Editorial paper

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Screening for latent tuberculosis: the way forward for tuberculosis elimination

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The End TB Strategy milestones include a 50% reduction in incidence of tuberculosis (TB) by 2025 and 90% by 2035, but the actual reduction up to 2021 was 10% (Global TB Report 2022). The TB prevention target was 30 million by 2022, whereas the achieved number is 12.5 million or 42.5% of the target [1].

About a quarter of the global population is estimated to have been infected with TB [2], but most people will not go on to develop TB disease and some will clear the infection [3]. Tuberculosis infection without signs of disease is called latent TB infection (LTBI).

One of the key components of the End TB Strategy is "Integrated, Patient-Centred Care And Prevention" listing "preventive treatment of persons at high risk, and vaccination against TB" as key intervention components [1].

Here, we will focus on the "preventive treatment of persons at high risk" and we regard people with LTBI as people with a high risk of developing active TB. It is generally estimated that 90% of people with a normal immune system exposed to TB will not develop active TB but have LTBI, which may later in life activate.

There are two risk groups where screening for LTBI with interferon-γ release assay (IGRA) could help reduce the future number of active TB cases:

- migrants from TB high endemic countries,
- immunosuppressed.

This paper focuses on screening for LTBI in migrants from TB high endemic countries.

A modelling study found that in 2014, the global burden of LTBI was 23% (95% uncertainty interval [UI]: 20.4–26.4%), amounting to approximately 1.7 billion people including a high burden in children [4]. Another modelling study of LTBI found the lifetime risk of developing active TB to be 17% (95% CI: 10.9–22.5%), compared to 12.6% (10.1–15%) assuming lifelong infection [5].

In patients with LTBI the infection with *Mycobacteria tuberculosis* leave an imprint on the immunological system which can be measured. Traditionally an immune response to *Mycobacteria tuberculosis* is measured by the Tuberculin Skin Test (TST) but this has in most settings been replaced with the IGRA.

The Tuberculin Skin Test is more often positive than IGRA in persons with LTBI and one study found that odds ratio (OR) for a positive TST was significantly higher than an IGRA (OR 1.46; 95% confidence interval 1.07–2.01) [6].

One study found that in immunocompetent BCG-vaccinated individuals, the IGRA positive rate in low-TB burden areas was significantly lower than the TST positive rate (OR 0.36 [95% CI: 0.31 to 0.41] vs. 0.53 [0.46 to 0.61]) [7]. The higher positivity rate for TST is due to reactivity induced by the Bacillus Calmette-Guérin (BCG) immunization where the IGRA assay does not include antigens from the BCG vaccine. The IGRA test showed indeterminate results in 6.9% of TB-exposed children below five years of age [8]. Additionally, unlike IGRA, the TST requires 2 visits for reading results, making it impractical for large screening programs.

A study of the 1,414 contacts to active TB patients (141 children) found a high rate of progression to active TB of those who are IGRA positive (12.9%), compared to 3.1% found for those who were TST positive [9]. A large multicenter study from Spain recommended a dual test-

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ing strategy using both TST and IGRA finding a κ coefficient of 0.48, 95% CI: 0.36–0.60 [10].

A study of migrants in the United Kingdom found that LTBI was related to the country of origin [11]. The overall IGRA positive rate was 23%, 28.9% in migrants from East and South East Asia and 42.5% from Sub-Saharan Africa [11]. A large, multicenter study found that a positive IGRA gave a 25 times higher risk of developing active TB [12].

A study from Norway included 50, 389 IGRA results from 44,875 individuals, of whom 22% (n = 9878) QFT were IGRA positive and 257 developed active TB [13]. The study also found that the risk of progressing from LTBI to active TB was related to the strength of the IGRA. The hazard ratios (HRs) for TB were 8.8 (95% CI: 4.7–16.5), 19.2 (95% CI: 11.6–31.6) and 31.3 (95% CI: 19.8–49.5) times higher with interferon-γ (IFN-γ) levels of 0.35 to < 1.00, 1.00 to < 4.00 and > 4.00 IU/ml, respectively, compared with negative tests (< 0.35 IU/ml) [13].

A study including 2512 young children found that IGRA at IFN-γ values higher than 4.00 IU/ml was associated with substantially increased active TB incidence (28.0 per 100 person-years [95% CI: 14.9–45.7]) compared with non-converters (incidence rate ratio – IRR 42.5 [95% CI: 17.2–99.7]; $p < 0.0001$), and compared with children with IFN-γ values between 0.35 and 4.00 IU/ml (IRR 11.4 [95% CI: 2.4–107.2]; $p = 0.00047$) [14].

In a study from Oman, 1049 subjects were surveyed. The overall IGRA-positive rate was 22.4% (234/1042), 30.9% and 21.2% of African and Asian migrants, respectively. Fifty-eight of the participants had a strong IGRA reactivity defined as more than 4 IU/ml [15].

Oman went further and estimated the cost of screening using an IGRA applied to all migrants from high TB endemic countries, followed by preventive TB treatment. Using a Markov model seven different scenarios were compared, with a comparison of the direct cost and the quality-adjusted life-years (QALYs) saved. The conclusions was that IGRA testing followed by 3 months of preventive treatment with rifapentine/isoniazid (3HP) was the most cost-effective intervention. Therefore the country included an LTBI screening program for new arrivals from high endemic countries in their TB elimination strategy plan [14].

Preventive treatment traditionally was 6 months of isoniazid, but a recent study found that one month of rifapentine plus isoniazid was non-inferior to 9 months of isoniazid for preventing tuberculosis in HIV-infected patients. The primary end point was reported in 32 of 1488 patients (2%) in the 1-month group and in 33 of 1498 (2%) in the 9-month group, for an incidence rate of 0.65 per 100 person-years and 0.67 per 100 person-years, respectively (rate difference in the 1-month group, –0.02 per 100 person-years; upper limit of the 95% confidence interval, 0.30) [16].

Challenges that can face such programs are large number of migrants arriving per year, compliance with medication and treatment completeness as screening alone will not add any value for the progress of TB elimination. A meta-analysis highlighted that LTBI treatment initiation and completion in migrants improved considerably from 2010 to 2020 in Europe, but drop out was reported along the entire treatment pathway [17].

Conclusions

Migrants from highly endemic areas, people exposed to active TB, and patients due to start immunosuppressive treatment are at high risk of developing active tuberculosis. To meet the target of eradicating tuberculosis in low-incidence countries screening and treatment programs must be strengthened along with understanding the diversity and barriers to migrants initiating and completing treatment. The treatment cascade for individuals at risk starting the treatment should ensure retaining these individuals at all stages in order to meet targets.

Individuals with a high risk of developing active tuberculosis such as migrants from highly endemic areas, people exposed to active TB, and patients due to start immunosuppressive treatment should be screened with an IGRA test. In migrants from TB high endemic areas at least those with a strongly positive IGRA should be offered preventive treatment.

For patients planned to start immunosuppressive treatment, all patients with a positive IGRA should be offered preventive treatment.

The authors declare no conflict of interest.

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