



Numbers needed to treat to prevent tuberculosis

To the Editor:

A new action framework advocacy document for tuberculosis elimination in low-incidence countries has recently been published in this journal [1]. We completely agree with the importance of addressing the goal of elimination of tuberculosis, which may be achievable in regions such as Western Europe and North America, but we are concerned that this goal may be overly ambitious at this point in time. As protective immunity can, unfortunately, not be achieved by a vaccine or other immune-based intervention, tuberculosis control still relies on early identification and treatment of active tuberculosis, and preventive chemotherapy of individuals with latent *Mycobacterium tuberculosis* infection (LTBI). However, both the tuberculin skin test (TST) and interferon- γ release assays (IGRAs) (the ELISA-based QuantiFERON-TB Gold In-Tube assay (QIAGEN, Venlo, the Netherlands) or the ELISPOT-based T-SPOT.TB assay (Oxford Immunotec, Oxford, UK)) that are recommended to diagnose LTBI have a low positive predictive value for the future development of tuberculosis, and are therefore insufficient as biomarkers to identify individuals developing active disease. With tuberculosis being a rare event, the vast majority of individuals with positive test results will never develop disease [2]. Moreover, in immunocompromised individuals, especially in patients with HIV infection, the negative predictive value of an immunodiagnostic test is insufficient to rule out the future development of tuberculosis, as was recently demonstrated in a large study in Europe [3]. Thus, systematic testing and treatment of LTBI of risk groups [1] is considered difficult to implement.

In order to optimise allocation of the available resources for tuberculosis elimination, the first step would be an improvement in the knowledge of risk groups for tuberculosis in low-incidence countries. More recently, it has become evident that the risk of the development of tuberculosis among patient groups classically considered at risk is highly variable, and is not necessarily associated with the results of immunodiagnostic testing by the TST or IGRAs [2–5]. More detailed knowledge of groups at actual risk of tuberculosis and on immunodiagnostic test performance in these risk groups may provide better guidance for physicians on priorities for targeting tuberculosis testing and LTBI treatment in low-incidence countries.

The decision to administer prophylactic treatment to a certain risk group should depend on the estimated number needed to treat to prevent one case of tuberculosis. Although not selected by a systematic approach, we made use of the fact that several studies with large sample sizes from low-incidence countries of tuberculosis were recently published from three major groups classically considered at risk for progression. In these studies, tuberculosis contacts [2, 4, 5], immunocompromised hosts [3] and healthcare workers [6–8] were evaluated for LTBI and subsequent progression. We have calculated the number needed to treat to prevent one case of tuberculosis (table 1), and found that the number needed to treat was very similar across three studies evaluating 1579, 5020 and 4774 tuberculosis contacts, respectively, with a positive TST or IGRA, ranging from 30 to 37 [2, 4, 5] (table 1). In immunocompromised individuals with a positive test ($n=1537$) [3], the number needed to treat to prevent a case was higher and ranged from approximately 50 to 80 (table 1). Notably, as incident cases of tuberculosis were mainly HIV positive, the number of HIV-infected persons with a positive test needed to treat was lower (range 14.0–25.5) and tuberculosis cases were only found in patients with ongoing viral replication [3]. It should be emphasised that incident tuberculosis cases also occurred in individuals with negative test results [2, 3, 5], especially among patients with HIV infection. In patients with chronic renal failure ($n=270$) or rheumatoid arthritis ($n=199$), stem cell ($n=103$) or solid organ transplant recipients ($n=197$) [3], and healthcare workers ($n>15\,000$) [6–8], the number of individuals with LTBI needed to treat to prevent one case could not be calculated because no tuberculosis cases occurred during 2 years of follow up in these cohorts.

In the absence of better biomarkers [9], comparing the number needed to treat to prevent one case is helpful to define groups with highest risk of developing tuberculosis and to prioritise existing prevention strategies. These strategies should particularly focus on HIV-infected individuals, preferentially with ongoing viral replication, and on close contacts of infectious cases of tuberculosis, although higher numbers are needed to screen and treat among contacts. In contrast, given the low number or even absence of incident cases in other groups classically considered at risk, screening approaches more closely targeted to individuals with additional risk factors would seem more effective to identify candidates who will most likely benefit from preventive chemotherapy [10]. Finally, some groups formerly considered at

TABLE 1 Numbers of individuals with positive immunodiagnostic results needed to treat (NNT) to prevent a case of tuberculosis

Population	First author [ref.]	Subpopulations	NNT	Test
Contacts	ZELLWEGER [2]		37.0	ELISA
			36.5	ELISPOT
	GEIS [4]		34.5	ELISA
	SLOOT [5]	All	88.9	ELISA
		Close contacts (first circle)	30.4	and/or TST
Immunocompromised patients	SESTER [3]	HIV, CRF, SOT, SCT, RA	49.7	TST
			79.5	ELISA
			64.3	ELISPOT
		HIV	14.0	TST
			25.5	ELISA
		21.3	ELISPOT	

The low number of TB cases present in each of the studies precludes the calculation of meaningful confidence intervals around the NNT. TST: tuberculin skin test; CRF: chronic renal failure; SOT: solid organ transplantation; SCT: stem cell transplantation; RA: rheumatoid arthritis.

risk of tuberculosis (e.g. healthcare workers) are no longer risk groups in low-incidence countries [6–8], unless having had substantial contact to a patient with tuberculosis. It should be stated that given the inadequate test characteristics of the current diagnostics, not all tuberculosis will be prevented by these strategies, since active disease will continue to occur in those tested negative.



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Comparing the NNT to prevent one case can help define groups at highest TB risk and prioritise prevention strategies <http://ow.ly/TITzR>

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From the authors:

We thank Martina Sester and colleagues for their careful reading of our paper [1] and for their support to the prospect of tuberculosis (TB) elimination in low-incidence countries in a foreseeable future. While we respect the views of the authors that the targets may appear too ambitious, we believe that, if the scientific community stay focussed on innovative approaches that can translate into scalable and effective interventions, we could reap the benefits of such interventions within the space of the next two decades [2]. Figure 1 shows the trend in TB incidence into the future, should current efforts to control TB – including the treatment of latent *Mycobacterium tuberculosis* infection (LTBI) – be intensified and boosted by new techniques and approaches.

When discussing the importance of preventive chemotherapy for LTBI in the context of TB elimination, the authors point out two critical issues: the limitations of diagnostic tests for LTBI, and the importance of appropriately defining target populations for systematic LTBI testing. To provide guidance in this area, the World Health Organization (WHO) has recently issued guidelines on LTBI management [4].

Both tuberculin skin testing (TST) and interferon- γ release assays (IGRAs) have a poor positive predictive value to determine which individuals with presumed latent infection are more likely to develop active TB, implying that a high proportion of treated individuals would receive medication unnecessarily. Nonetheless, these tests still have a role in helping clinicians improve the health outcomes of their patients and to progress towards TB elimination. Conversely, the negative predictive value of TST and IGRAs is high enough to exclude most individuals who would not benefit from LTBI treatment [5]. Contrary to what Martina Sester and colleagues maintain, the number of active TB cases that will continue to occur among those testing negative is thus unlikely to have a significant public health impact.

We agree with Martina Sester and colleagues that to optimise the allocation of available resources, appropriate selection of risk groups for systematic LTBI testing and treatment is crucial. WHO recommends that individuals with a positive TST or IGRA should be treated for LTBI if they have the following risks: HIV infection, are contacts of pulmonary TB cases, initiate anti-tumour necrosis factor treatment, receive dialysis, prepare for transplantation, or have silicosis. The WHO guidelines group – composed of leading world experts using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach [6] – made a strong recommendation for LTBI treatment in these groups, on the premise of both direct and surrogate evidence for an increased risk of progression from infection to disease when compared with the general population, and much less upon a positive LTBI test. Martina Sester and colleagues argue that the number of individuals who need to take prophylactic medication in order to prevent one active case (number needed to treat (NNT)) would have been a better outcome measure to select at-risk populations. While this appears to be a logical approach, it also has



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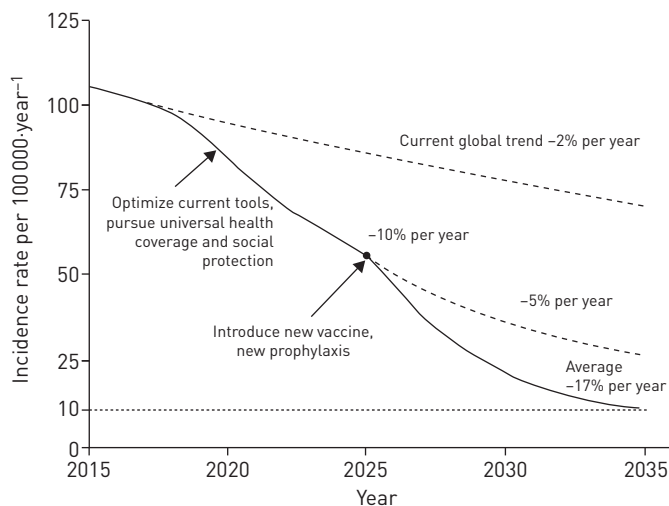


FIGURE 1 Projected trend in the decline of global tuberculosis incidence, from 110 cases per 100 000 in 2015 to 10 cases per 100 000 or less by 2035. Reproduced from [3] with permission from the publisher.