Tuberculosis in adult contacts of an index case: Can we predict in India?

Saunders MJ, Wingfield T, Tovar MA, Baldwin MR, Datta S, Zevallos K, Montoya R, Valencia TR, Friedland JS, Moulton LH, Gilman RH, Evans CA. (Section of Infectious Diseases and Immunity, Imperial College London, and Wellcome Trust Imperial College Centre for Global Health Research, London, UK; Innovation for Health and Development [IFHAD], Laboratory of Research and Development, Universidad Peruana Cayetano Heredia, Lima, Peru; Innovación Por la Salud Y Desarrollo [IPSYD], Asociación Benéfica PRISMA, Lima, Peru; Institute for Infection and Global Health, University of Liverpool, Liverpool, UK; Tropical and Infectious Diseases Unit, Royal Liverpool and Broadgreen University Hospitals Trust, Liverpool, UK; Columbia University, College of Physicians and Surgeons, New York, NY, USA; and Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA.) A score to predict and stratify risk of tuberculosis in adult contacts of tuberculosis index cases: A prospective derivation and external validation cohort study. *Lancet Infect Dis* 2017;**17:**1190–9. doi: 10.1016/S1473-3099(17)30447-4.

SUMMARY

Household members and close associates of patients with tuberculosis (TB) comprise a high-risk group for TB and as such their examination is crucial in prevention and control of TB.[1] Saunders *et al*. have developed a score to predict the risk of TB among adult contacts of patients with TB using various established factors that play a role in the development of disease among contacts. The study population consisted of two cohorts from Peru. The first cohort was a derivation cohort of contacts of index cases of Ventanilla district. They were recruited between 2002 and 2006 and followed up till 2016. A baseline assessment for risk factors was completed for the contacts. During this period, the symptomatic contacts were offered testing for TB by household visits for the first 6 months followed by prevalence surveys every 4 years. Any self-reported diagnosis of TB outside the study area was also noted. The investigators used Cox regression modelling to derive a risk score which used nine clinical and demographic factors that could be readily collected and predicted the contact's 10 years' TB risk independently of the results of the tuberculin skin test (TST). The risk factors used for the model were sustained exposure to index case, exposure to male index case, lower socioeconomic position, exposure to indoor air pollution, history of TB in any of the household member, fewer windows per room and the contact's characteristics such as body mass index (BMI), history of previous TB and age group of 15–19 or >59 years. They developed a simple integer-point risk score, which had similar accuracy to those derived from exact regression coefficients. BMI was taken as such in the score and points were assigned for other risk factors.

The scores were arbitrarily classified as low risk (19 points and above), medium risk (12–18 points) and high risk (11 points or fewer). The scores were internally validated by repeatedly fitting the model with 200 bootstrap samples, and optimism-adjusted C statistic was calculated. The scores were externally validated in a cohort of contacts recruited in 2014–15. This population was different from the derivation cohort in living condition, socioeconomic status and demographics. Of the recruited 2017 contacts in the derivation cohort, 178 developed TB with an incidence of 0.93/100 person-years. The incidence among contacts was highest in the first 4 years post-exposure and was twice that of the local population. About 30%, 44% and 27% of them were assigned as low risk, medium risk and high risk, respectively. Among the 178 contacts, 10% in the low-risk group, 30% in the medium-risk group and 60% in the high-risk group developed TB. The 10-year observed risk in the low risk was 2.8% (95% CI 1.7%–4.4%), medium-risk was 6.2% (4.8%–8.1%) and high-risk groups was 20.6% (17.3%–24.4%). The C statistic was 0.72. The optimism adjusted C statistic after bootstrap resampling internal validation was 0.71. The numbers needed to treat to prevent one case of TB over 10 years in the low-risk group was 48, medium-risk was 22 and high-risk group was 6 assuming an effectiveness of 75% by preventive therapy. There was no significant difference in the proportions of contacts that had positive TST between the risk groups (p=0.13). Modelling done including TST results (C statistic 73) added little predictive value to the original risk model (C statistic 72). The overall incidence in the validation cohort was 1.7/100 person-years. About 30% of contacts of the validation cohort were classified as low risk, 48% as medium risk, and 22% as high risk. The observed risk of TB for these risk groups at 2.5 years was 1.4% (95% CI 0.70%–2.8%), 3.9% (2.5%–5.9%) and 8.6% (5.9%–12.6%), respectively.

COMMENT

Tuberculosis is the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS.[2] The WHO's 'end TB' strategy aims to end the global TB epidemic, with targets to reduce TB deaths by 95% and to reduce new cases by 90% between 2015 and 2035.[3] To achieve the targets of the end TB strategy, earlier identification of TB needs to be given great importance. Contacts of patients with TB are highly susceptible to acquire TB because of their proximity with the index patient.[4] In high-income countries, contact investigation of patients with TB is a priority for control of TB. It is also being considered in resource-limited settings.[5] A systematic review has shown that 3.5%–5.5% among contacts of an index patient of TB were found to have previously undiagnosed and active TB.[6,7] In spite of its importance, adult contacts are rarely prioritized for complete screening or provided preventive therapy in National TB programmes due to lack of resources.[5] Scores that are easily implementable at the field level and could predict the risk for infection among the contacts would help in prioritizing individuals to provide preventive therapy.

This study has devised an easily calculable risk score which can be used at the field level to predict the 10 years risk of developing TB among contacts of patients with TB without any invasive or laboratory test. The study was conducted in a setting that had a medium incidence of TB. In such settings, screening of contacts of patients with TB should be done to detect cases early and to provide preventive therapy for contacts who are highly likely to develop TB later, to achieve the targets of the end TB strategy. The study has formulated a much needed 'risk score' to prioritize the contacts for preventive therapy. Such prioritization could be cost-effective.

The study design and methodology were appropriate. The study has many merits and a few concerns. The first concern is that the cut-off for the risk score was defined arbitrarily. If the score has to be replicated in other settings, it needs to be validated. This applies to the risk factors that have been used in the score. The risk factors represent a complex interaction between host characteristics, community characteristics and the strain of the infecting organism, which again may vary from place-to-place and needs setting-specific validation. The other concern is that the 10 years' follow-up was done only in the derivation cohort and not in the validation cohort, hence the conclusion regarding the ability of the score to predict a contact's 10 years risk of developing TB

could have been done *post hoc*. Another concern is that 'Sustained exposure to the index case' was defined differently in the validation cohort from that of the derivation cohort, which might have affected the robustness of the external validation. The 12 variables used to compute 'Lower community household socioeconomic position' have not been mentioned in the paper. This information is important as it is one of the key risk factors on which the score is based and the 'most likely' risk factor to show large variations across different settings. Such information would be useful if the score needs to be validated in other settings. Many other well-established risk factors such as diabetes and drug resistance were not included in the score; such factors need to be included in the population, which have high prevalence of such risk factors. Although household contacts may be at high risk of acquiring TB, the contribution of the total new TB caseload from family contacts is minimal. Transmission of TB occurs mainly in the community.[8,9] Variables addressing community transmission could have been used in the score. The fact that capturing community transmission is difficult needs to be accepted. Apart from these few concerns, the study has many merits.

Efforts were made to calculate the TB infection rate for each year of follow-up. They have used whole numbers for risk score instead of exact regression coefficients. This provides a big advantage that it can be easily used at the field level with minimal training. Statistical calculations were made appropriately to match the regression coefficients with the whole number used for risk scoring. Analysis was done to show the risk of developing TB at varying time points, namely 1, 2.5, 5 and 10 years after exposure between the risk groups. Furthermore, sensitivity analysis was done excluding the contacts that were started on treatment within 6 months of exposure. This is crucial as the ultimate aim of such risk scores is to offer preventive therapy for contacts and those who develop disease within 6 months may not benefit much from preventive therapies. They have calculated the number needed to treat for preventive therapy across each risk group which can give an insight of how cost-effective this score can be, if it is used in resource-constrained settings. The study has used extensive and sound statistical inputs especially for the validation making the results robust. An important strength of the study is that it has used simple factors for scoring which could be easily applied at the field level even in resource-limited settings. All the variables used for the risk score are proven factors for developing TB. The score in this study did not consider TST results. A study done by Mandalakas *et al*, considered TST and developed a similar algorithm to predict risk among child contacts.[10] Saunders *et al*. have explored the possibility of adding TST results to the model, but it showed no significant changes in the predictive power. Using TST for prediction of risk may have limited value in adult contacts in high-burden countries where most of them would be exposed to the infection. Moreover, their justification for not adding TST to the model is valid because TST has low specificity, needs repeated clinical visits, has many operational issues such as availability of TST, and training staff to do and interpret the test.[11] In such situations, a risk score independent of TST may be useful to predict the risk of TB. They have used simple operational definitions for factors such as indoor air pollution rather than using expensive instruments to quantify exposure. These can be applied easily in resource-limited settings too. The study results have shown that grade of smear positivity and self-reported frequency of a cough were unreliable markers of infectiousness and have extended the scope of future research in the use of objective acoustic parameters to infectiousness. Saunders *et al*. have made an important advance in risk stratification among adult contacts. This would help in targeted screening, surveillance and offering preventive therapies among adult contacts of TB cases.

Applicability of the score in India

India has a large population with latent TB and it is crucial to identify contacts who might develop the disease. It is impractical to treat all those with latent infection. However, it would be realistic to treat those who are at a higher risk for reactivation.[12] Currently, the Revised National Tuberculosis Control Programme (RNTCP) recommends screening of all household contacts of patients with TB and in the absence of active disease recommends preventive therapy only for child contacts who are ≤6 years of age.[13] This risk score offers a practical and easy tool that can be used in Indian field settings to identify adult contacts at the highest risk of developing TB. Targeting such individuals for preventive therapy might prove to be a good strategy in complementing the other control strategies to combat TB in India.

Conflicts of interest. None declared

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