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

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To the Editors:

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 (PT) the development of more specific, in-vitro assays for LTBI – interferon-gamma release assays (IGRA) – has offered an alternative method for LTBI diagnosis. Though, IGRA 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 PT 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 described the uptake of PT.

Our study covered a population of 3.2 million with a reported TB-incidence of 7.5 cases/100,000 population in 2008. From 2008 to 2010, we prospectively recruited all IGRA-positive tested contacts of newly detected sputum smear and/or culture positive notified TB cases at twelve local public health authorities (LPHA) in Hesse, Germany. Only contacts with a history of TB disease were excluded. Our study covered a population of 3.2 million with a reported TB-incidence of 7.5 cases/100,000 population in 2008. From 2008 to 2010, we prospectively recruited all IGRA-positive tested contacts of newly detected sputum smear and/or culture positive notified TB cases at twelve local public health authorities (LPHA) 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 LPHA: a dual-step approach – IGRA only performed if 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 PT – usually isoniazid for 6 to 9 months – and closely

monitored for active TB by responsible LPHAs for about one year. During follow-up visits participants were asked for symptoms suggestive of active TB. If suspicion aroused further investigations were carried out to confirm active TB which we defined as clinically apparent disease requiring anti-tuberculous treatment. All participants underwent chest x-ray 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. Besides the manufacturer's cut-off at 0.35IU/ml we compared in our analysis different cut-off values (1.0IU/ml to >10.0IU/ml) possibly reflecting a higher mycobacterial load and higher risk for progression [5]. This might allow narrowing down the number of contacts eligible for PT, possibly resulting in more effective and accepted interventions.

We calculated TB incidence rate (TBIR) as number of new cases per 100 person-years (PY) of observation and PPV as number of incident TB cases per total number of participants stratified by PT 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, Texas) for all statistical analyses. Data were pseudonymized 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 1,579 contacts 306 were IGRA-positive (cut-off ≥0.35IU/ml) and enrolled in our study, 52 were lost during follow-up and excluded from further analysis. Among participants aged ≥15 years, 20% (47/237) started PT, of whom 77% (36/47) received a full-course. PT was initiated in 11 of 17 (65%) children younger than 15 years. All (11/11) completed treatment.

During the follow-up period of 207 IGRA-positive contacts without or not completed PT six developed clinically apparent TB (characteristics shown in table 1), yielding a total TBIR

of 2.0 cases/100PY (95% confidence interval [CI]: 0.7-4.4/100PY), PPV of 2.9% and NNT of 52.8 contacts. None of the 47 contacts who completed PT developed TB, corresponding to a total TBIR of 0.0 cases/100PY (one-sided 97.5% CI: 0.0-7.1/100PY). By using different cut-off values (table 2) the PPV progressively increased up to 9.3%, decreasing the NNT to a third (NNT=16.6 for cut-off value of 10.0IU/ml). However, one contact developing active TB was missed in cut-off values ≥3.0IU/ml.

Our study provides several important findings. Firstly, uptake of PT was low in our study population. Secondly, a small fraction of IGRA-positives identified by routine contact investigation progresses towards active TB. Thirdly, raising the cut-off value of 2.0IU/ml would have reduced the number of contact persons receiving INH without missing new incident cases.

Compared to similar studies described in the latest meta-analyses [2, 3] the overall uptake of PT was low in our study population compromising the effectiveness of TB control efforts. Decreasing the failure of contacts with LTBI to accept or complete PT is the bottleneck for success. Even though we did not collect data on reasons for declining PT 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 United States, only 17% of eligible subjects declined PT when it was recommended by the attending physician [8]. This assumption is strengthened by our observation of a high proportion of PT initiation in IGRA-positive children, suggesting that for this age group PT is perceived as having a favourable risk-benefit ratio.

When using the manufacturer's cut-off value we observed similar progression rates as 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, where no strict inclusion criteria to maximize

probability of contacts being infected were 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 infection having different immunological features. Diel et al. [11] observed a correlation between disease progression and interferon-gamma(IFNg)-levels. However, three out of 19 contacts who developed active TB had IFNg-levels of less than 1.0IU/ml. Haldar et al. [12] did not find a difference when comparing the magnitude of IFNg-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. Usage of new cut-off values might convince medical doctors of the usefulness of PT 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 of participants, 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, smear positivity) may increase the measured risk of progression among IGRA-positive contacts. In future, contacts would benefit from PT regimens of shorter duration with fewer side effects that are currently 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 public health interventions like PT, 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 PT. 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].

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

All authors contributed to the study design and interpretation of results. SG performed the analysis and wrote the manuscript draft. SG, GBW, UG and GB contributed to data gathering. All authors revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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TABLES

Table 1 – Characteristics of tuberculosis (TB) case contacts developing active TB in Hesse, 2008-10*.

No.	age	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	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

* Abbreviations used: EP, extrapulmonary; XRP, X-ray positive; SNCP, sputum negative/culture positive; BCG, Bacille Calmette–Guérin vaccine; TST, tuberculin skin test; IGRA, interferon-gamma release assay

TST: tuberculin skin test; IGRA: Interferon gamma release assay

Table 2 – Changing values for "positive predictive value" and "number needed to treat" by using different cut-off values for IGRA positivity

IGRA cut-off (in IU/ml)	Total number of IGRA-positive contacts	Total number of contacts without PT	Contacts without PT only		missed TB cases
			Positive predictive value (PPV)	Number needed to treat (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

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