the predicted costs of inaction. Besides the prevented costs that we considered, additional costs such as those related to unemployment are usually added [29]. Thus, the monetary return of the screening program should be larger.

Companies prevented 48 % of costs they would have if they let their workers fell ill with TB. We assumed that workers would be absent from work for two months if they had TB disease, but this is an underestimate because an absenteeism of several months usually takes place when TB and silicosis coexist [30] and evidence is being collected on how TB-affected households remain economically vulnerable even after TB treatment completion, with limited recovery in income and employment [29].

The screening program increased the net costs of the NHS. Nevertheless, NHS costs can be minimized with a scheme for preventive treatment consisting of rifapentine and isoniazid for three months on a weekly dose, which are not only cheaper but also have better treatment completion rates [31]. In our study, we estimated that only 29 workers (19.3 %) of the 150 workers who were diagnosed with TB infection and initiated preventive treatment would have developed TB without screening and preventive treatment. Available tests lack accuracy in identifying the progressors from infection to TB disease [32]. When better predictors of progression to TB disease are found, we could reduce the number of people that get the preventive treatment without directly benefiting from it and increase cost-benefit.

In Italy, TB infection screening of health care workers with high-risk duties or job tasks in settings at high risk of TB contagion cost €6756.40 per seroconversion and a rate of conversion to IGRA positive of 0.6 % (9/1471 subjects) was found [8]. We found that 9.5 % workers converted from IGRA negative to IGRA positive and an average cost per TB infection diagnosis of €427.82, which suggests that screening quarry workers from a high-incidence area was more cost-effective than screening health care personnel from a low-incidence country working in high-risk settings.

In a 2024 systematic review, participants with a positive IGRA result at baseline and those from high-burden settings benefited the most from TB preventive treatment [27].

Integrating screening and treatment for other prevalent diseases among targeted risk groups into TB outreach interventions improve cost-effectiveness [33]. In this screening program we found three early diagnosis of TB disease which potentially prevented transmission and additional community cases (a benefit that we did not measure). Besides, this screening program also detected silicosis (through history of silica exposure and radiological findings), an occupational disease that is responsible for an important amount of disability-adjusted life years [34] and that benefit of early diagnosis of silicosis was also not measured.

In conclusion, the monetary benefit from the prevention of 29 prevented TB cases was greater than the costs of a TB infection screening program directed to quarry workers in a high-incidence area from the perspective of the society. Companies and workers saved substantial costs they would have incurred if screening had not been implemented. TB infection tests that are better predictors of progression to TB disease and shorter preventive treatment schemes that are cheaper and with better adherence could reduce costs from the perspective of the NHS.

CRediT authorship contribution statement

Sofia Sousa: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Carlos Carvalho:** Writing –

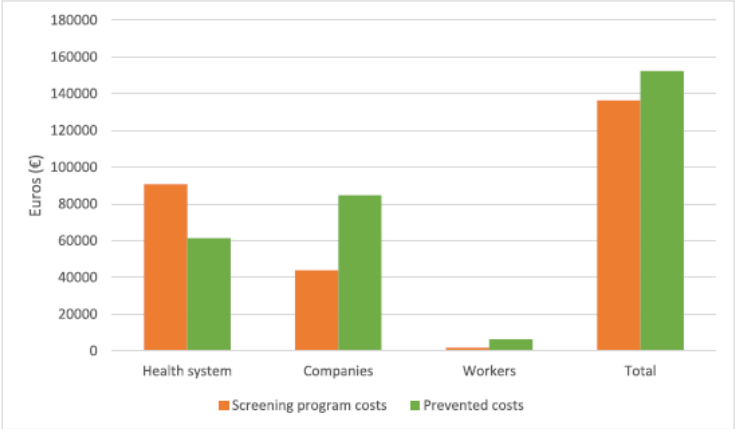

Fig. 1. Comparison of screening program costs with prevented costs under different perspectives (health system, companies, workers and total).

review & editing, Formal analysis, Data curation, Conceptualization, Methodology. **Sofia Santos**: Validation, Resources, Methodology, Investigation, Data curation. **Catarina Magalhães Alves**: Writing – review & editing, Validation, Resources, Formal analysis, Data curation, Conceptualization. **Guilherme Gonçalves**: Writing – review & editing, Validation, Supervision, Conceptualization. **Álvaro Almeida**: Writing – review & editing, Supervision, Formal analysis, Validation, Conceptualization, Methodology. **Raquel Duarte**: Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors have no declarations of interest to declare.

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4. Discussion and Conclusions

This thesis contributed to the understanding of the TB transmission dynamics among a group of quarry workers in a high-incidence area, and it measured the effect and cost-benefit of a strategy consisting of an annual TB screening directed to the group.

Active transmission of TB among stone quarry workers was present, with several outbreaks occurring simultaneously, as documented through Whole Genome Sequencing (WGS). It seemed to be driven by multiple factors (social and work-related); having a previous episode of TB was more common among clustered cases, suggesting the increased vulnerability of quarry workers to getting TB. Quarry workers were important to maintain transmission, but they could be the weakest link in a high-incidence community. Social contacts in community public places where epidemiological links are difficult to establish (such as coffee shops) seemed to contribute to maintaining ongoing active transmission.

Quarry workers are especially at risk for TB. World Health Organization (WHO) recommends that current and former workers with silica exposure should be systematically screened for TB disease (World Health Organization, 2021). Regarding TB infection systematic screening, the WHO recommends it for people with silicosis (World Health Organization, 2020).

For TB infection screening, we found that the IGRA-only strategy yielded higher screening effectiveness for diagnosing TB infection (aOR 2.12, 95%CI: 1.53 - 2.94). The incremental cost-effectiveness ratio (ICER) was €106 per TB infection diagnosis, representing increased effectiveness with a slightly increased cost of IGRA-only screening strategy.

Systematic diagnosis of TB infection, together with preventive treatment directed to groups with vulnerabilities in high or low-incidence settings, have been pointed out as an important strategy to achieve TB elimination. In line with the End TB strategy, a TB disease and TB infection screening (using IGRA) directed to quarry workers was implemented from 2018 to 2022 by the public health units with the regional and National TB Program (NTP) teams in *Penafiel* and *Marco de Canaveses*.

Among 997 workers screened during a four-year period, with an average of 2.06 screenings per worker, three cases of TB disease were diagnosed, and a prevalence of TB infection of 19.8% was found. Radiological findings compatible with silicosis were identified in 25% of workers. An overall rate of infection of 3.2 per 100 person-year among quarry workers was found, with silicosis, diabetes and older age being independent and significant risk factors for TB infection. Our results supported the idea that regular TB infection screening could be considered for people exposed to silica dust, especially if they accumulate other risk factors.

Other authors have also suggested that preventive treatment could be considered for any workers with prolonged silica exposure, whether or not silicosis has developed, especially in geographical regions with a high prevalence of TB (Yew *et al.*, 2019).

Determining changes in the risk of infection was considered an informative indicator for changes in transmission patterns of *M. tuberculosis* in a community (Rieder, 2005). The annual rate of infection (ARI) in quarry workers decreased about three times faster compared to the TB notification rate in the general population between 2018 and 2022. Our data suggested that annual TB infection screening of a group of quarry workers in a TB high-incidence area contributed to the decrease of the rate of TB infection among the group in a period when TB incidence in the general population did not decrease at the same level.

Some overall limitations should be addressed. The dose of silica exposure, either cumulative or present, was not possible to measure. In future studies, quantifying silica exposure and other relevant factors such as alcohol and tobacco use (collected as dichotomous variables and not quantified) could help explain how much of the TB infection risk in these groups is attributed to any of those variables. Additionally, reinfection and the heterogeneous distribution of reinfection were pointed out as important drivers of transmission that are not measured by the ARI (Andrews *et al.*, 2012; Horsburgh *et al.*, 2023). ARI does not reflect the risk of infection among previously infected individuals. The durability of preventive therapy has been a concern in high-burden settings where the force of infection likely contributes to observed TB cases shortly after TB preventive treatment completion due to exogenous reinfection (Samandari *et al.*, 2011; Churchyard *et al.*, 2014; Salazar-Austin *et al.*, 2019). As the risk of reinfection of previously treated persons exists, preventive treatment might fail to provide durable protection.

As ending poverty and expanding social protection coverage results in a reduction in TB incidence (Carter *et al.*, 2018), efforts by the whole society should be made to address socioeconomic health determinants in deprived areas such as those predominantly affected by TB. Interventions that increase access to health care and other relevant services should be targeted.

Silicosis is an old problem that needs attention. In 2019, 2.65 million global prevalent cases of silicosis were reported globally, with an incidence rate and death rate of 1.7 and 0.2 per 100,000 population, respectively (Global Health Metrics, 2019). The prevalent cases and deaths due to silicosis might be much higher as underreporting of occupational diseases is an important issue (Kyung *et al.*, 2023; Rupani, 2023c; Spagnolo *et al.*, 2023).

A unit increase in silicosis incidence significantly increases TB mortality and morbidity (Albadrani, 2023). Preventing silicosis and exposure to silica could contribute to achieving End TB, and it should be a priority as silicosis is preventable and highly disabling. An

effective silicotuberculosis prevention strategy must be based on primary and secondary prevention (Kortum and Bozsoki, 2007). Primary prevention includes controlling silica dust at the source through environmental and individual methods (European Commission - Employment, 2016). Secondary prevention includes monitoring worker health in the workplace, assessing health risks and early disease detection (European Commission - Employment, 2016). In Portugal, current legislation determines the responsibilities of employers in controlling work-related risks and ensuring individual health surveillance (Diário da República, 2009).

Appropriate legislation to protect miners in Southern Africa from the threat of TB and occupational diseases was considered mandatory in the Southern African Development Community when, in 2012, these countries Heads of State signed the “Declaration on TB in the mining sector”. The declaration stated that mineworkers have contributed significantly to the wealth of the region at great personal cost to their health and welfare and that given the fact that the mining sector is one of the hardest TB-hit sectors, immediate action was needed to protect mineworkers from occupational lung diseases and suffering (Baleta, 2012).

Portugal has a specific silicosis preventive legislation since 1962 (Diário da República, 1962), addressing the need to perform an admission examination consisting of a general clinical examination with chest X-ray (CXR). Radiographic screening carried out by the Ministry of Health and Assistance services in 54 mines at that time revealed that, in 14,835 miners, the percentage of workers with silicosis varied between 0.44% and more than 30% of the staff in each mine, what was considered to demonstrate that it was possible to reduce the risks of being affected by silicosis (Diário da República, 1962). In 2005, a study into occupational illnesses performed in the Porto district showed that silicosis was the most reported occupational pathology. About 100 new cases per year were reported in 2000-2005, representing 85% of the respiratory occupational diseases (Santos *et al.*, 2010).

In 2018-2019, we estimated that 25% of screened quarry workers had silicosis, i.e., 173 in 690 CRX performed in that period showed radiological signs of silicosis. About half of those diagnosed with silicosis were not aware of their condition and were considered new diagnoses (Sousa *et al.*, 2019). This prevalence was similar to those found in low-income countries (Moyo *et al.*, 2024). In Australia, a screening programme included 799 workers, of whom 98 (12.3%) had silicosis (The Lancet Respiratory Medicine, 2019). A National Silicosis Prevention Strategy 2023-2028 was implemented in Australia (Lung Foundation Australia, 2023) and is also needed in Portugal.

A surveillance system needs to be established for the early detection and tracking of all patients with silicosis (Rupani, 2023b), including in Portugal, where national data from notifications of silicosis were not routinely reported. As the International Labor Organization/World Health Organization (ILO/WHO) International Programme on the Global Elimination of Silicosis was launched in 1995 and called for the elimination of silicosis worldwide by 2030 (Pan American Health Organization, 2008), action is needed now.

Similar TB screening strategies directed at mining sector workers have been implemented worldwide (Nandi *et al.*, 2020; Young *et al.*, 2020; Ohene *et al.*, 2021; Moyo *et al.*, 2022). South Africa has taken the lead by introducing TB screening for mine workers (Stop TB Partnership, 2019). Through the Mine Health and Safety Council, the industry committed in 2014 to reducing TB incidence to be at or below the South African TB incidence by 2024 (Minerals Council South Africa, 2020). An annual TB disease active case-finding (ACF) strategy was implemented; the number of pulmonary TB cases diagnosed was 4,639 in 2008 and 1,716 in 2018 (Minerals Council South Africa, 2020). The estimated TB incidence declined from 1,068 cases per 100,000 population in 2015 to 435 cases per 100,000 in 2018 (Minerals Council South Africa, 2020).

The *Thibela TB*, a cluster randomised study performed in 2006–2011 in South Africa, showed reduced individual-level TB incidence but no detectable population-level impact when comparing routine TB preventive treatment targeted to those identified as at higher risk of TB (due to HIV infection or silicosis) against a community-wide approach in which TB preventive treatment was offered to all gold miners workers (Vynnycky *et al.*, 2015). Mass screening and preventive treatment had no significant effect on TB control in South African gold mines despite the successful use of isoniazid in preventing TB during preventive treatment (Churchyard *et al.*, 2014). In the intervention clusters, 27,126 miners (66.2%) underwent screening. Of these miners, 23,659 (87.2%) started taking isoniazid for at least six months. The intervention did not reduce the incidence of TB (3.02 per 100 person-years vs. 2.95 per 100 person-years) or the prevalence of TB (2.35% vs. 2.14%) in the intervention and control clusters, respectively. Isoniazid only reduced TB incidence in the intervention clusters during preventive treatment (1.10 cases per 100 person-years vs. 2.91 cases per 100 person-years), but there was a subsequent rapid loss of protection (Churchyard *et al.*, 2014). The authors concluded that effective TB control in gold mines required a combination prevention approach, including health systems improvements to minimise treatment delay, improved diagnostics, and effective, durable preventive treatment regimens (Vynnycky *et al.*, 2015). Additionally, TB screening should be combined with screening for other diseases, such as silicosis, and especially with health-promotion

activities to reduce occupational exposure to silica (Churchyard *et al.*, 2004; World Health Organization, 2021).

From May 2017 to January 2018, Ghana implemented an ACF strategy among artisanal gold mining communities. Ninety-five TB cases were identified, corresponding to 910 TB cases per 100,000 population screened. The number needed to screen (NNS) was 110 (Ohene *et al.*, 2021).

In Malawi, in 2019, of the 2400 miners approached, 2013 (84%) were interviewed. Of these, 1435 (71%) were males, 1438 (71%) had known HIV status and 272 (14%) had pulmonary TB (Rambiki *et al.*, 2020).

In Zimbabwe, from 1 October 2020 to 30 September 2023, 10,668 small-scale miners were screened, with a high number of cases of silicosis (21%) and TB (7.4%) found (Moyo *et al.*, 2024). Among those diagnosed with silicosis, 1665 artisanal and small-scale miners were eligible for TB preventive treatment (TPT), and 1212 (73%) initiated TPT (Moyo *et al.*, 2024). Screening for TB, HIV and silicosis using workplace-based screening and occupational health clinics was considered an effective strategy in Zimbabwe (Moyo *et al.*, 2024).

In India, a cross-sectional study was conducted among 935 workers in sandstone mining who performed a CXR; 6.4% of the CXR showed evidence of TB (Nandi *et al.*, 2020).

In countries where TB incidence is above 100 cases per 100,000 population-year, ACF strategies directed at searching for undiagnosed pulmonary TB were prioritised. The NNS for an ACF strategy depends heavily on the population screened; as health system resources are often limited, identifying high-yield populations for screening is important to maximise program efficiency and reduce TB burden among groups at greatest risk (Naufal *et al.*, 2022). We found a prevalence of TB infection of 19.8%, corresponding to an NNS of five. Regarding TB disease, we found a prevalence of 0.30%, corresponding to an NNS of 333. In a retrospective cohort study in Denmark, a low-incidence country, the NNS to find one case of TB infection was seven among adult refugees and 19 among children, while NNS for TB disease was 266 and 164, respectively (Stærke *et al.*, 2022).

Some authors suggested that as most cases of TB in highly endemic areas occur in persons without recognised risk factors, targeted TB preventive treatment was unlikely to have a substantial population-wide impact (Suzanne Verver, Robin M Warren, Zahn Munch, Madalene Richardson, Gian D van der Spuy, Martien W Borgdorff, Marcel A Behr, Nulda Beyers, 2004; Rangaka *et al.*, 2015). The effect of screening high-risk groups alone on the pool of prevalent cases of TB could be relatively small (Kasaie *et al.*, 2014). Then, some authors suggested that community-based ACF for TB might be effective in changing

epidemiology if delivered with high coverage and intensity (Marks *et al.*, 2019; Burke *et al.*, 2021). In areas with a high burden of TB, they suggested that it would probably be necessary to screen the entire population and treat all, or nearly all, prevalent cases of TB to reduce transmission (Marks *et al.*, 2019).

In 2022, 31.2% of TB cases in Portugal did not have an identified risk factor associated; in the municipalities of *Penafiel* and *Marco de Canaveses*, that percentage was higher (46.4%) (Direção-Geral da Saúde, 2024). Information regarding risk factors may be missing in the surveillance systems. On the other hand, regardless of the risk factors that an individual has, exposure to *Mycobacterium tuberculosis* is needed to develop TB disease. When we compared the cost-effectiveness of TB infection screening strategies, we found that 27% of the screened contacts of people with respiratory TB were diagnosed with TB infection. The current epidemiological investigation does not integrate WGS data, and linkages between cases are not always found. The contact screening strategy could be optimised further if this integration occurred, with targeted screenings being more efficient and chains of transmission broken.

Given the fact that the TB notification rate in *Penafiel* and *Marco de Canaveses* was 56.6 cases per 100,000 population in 2018-2022 (Direção-Geral da Saúde, 2024), we could estimate that a large number of people would need to be screened to find one case of TB disease if a strategy of ACF was randomly addressed to the whole community, with important expenses associated. WHO recommended that general population screening be considered in defined areas with a prevalence of undetected TB of 0.5% or more (World Health Organization, 2021), which is not the case in these communities.

Regarding TB infection, as any treatment entails risk of harm and opportunity costs, TPT should be selectively targeted to population groups at the highest risk of progression to TB disease, who would benefit most from it (World Health Organization, 2021). Randomly applying TPT in a population is not only unsafe, but it is also not expected to have a sustainable impact on TB incidence (Churchyard *et al.*, 2014).

We found that the monetary benefit of a TB infection screening program directed to quarry workers in a high-incidence area was greater than its cost from the perspective of the whole society; companies and workers saved most of the predicted costs of inaction. Besides reducing disability and improving quality of life (which we did not measure in this cost-benefit analysis), investing in prevention allowed individuals and companies to avoid important expenses. Additionally, this screening program integrated screening for other prevalent diseases among targeted risk groups, namely silicosis. As prevention and surveillance of occupational diseases is an obligation of employers, and the TB screening program

reinforced the need to perform a regular CXR, those screening costs should already be paid by companies anyway.

Due to TB, people face costs or suffer income loss equivalent on average to more than 50% of their income (World Health Organization, 2015b). The economic impact of TB in communities with higher socioeconomic deprivation, where TB is also more frequent (Apolinário *et al.*, 2017; Oliveira *et al.*, 2022), may help induce a vicious circle of disadvantage. Hence, the fact that the screening program positively impacted companies and workers especially probably had an important economic impact on the community.

If better TB infection tests exist, i.e., tests that are better predictors of progression to TB disease, and cheaper and shorter preventive treatment schemes are implemented, overall costs and NHS costs could be reduced further. The development of biomarkers that accurately detect likely disease progressors would dramatically reduce the number of individuals requiring TPT (Fox *et al.*, 2021). Shorter and more acceptable TB preventive treatment regimens using less toxic drugs have recently been recommended by WHO (World Health Organization, 2021). However, for these shorter-duration TB preventive treatment regimens to substantially alter the current TB epidemic trajectory, robust operational research is required to guide its implementation in different settings (Fox *et al.*, 2021).

TB infection's high prevalence has been seen as a critical barrier to global TB eradication. Yet there is some evidence that self-clearance of *Mycobacterium tuberculosis* infection can occur (Behr *et al.*, 2021; Emery *et al.*, 2021). Longitudinal studies and clinical trials showed that TB immunoreactivity can persist after curative treatment. Most people with TB immunoreactivity do not develop TB disease upon immunosuppression, suggesting they have cleared their infection while retaining immunological memory (Behr, Edelstein and Ramakrishnan, 2019).

Owing to the self-clearance of *Mycobacterium tuberculosis* infection, the population with a viable infection may be markedly smaller than generally assumed. Coupling these wide-ranging implications for TB epidemiology with the ability to identify individuals who have self-cleared could dramatically improve the targeting of preventive programmes, bringing TB elimination within reach of feasibility (Emery *et al.*, 2021).

The multisectoral accountability framework for TB aims to support the effective accountability of governments and all stakeholders to accelerate progress to end the TB epidemic (World Health Organization, 2019). In line with this, occupational health services performed screening activities in collaboration with public health units, TB outpatient centres, and the laboratory. Municipalities and national industry associations were involved as partners; their roles included launching the project and related public events. TB sessions

directed to employers and workers were assured on a regular basis. Occupational health professionals were trained in TB screening, and communication between the different healthcare services and sectors was strengthened. Employers and quarry workers were systematically informed about the project through information sessions. The project fostered occupational health service cooperation, political commitment to the problem, the involvement of other relevant local stakeholders and raised awareness of TB and silicosis in the overall community (Sousa *et al.*, 2019).

To ensure sustainability, it was considered crucial to include frontline staff from the start and to give regular feedback on the monitoring and evaluation parameters (Lawson, Weekes and Hill, 2018), and that was obtained. Occupational health professionals did not previously administer CXR routinely to stone quarry workers, but this good practice was enhanced during the implementation of the project. As occupational health professionals were trained for TB and were committed to continuing regular screening as part of workers' health vigilance, sustainability is expected to occur. Increasing TB-related skills in occupational health professionals may also increase quarry workers' health literacy (Sousa *et al.*, 2019).

Actions to promote TB and silicosis prevention at different levels (from primordial to quaternary prevention) are continuously needed, including reinforcement of the use of personal and collective protective equipment; promotion of early diagnosis of silicosis (and TB) through periodic CXR by occupational health services; ensuring that primary care services (including TB outpatient centres) and occupational health services have the resources and knowledge needed to prevent, diagnose and treat TB and silicosis; and facilitating communication between all health service levels (public health, primary care services, occupational health services and hospitals) (Sousa *et al.*, 2019).

Endemic communities and high-risk populations are often stigmatised (Courtwright and Turner, 2010; Ashaba *et al.*, 2021). Interventions should address this and be integrated into the overall healthcare delivery (Myburgh *et al.*, 2023). By including TB in the regular screening of silicosis by occupational health services, it is possible to reduce stigma and its consequences.

This thesis adds to previous research that although screening directed to vulnerable groups is an important strategy to eliminate TB and contributed to the faster decrease in the rate of infection among quarry workers, the burden of TB in communities where ongoing active transmission occurs can continuously put most vulnerable groups at risk of infection (and reinfection) if no other measures are implemented. Genotyping all *Mycobacterium tuberculosis* strains in the TB high-incidence communities through WGS could help identify missing links between cases and all public places that are hot spots for TB. Implementing WGS, together with public health authorities' routine interventions of epidemiological

investigation and contacts' screening, could effectively break chains of transmission. The screening strategy directed to quarry workers, consisting of a symptom questionnaire, CXR, and IGRA, should be maintained in high-incidence areas to align with the End TB strategy. Furthermore, besides ensuring systematic TB infection screening for patients with silicosis, whether they are working (as addressed in this screening program) or not, as recommended by WHO, regular TB infection screening could be considered for people exposed to silica dust in TB high-incidence areas, especially if other risk factors such as older age and diabetes coexist. The development of innovative technologies to address TB infection, specifically tests that are better predictors of progression to TB, as forecasted in Pilar 3 of the End TB strategy, could increase further the screening effectiveness.

In conclusion, the results of this thesis support the effectiveness of a TB screening strategy directed at quarry workers from high-incidence areas in reducing their overall risk of infection with economic benefit. As the burden of silicosis is one of the main determinants of TB in mining communities, improving working conditions, eliminating silicosis and reducing exposure to silica should be a priority to end TB. Combining TB and silicosis screening contributes to an increase in screening effectiveness and should continue in the future, with costs being shared between companies and the NHS. Enforcing TB screening directed to high-risk groups of quarry workers and enhancing case detection in the high-incidence communities through the integration of genotyping with epidemiological investigation/contact screening, together with innovation that is expected to occur regarding TB infection tests and schemes, could lead the way to control (or eliminate) TB.

5. Future Research

Evaluating public health programs is paramount to delivering cost-effective interventions. This thesis assessed the short and medium-term effectiveness of a TB screening strategy directed at quarry workers from a high-incidence area, but TB screening effects continue to unfold. Additionally, qualitative data may add important clues on how to increase screening effectiveness in this vulnerable group. Then, several areas warrant further research: 1) to study the long-term effects of the TB screening strategy on TB incidence among quarry workers and the overall communities where they live and work; 2) to calculate the risk of developing TB disease in the screened workers that completed preventive treatment, and identify factors associated with reinfection; 3) to estimate the burden of reinfection among quarry workers with TB disease, through genotyping stains of all the episodes of TB developing in an individual; 4) to quantify the risk of TB infection in quarry workers associated with factors such as alcohol and tobacco use, and to study effective interventions to reduce the prevalence of those risk factors among quarry workers; 5) to quantify silica exposure in the sector and its relation with the improvement of working conditions and reinforcement of collective and personal protection equipment use; 6) to perform qualitative studies on the obstacles identified by workers to do not adhere to screening or preventive treatment, as well as to identify factors of non-compliance with collective or personal protection equipment by employers and employees, respectively; 7) to compare the cost-effectiveness of different strategies to reduce TB risk in quarry workers, including silicosis and silica exposure prevention and TB screening; 8) to compare workers with a first IGRA positive with workers that converted from negative to positive IGRA to identify factors presumably associated with recent infection. Finally, to increase understanding of the TB transmission dynamics in the communities, it would be beneficial 9) to identify factors associated with being part of a cluster of TB cases in the TB high-incidence communities through genotyping of all strains of *Mycobacterium tuberculosis* isolated in the high-incidence communities.

Addressing these research topics could help achieve End TB targets in this high-incidence area. They could contribute to developing more effective strategies and improving screening implementation issues addressing vulnerable groups.

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