How can we achieve better prevention of progression to tuberculosis among contacts?

To the Editor:

Strategies for control and elimination of tuberculosis (TB) in low-incidence settings are directed toward treatment of recently acquired latent tuberculosis infection (LTBI) in TB contacts [1]. To identify this target population for preventive treatment the development of more specific, *in vitro* assays for LTBI, the interferon (INF)-γ release assays (IGRAs), has offered an alternative method for LTBI diagnosis. Although IGRAs are increasingly recommended in national guidelines, evidence that positive IGRA results are prognostic for developing TB is still limited [2, 3], especially outside of prospective studies with well-defined inclusion criteria. Therefore, we investigated progression towards active TB among IGRA positive contacts of active TB cases under routine field conditions and calculated the positive predictive value (PPV) for progression and the number needed to treat (NNT) with preventive treatment to prevent one incident TB case. Additionally, we introduced different cut-off values for IGRA positivity and compared the computed progression rates. Among all contacts with a positive tuberculosis-specific IGRA we describe the uptake of preventive treatment.

Our study covered a population of 3.2 million with a reported TB incidence of 7.5 cases per 100 000 population in 2008. From 2008 to 2010, we prospectively recruited all IGRA-positive contacts of newly detected sputum smear and/or culture positive notified TB cases at 12 local public health authorities (LPHAs) in Hesse, Germany. Only contacts with a history of TB disease were excluded.

The German recommendations for contact investigations, published in 2007 [4], served as the basis for the LPHAs investigations: a dual-step approach in which IGRA is only performed if the tuberculin skin test (TST) is positive. However, LPHAs deviated from this recommendation and performed TST in less than 27% of all IGRA tested contacts. All our study participants, namely all IGRA-positive contacts, were eligible for preventive treatment, usually with isoniazid for 6–9 months, and were closely monitored for active TB by the responsible LPHA for ∼1 year. During follow-up visits participants were asked about symptoms suggestive of active TB. If suspicion was aroused further investigations were carried out to confirm active TB, which we defined as clinically apparent disease requiring antituberculous treatment. All participants underwent chest radiography screening at completion of follow-up.

We used the commercially available IGRA: QuantiFERON-TB Gold In-Tube (Cellestis Limited, Carnegie, Australia) according to the manufacturer's protocol. In addition to the manufacturer's cut-off at 0.35 IU·mL^{-1} we compared different cut-off values (1.0 IU·mL^{-1} to >10.0 IU·mL^{-1}) in our analysis possibly reflecting a higher mycobacterial load and higher risk for progression [5]. This might allow narrowing down the number of contacts eligible for preventive treatment, possibly resulting in more effective and accepted interventions.

We calculated TB incidence rate as the number of new cases per 100 person-years of observation and PPV as the number of incident TB cases per total number of participants, stratified by preventive treatment completion. To estimate the impact of preventive treatment we computed NNT as (1/PPV)/0.65 assuming an efficacy of 65% [6]. We used Stata 11 (Stata Corporation, College Station, TX, USA) for all statistical analyses. Data were pseudonymised for the investigators according to the requirements of the Hessian data protection office, Wiesbaden, Germany. Ethical approval in accordance with the Helsinki Declaration was not requested as only data collected during routine practices were obtained.

Of 1579 contacts 306 were IGRA-positive (cut-off ⩾0.35 IU·mL^{-1}) and enrolled in our study, 52 were lost during follow-up and excluded from further analysis. Among participants aged ⩾15 years, 20% (47 out of 237) started preventive treatment, of whom 77% (36 out of 47) received a full-course. Preventive treatment was initiated in 11 (65%) out of 17 children aged <15 years. All 11 completed treatment.

During the follow-up period of the 207 IGRA-positive contacts who did not receive or did not complete preventive treatment six developed clinically apparent TB (characteristics shown in table 1), yielding a total TB incidence rate of 2.0 cases per 100 person-years (95% CI 0.7–4.4 cases per 100 person-years), a PPV of

TABLE 1 Characteristics of tuberculosis (TB) case contacts developing active TB in Hesse, Germany, 2008–2010

Subject	Age years	Sex	Origin	BCG vaccine	Type of TB	Time from exposure to illness months	Exposure time hours	Exposure setting	TST result mm	IGRA IU·mL^{-1}
1	26	Female	Foreign born	No	EP	9	>40	Visitor	Positive	2.1
2	42	Female	German	No	XRP	2	>40	Household	15	⩾10
3	20	Female	German	Yes	SNCP	6	>40	Household	40	⩾10
4	15	Female	German	Yes	SNCP	6	>40	Household	16	⩾10
5	20	Male	German	Not known	XRP	4	>40	Household	Not done	⩾10
6	20	Male	German	No	SNCP	6	>40	School	12	⩾10

BCG: Bacille Calmette–Guérin; TST: tuberculin skin test; IGRA: interferon-γ release assay; EP: extrapulmonary; XRP: X-ray positive; SNCP: sputum negative/culture positive.

TABLE 2 Changing values for positive predictive value (PPV) and number needed to treat (NNT) using different cut-off values for interferon-γ release assay (IGRA) positivity

IGRA cut-off IU·mL^{-1}	Total IGRA-positive contacts	Total contacts without PT	Contacts without PT only		Missed TB cases
			PPV %	NNT	
0.35	254	206	2.9	52.8	0
1.0	206	166	3.6	42.6	0
2.0	159	123	4.9	31.5	0
3.0	135	101	5.0	31.1	1
4.0	121	88	5.7	27.1	1
5.0	111	79	6.3	24.3	1
6.0	104	73	6.8	22.5	1
7.0	96	66	7.6	20.3	1
8.0	89	60	8.3	18.5	1
9.0	85	58	8.6	17.8	1
>10.0	76	54	9.3	16.6	1

Data are presented as n, unless otherwise stated. PT: preventive treatment.

2.9% and NNT of 52.8 contacts. None of the 47 contacts who completed preventive treatment developed TB, corresponding to a total TB incidence rate of 0.0 cases per 100 person-years (one-sided 97.5% CI 0.0–7.1 cases per 100 person-years). By using different cut-off values (table 2) the PPV progressively increased up to 9.3%, decreasing the NNT by two-thirds (NNT=16.6 contacts for a cut-off value of 10.0 IU·mL^{-1}). However, one contact developing active TB was missed in cut-off values $\geqslant$3.0 IU·mL^{-1}.

Our study provides several important findings. First, uptake of preventive treatment was low in our study population. Secondly, a small fraction of the IGRA-positive contacts identified by routine contact investigation go on to progress towards active TB. Thirdly, raising the IGRA cut-off value to 2.0 IU·mL^{-1} would have reduced the number of contact persons receiving isoniazid without missing new incident cases.

Compared with similar studies described in the latest meta-analyses [2, 3] the overall uptake of preventive treatment was low in our study population, compromising the effectiveness of TB control efforts. Decreasing the failure of contacts with LTBI to accept or complete preventive treatment is the limiting factor for success. Although we did not collect data on reasons for declining preventive treatment, we assume that the major factor for this is the attending physician, who did not recommend treatment since only a minority of eligible contacts will develop TB [7]. In a recent study from the USA, only 17% of eligible subjects declined preventive treatment when it was recommended by the attending physician [8]. This assumption is strengthened by our observation of a high proportion of preventive treatment initiation in IGRA-positive children, suggesting that for this age group preventive treatment is perceived as having a favourable risk-benefit ratio.

When using the manufacturer's IGRA cut-off value we observed similar progression rates to those previously reported [2, 3]. Particularly, our incidence rate is commensurate with an estimated incidence of 2.8 cases per 100 person-years in a large cohort of IGRA-positive contacts in Japan, a low prevalence country like Germany, in which no strict inclusion criteria to maximise the probability of contacts being infected was applied [9]. Given the low yield of progression to TB adjusting the cut-off value appears an appropriate procedure; the manufacturer's recommended cut-off value was determined with data from 118 patients with culture-confirmed TB [10] and, therefore, might not be suitable for diagnosing recent latent infections having different immunological features. DIEL *et al.* [11] observed a correlation between disease progression and IFN-γ levels. However, three out of 19 contacts who developed active TB had IFN-γ levels <1.0 IU·mL^{-1}. HALDAR *et al.* [12] did not find a difference when comparing the magnitude of IFN-γ levels and disease progression.

To reduce the burden of TB in low prevalence countries the current strategy of monitoring TB contacts remains an important backbone. Nevertheless, there is a need to improve the current risk–benefit ratio. Therefore, several strategies should be considered. Use of new cut-off values might convince medical doctors of the usefulness of preventive treatment when progression rates increase and NNT declines. Not only laboratory results, especially quantitative values to judge the magnitude of IGRA response, but also the contact's medical and exposure history (*e.g.* immunosuppression, age, nature and degree of contact, chances of remote exposure to explain a positive IGRA) can influence the risk–benefit ratio. Firstly, this can

overcome the inability of IGRAs to distinguish between recent and remote acquisition of LTBI, secondly stricter inclusion criteria for LTBI testing (*e.g.* duration of exposure or smear positivity) may increase the measured risk of progression among IGRA-positive contacts. In the future, contacts would benefit from preventive treatment regimens of shorter duration, with fewer side-effects that are currently being evaluated.

Our results are limited by the small number of IGRA-positive contacts at risk, the low number of individuals who developed active TB and the short follow-up time.

In conclusion, LTBI screening is a useful public health measure to identify a high-risk population for interventions like preventive treatment, health education or intensified surveillance. Nevertheless, the risk–benefit ratio has to be improved in order to convince attending physicians, as well as affected contacts, about the usefulness of preventive treatment. The most promising approach in our view would be to re-evaluate the recommended cut-off value in further studies and meta-analyses in order to improve IGRA testing for latent infection until more predictive biomarkers become available [2, 3].

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Re-evaluation of recommended cut-off values should be undertaken to improve IGRA testing for latent TB http://ow.ly/o5prC

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