The identification of prevalent tuberculosis disease through infection screening among high-risk migrants in the Netherlands

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To the Editor:

In the consolidated guidelines for tuberculosis (TB) prevention and systematic screening for TB disease, the World Health Organization (WHO) recommends countries with a low TB incidence to consider systematic screening for TB disease as well as testing for TB infection (TBI) and preventive TB treatment (TPT) for migrants from high TB burden countries [1, 2]. Many low TB burden countries, including the Netherlands, perform TB screening among those migrants [3]. In the Netherlands, migrants are mandatorily screened for TB by chest radiography (CXR) within 3 months after entry; migrants from countries with an estimated WHO TB incidence of >200 per 100 000 are also offered voluntary biannual follow-up screening for 2 years. As part of the Dutch TB ENDPoint project, three implementation studies showed practical feasibility of TBI screening and treatment among newly arriving immigrants of all ages [4], asylum seekers aged ⩾12 years [5], and settled (Eritrean) migrants of all ages [6]. The TBI screening algorithm consisted of TB symptom screening and TBI testing (tuberculin skin test (TST) and/or interferon-γ release assay (IGRA)), with an additional CXR to exclude TB disease among persons with TB symptoms or positive TBI test [7]. To consider the replacement of CXR screening with this TBI screening algorithm, evidence is needed on the effectiveness of the TBI screening, including the assessment of the risk of missing persons with TB disease at the time of screening.

To identify individuals with prevalent TB disease (*i.e.* TB diagnosis within 6 months of TBI screening) and individuals with incident TB disease (*i.e.* TB diagnosis at least 6 months post TBI screening), we used cohort data from the three implementation studies (TB ENDPoint dataset) and matched it (by author H. Schimmel) to records (2016–2019) notified to the Netherlands Tuberculosis Register (Osiris-NTR) through identical Osiris-NTR numbers or patient registration numbers of public health services [8]. For remaining potential matching records, public health services were approached for verification of the person-identifiable data. Data on TB diagnosis of the verified matched records were added to the pseudonymised TB ENDPoint dataset for descriptive data analysis.

Research involving population health screening subjected to licensing as stated in the Population Screening Act (WBO), is not subjected to the Dutch Medical Research Involving Human Subjects Act. The public health services, who were responsible for the TBI screening part of involved studies, are licensed under the WBO act to perform screening for TB, including latent TBI (https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/laws/population-screening-act). Consequently, the medical ethical committee of University Medical Centre Amsterdam waived the need for ethical approval of the three implementation studies [4–6] which are part of the larger TB ENDPoint project. We obtained permission of the registration committee of the Netherlands TB register (NTR) to collect and analyse data from the NTR database. We followed the ethical principles of the Declaration of Helsinki, adopted by the World Medical Association.

Figure 1 presents the TBI screening and treatment cascade of care of 1541 screened migrants. Of 339 (22%) IGRA positive migrants, eight (0.5%) were diagnosed with prevalent TB disease: 3/566 (0.5%) immigrants; 4/718 (0.6%) asylum seekers; and 1/257 (0.4%) settled Eritreans. Of eight patients diagnosed with TB, seven had extrapulmonary TB (ETB) (four with peripheral lymph node TB; three with

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TB symptom and TB infection screening has potential to replace current chest radiography screening among high TB risk migrants in low burden countries. Screening programmes should be evaluated through epidemiological data and assessing progression rates. https://bit.ly/362r25u

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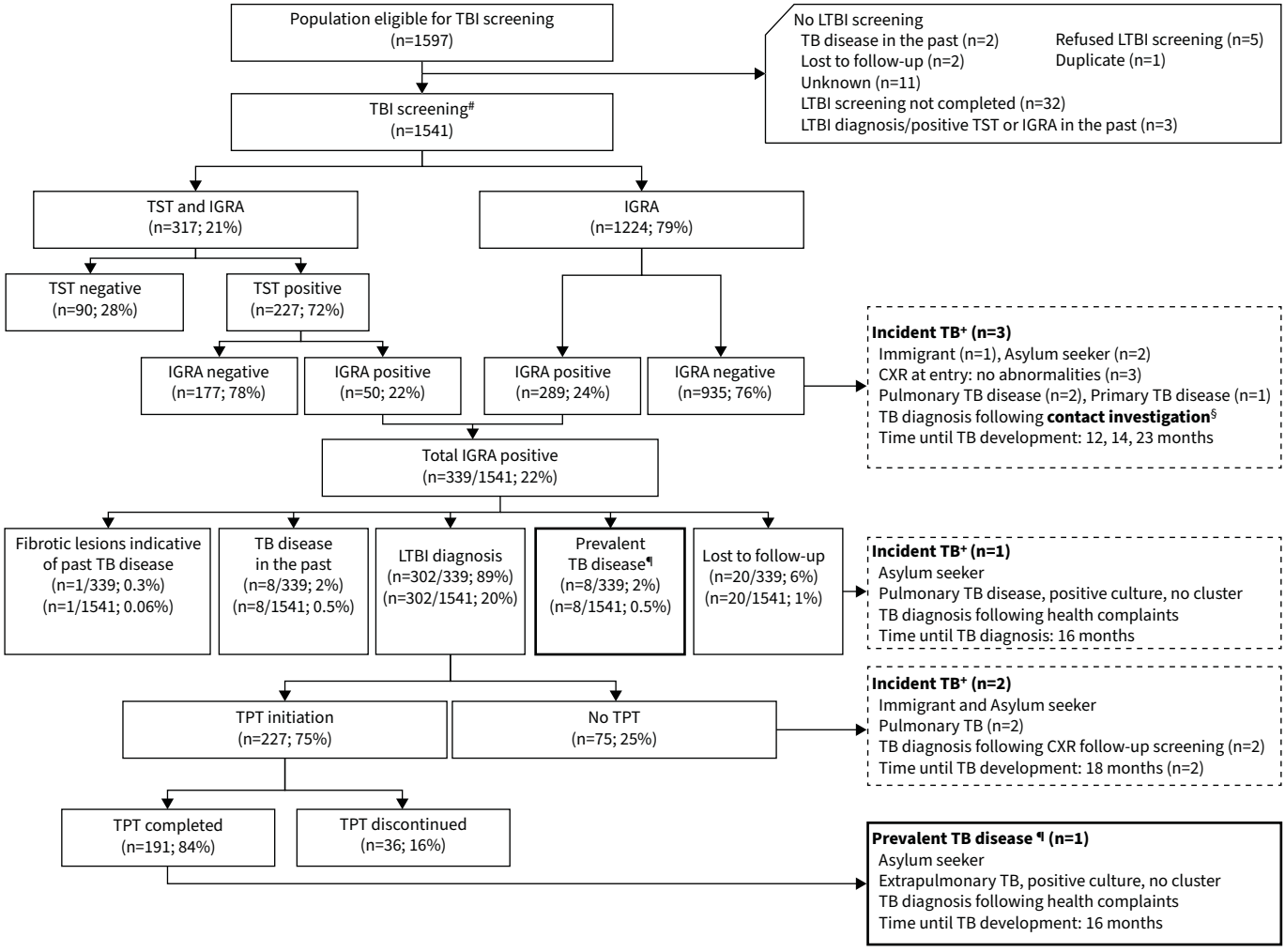

FIGURE 1 Tuberculosis (TB) infection screening and TB preventive treatment cascade of care. CXR: chest radiography; IGRA: interferon-γ release assay; LTBI: latent tuberculosis infection; TBI: tuberculosis infection; TPT: tuberculosis preventive treatment; TST: tuberculin skin test. #: TBI screening consists of both TB symptom screening and LTBI testing (TST and IGRA). Persons with a positive TB symptom questionnaire or LTBI test result receive CXR and consult with a TB physician to exclude TB disease. ¶: prevalent TB disease: TB disease diagnosed within 6 months of TBI screening. +: incident TB disease: TB disease diagnosed at least 6 months post TBI screening. §: one variable number tandem repeat cluster and two with direct epidemiological relation with source patient.

intrathoracic lymph node TB) and one had pulmonary TB (PTB). Cultures were performed in four TB patients, of whom one was positive (figure 1).

The median follow-up period was 36 months (interquartile range (IQR) 16 months; median for pilot 1: 43 months, IQR 2 months; pilot 2: 34 months, IQR 8 months; pilot 3: 23 months, IQR 1 month, respectively). Figure 1 shows that during the follow-up period, seven individuals were identified with TB disease (median follow-up time 17 months, IRQ 6 months). All three incident IGRA negative TB patients were diagnosed with TB disease in a TB contact investigation, and had a link to the source patient either through DNA clustering of *Mycobacterium tuberculosis* isolates or through a direct epidemiological relation. Furthermore, four IGRA positive TB patients were identified, of whom one was lost to follow-up immediately after the screening and before follow-up examination could take place; two declined TPT after LTBI diagnosis; one completed TPT after LTBI diagnosis. The latter patient was missed, as in retrospect the patient reported an enlarged peripheral lymph node was already present at the time of TBI screening (figure 1).

The TB prevalence in the TBI pilot screening was high when compared to CXR screening (TB prevalence: 0.5% *versus* 0.08% among immigrants in TBI *versus* CXR entry screening [9], and 0.6% *versus* 0.3%

among asylum seekers in TBI *versus* CXR follow-up screening [10], respectively). The screening algorithm missed one ETB patient because of inadequately ruling out TB disease at the time of LTBI diagnosis, and potentially missed one person with PTB disease who was lost to follow-up after TBI screening.

TBI screening tests, such as TST and IGRA, have suboptimal sensitivity, which is worsened among persons with underlying illnesses and immunocompromised conditions. False-negative TBI screening tests may pose a risk to miss persons with TBI or TB disease [11]. A strength of our study is that it included epidemiological and DNA fingerprinting data, which could determine if in-country transmission had occurred after the TBI screening. In our study, all incident TB could be attributed to reactivation of TBI identified through screening or to infection after recent exposure, and thus did not identify TB patients with a false-negative IGRA. We identified six studies evaluating the TBI screening cascade of care among newly arriving migrants that included an evaluation of persons who developed TB disease following the TBI screening. Of those, one study did not stratify for IGRA test result among the migrant TB patients [12], and two studies only included IGRA positive migrants in their follow-up [13, 14]. Three studies reported on TB patients with negative TBI test results. Zenner *et al*. [15] reported on four (0.3%) incident TB patients among 1341 IGRA-negative persons (median follow-up: 2.3 years, IQR 1.8–2.7 years). Furthermore, Harstad *et al*. [16] reported one (of 823 persons screened at arrival; 0.1%) IGRA- and HIV-negative, but TST- and CXR-positive, PTB patient. Finally, Pontarelli *et al*. [17] reported four (of 2567 persons screened; 0.2%) incident TB patients (follow-up between 0.6 and 1.3 years) with negative TB symptom screening and a negative (n=3) or unread (n=1) TST test. None of these studies reported on underlying immunocompromising conditions that could have contributed to a potentially false-negative IGRA test result among those who developed TB disease. Neither did these studies include epidemiological data that could exclude the development of TB due to recent transmission. Hence, it cannot be concluded these patients were missed during TBI screening.

Remarkably, the TB prevalence in our study was high compared to the prevalence in the routine CXR screening programme. Thus, we argue that the risk of missing TB patients through TBI screening (including CXR for persons with TB symptoms or a positive TBI test) is minimal. Furthermore, we found a high prevalence of ETB disease. It is unlikely that the patients with peripheral lymph node TB would have been detected by the CXR screening, as only intrathoracic forms of extrapulmonary TB disease can be identified through CXR screening. The early diagnosis of ETB is an additional benefit of TBI screening, as it contributes to improved health outcomes, and prevents adverse social and economic consequences for the individual [18]. All this adds evidence to the potential for this algorithm to replace CXR as the initial screening method. A limitation of our study is that 20 (6%) asylum seekers (aged 19–31 years) were lost to follow-up after the TBI screening, and an unknown number of migrants may have moved out of the country during the follow-up period. Therefore, we may have underestimated the number of patients who developed TB in this sub-population.

This research letter adds to the available evidence on TB progression rates among migrants screened upon arrival in low TB incidence countries. To inform TB programmes, we underline the importance for low TB incidence countries to set-up regular monitoring and evaluation programmes, including client-level comorbidity and epidemiological data, to study the effectiveness of TBI screening and TPT programmes and TB progression rates among newly arriving migrants.

Ineke Spruijt[1], Chantal Joren[1], Henrieke Schimmel[2], Frouke Procee[3], Yalda Alam[1], Susan van den Hof[2] and Connie Erkens[1]

[1]KNCV Tuberculosis Foundation, The Hague, The Netherlands. [2]National Institute for Public Health and the Environment (RIVM), Centre for Infectious Disease Control, Bilthoven, The Netherlands. [3]Dept of Tuberculosis Control, Public Health Service Amsterdam, Amsterdam, The Netherlands.

Corresponding author: Ineke Spruijt (ineke.spruijt@kncvtbc.org)

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However, no permission was sought to publish an anonymous dataset. Therefore, anonymous data supporting the study results can be made available only upon request, upon approval by the Dutch National Tuberculosis Registration Committee.

Author contributions: In collaboration with the other authors, C. Joren and I. Spruijt wrote the study's plan of analysis. C. Joren and H. Schimmel performed data management. C. Joren and I. Spruijt conducted statistical analysis. F. Procee, Y. Alam and I. Spruijt searched and extracted data from the literature. I. Spruijt and C. Erkens wrote the manuscript. All authors read, commented on and approved the final manuscript.

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