development of tuberculosis: body-mass index, previous tuberculosis, age, sustained exposure to the index patient, the index patient being male, lower community household socioeconomic position, indoor air pollution, previous tuberculosis among household members, and living in a household with a low number of windows per room. The prediction score incorporates all important host and environmental factors. However, pathogen-related factors (eg, resuscitation promoting factors, coded by *rpf* genes) also have an important role in reactivation of mycobacteria from dormancy.[3] In this study, both the derivation cohort and external validation cohort lived in nearby regions, and possibly shared the same strain of *Mycobacterium tuberculosis*. Non-inclusion of pathogen-related factors might lead to varying predictability in different regions with use of this prediction score.

Nevertheless, this kind of prediction tool is needed to identify high-risk contacts for preventive therapy. Indeed, easy applicability and not having to rely on a tuberculin skin test will increase its utility in resource-limited countries with a high tuberculosis burden.

We declare no competing interests.

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Authors' reply

We thank Sandra Arend and Jonathan Uzorka for their interest in our study. They argue that because our risk score predicts tuberculosis independently of the contact tuberculin skin test (TST) results and index case smear grade, it is likely that subsequent re-exposure to tuberculosis was an important risk factor. Therefore, they debate the justification for our calculation of numbers needed to treat (NNT) with preventive therapy at the time of known exposure to prevent each tuberculosis case. Although we agree that re-exposure might have been an important, unmeasured risk factor in our population, the highest rate of tuberculosis among contacts was in the first year after known exposure, and nearly all the cases occurred during the first 3 years. Furthermore, prolonged exposure to the index case was an important risk factor. Taken together, these findings suggest that the known exposure was by far the most important factor in determining tuberculosis risk.[1] However, we appreciate the potential importance of subsequent re-exposure and therefore calculated the NNT to prevent each tuberculosis case within 5 as well as 10 years. Importantly, we calculated NNT principally to illustrate practical differences between risk groups. Because the cutoffs used to define risk groups were arbitrary and our risk score is a continuous variable, these NNTs inherently change depending on how a high-risk contact is defined.

Because addition of TST results to our predictive model did not substantially improve its power, Arend and Uzorka suggest that our results disagree with several studies that report an association between a positive TST and development of tuberculosis among contacts. As we described in our study report,[1] having a positive TST compared with a negative TST was associated with double the tuberculosis risk in our cohort (adjusted hazard ratio 1·8, p=0·02). Our finding that adding TST results to a composite risk score including nine other factors did not improve prediction might at first appear surprising, but is consistent with the known limitations of TST and the high prevalence of positivity in our cohort. Indeed, our results are very similar to those described in a systematic review.[2]

Our study included only index cases with laboratory-confirmed tuberculosis, the great majority of whom had smear-positive tuberculosis, so we could not meaningfully compare index cases who had smear-positive tuberculosis with those who had smear-negative tuberculosis. Although we agree with the evidence cited by Arend and Uzorka, the association between crude smear grade and infectiousness might not be that straightforward when considering risk of disease among contacts, because infectiousness is influenced by a variety of other factors, including the capacity to generate aerosolised *Mycobacterium tuberculosis* through coughing, the quantity of viable mycobacteria in sputum, the quality of the sputum sample, the length of exposure, and the contact's own health.[3–5]

We also thank Nidhi Tejan and colleagues for their enthusiastic response to our study. Tejan and colleagues make the point that non-inclusion of pathogen-related factors, frequently determined by genomics, might lead to varying predictability in different regions. We agree with the authors and encourage use, validation, and most importantly adaptation of our score across other settings to characterise this phenomenon and explore how other environmental, behavioural, and cultural factors might affect implementation. However, routinely incorporating factors that require expensive and cumbersome tests would substantially reduce the usability of our score in resource-limited settings.

Ending the tuberculosis epidemic calls for the expansion of contact investigation and preventive treatment.[6] Our study incorporates

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important results into a practical tool that could be used to benefit and prioritise people who currently receive little or no attention from tuberculosis programmes in resource-limited settings. We believe that this approach should be combined with interventions addressing the social determinants of tuberculosis, which are the true drivers of the global tuberculosis epidemic.[7,8]

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Proton-pump inhibitors and glecaprevir plus pibrentasvir in HCV infection

Drug interactions between proton-pump inhibitors and direct-acting antiviral drugs are a great concern in patients with hepatitis C virus infection, because of the potential for suboptimal plasma concentrations of direct-acting antiviral drugs leading to compromised outcomes.[1,2] In the phase 3 trial reported by Xavier Forns and colleagues,[3] 31 (21%) patients with hepatitis C virus infection and compensated cirrhosis receiving glecaprevir plus pibrentasvir were concurrently treated with proton-pump inhibitors. On the basis of a post-hoc subgroup analysis, the authors concluded that the concomitant use of proton-pump inhibitors did not affect the efficacy of glecaprevir and pibrentasvir;[3] however, no information on the type, dose, frequency, or duration of the concomitant proton-pump inhibitor was given.

The degree of the interactions between proton-pump inhibitors and glecaprevir plus pibrentasvir has been shown to be highly dependent on the type, dose, frequency, and duration of the proton-pump inhibitor.[4,5] In a dedicated drug–drug interaction study, no clinically meaningful change (<30%) in the plasma peak and systemic exposure of glecaprevir and pibrentasvir was observed when coadministered with 20 mg of omeprazole once per day, whereas a statistically significant reduction, by more than 50%, was observed for glecaprevir in response to 40 mg of omeprazole once per day.[4] On the basis of these findings, the European Medicines Agency (EMA) stated that glecaprevir plus pibrentasvir could be administered concurrently with no more than 20 mg of omeprazole once per day.[4] Furthermore, the concomitant use of 40 mg of omeprazole once per day is contraindicated, and not recommended because of the risk of impaired efficacy.[4,5]

The post-hoc subgroup analysis in the phase 3 trial by Forns and colleagues[3] should be interpreted with caution. If the proton-pump inhibitors were grouped together, rather than stratified by type, dose, frequency, and duration in the post-hoc analysis, the extent of such drug-drug interaction would be mitigated. As such, the clinical relevance of the drug interactions between proton-pump inhibitors and glecaprevir plus pibrentasvir cannot be ruled not. Moreover, the precise effect of long-term use of a specific proton-pump inhibitor at a specific dosing regimen on glecaprevir plus pibrentasvir efficacy cannot be determined. Given the limited sample size of patients who used concurrent proton-pump inhibitors in the phase 3 trial, we believe that Forns and colleagues'[3] conclusion that "use of concomitant proton-pump inhibitors had no effect on efficacy" is premature. We now support, in line with the labelling recommendation,[4] the avoidance of long-term use of glecaprevir plus pibrentasvir with 40 mg of omeprazole once per day.

We declare no competing interests.

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