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The predictive values of the tuberculin skin test and interferon-γ release assays for active tuberculosis development

The prospective cohort study by Ibrahim Abubakar and colleagues reports the predictive values of the tuberculin skin test (TST) and two interferon-γ release assays (IGRAs) for the development of active tuberculosis.[1] The detection of individuals with latent infection who are likely to progress to active disease presents major challenges. 1·7 billion individuals were estimated to be latently infected with tuberculosis globally and about 10% of those will develop active disease.[2] However, there are no available tests that precisely identify which individuals will develop disease. Consequently, preventive treatment is given to at-risk groups that inevitably include individuals who would not have progressed to disease.[3] Additionally, although anti-tuberculosis treatment with 4 months of rifampicin or 9 months of isoniazid can prevent development of active disease from latent infection,[4] poor adherence, toxic effects, and low cost–effectiveness ratio hinder application of these therapies in high-burden low-income countries. Accordingly, a low-cost method of predictive screening for latent tuberculosis is urgently needed. Notably, this study showed that TST-15, a TST with a threshold greater than 5 mm in individuals naive to BCG or 15 mm in those vaccinated with BCG, provided a low-cost screening method to predict the development of disease that was almost as accurate as more expensive IGRAs, even after BCG vaccination.

Abubakar and colleagues did not directly consider the possible effect of non-tuberculosis mycobacteria (NTM) infections, which are also a serious problem in countries with a high burden of tuberculosis. The cross-reactivity might increase the false positivity of TST. By contrast, the immune stimulators used in IGRAs are absent from BCG and NTM strains, and Abubakar and colleagues' study showed that the predictive value of IGRAs was slightly higher than that of TST-15. However, the higher cost of IGRAs hinders their application in lower-income countries. Previously, we reported on the use of recombinant fusion protein ESAT-6–CFP10 for skin tests of tuberculosis infection and showed that it had an accuracy similar to that of IGRAs in diagnosing patients with tuberculosis in clinical trials.[5,6] In a phase 2a trial (NCT02329730),[5] we have further shown that ESAT-6-CFP10 use has similar accuracy to that of T-SPOT.TB in diagnosing tuberculosis infection in healthy volunteers and in patients with active tuberculosis infection (table). Nevertheless, TST-5 (a TST with a threshold of 5 mm) showed significantly higher positivity in healthy volunteers, which indicates high cross-reactivity from BCG vaccination (table). The low cost of this approach will facilitate its application in low-income countries.

Abubakar and colleagues included migrants, defined as people who had arrived within 5 years from high-burden countries, in the high-risk group in their study. This grouping criterion is questionable because many migrants might not have contacted patients with active tuberculosis. In the online appendix, the authors showed that the TST positivity was lower in migrants than in contacts (20·8% *vs* 33·7% in TST-15). Additionally, the percentage of disease progression in migrants was lower than in contacts. Therefore, the inclusion of migrants might have resulted in

	Healthy volunteers			Patients with active tuberculosis		
	Cases	Positive cases	Positivity (%)	Cases	Positive cases	Positivity (%)
TST-5*	56	32	57·1%	53	45	84·9%
ESAT-6–CFP10†	56	4	7·1%	53	43	81·1%
T-SPOT.TB	56	5	8·9%	53	45	84·9%

TST=tuberculosis skin test. *Purified protein derivative skin test with a threshold of 5 mm with a 5 IU inoculation. †ESAT-6–CFP10 skin test with a threshold of 5 mm with a 10 μg antigen inoculation.

***Table*: Use of recombinant fusion protein ESAT-6–CFP10 for skin tests of tuberculosis infection in a phase 2a clinical trial**

under-indication of the predictive values, and these values might actually be very different in high-risk groups with different criteria.

It is regrettable that the opportunity to do sequential tests of immune responses during follow-up was missed. Dynamic changes in immune markers might reveal better indicators for disease emerging from latent infection. It has been shown that early CD4 T-cell activation was correlated with tuberculosis disease risk after infection,[7] and we found that the expression of KLRG1, a marker of terminally differentiated T cells, was increased in patients with tuberculosis.[8] Therefore, further studies combining assays of defined immune markers with TST, IGRAs, or ESAT-6–CFP10 skin test might reveal a better method to predict progression to disease.

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Treatment recommendations for trichomoniasis in women

Multidose metronidazole has been found to be superior to single-dose metronidazole for the treatment of trichomoniasis in a randomised controlled trial done in women with HIV infection,[1] in a meta-analysis of published comparisons,[2] and in our randomised controlled trial done in women without HIV infection, published in *The Lancet Infectious Diseases*.[3] The abundance of data indicates that multidose metronidazole should be the first line of treatment for trichomoniasis in women.

Zhen-Zhou Luo and colleagues[4] suggest that false positives from nucleic acid amplification tests (NAAT), re-infection, and non-adherence to treatment could have influenced the results of our study,[3] and suggest that more data are needed before changing treatment recommendations to multidose metronidazole. We disagree. In addition to our intention-to-treat analysis, we did numerous sensitivity analyses that showed that the findings of multidose metronidazole superiority were robust. In one of the analyses, we used culture alone as the outcome, to remove possible misclassifications that could occur from detection of remnant RNA during NAAT, and these findings corroborated our intention-to-treat analysis. Additionally, no test of cure was done before 3 weeks,[5] therefore we do not think that the use of NAAT as an outcome biased our results.

Regarding sexual exposure and medication non-adherence, 33·5% of women reported having sex between enrolment and test of cure, and 2·6% reported not taking all of the medication. Of 540 women followed, 137 (25·4%) had sex during follow-up with a partner they had at baseline, 33 (6·1%) with a new partner, and 15 (2·8%) with a partner from baseline and a new partner. There was no difference between groups in sexual exposure during follow-up (86 [31·9%] of 270 women in the single-dose group *vs* 95 [35·2%] of 270 in the multidose group; p=0·412). Unsurprisingly, women in the single-dose group were more likely to adhere to their medication (264 [99·2%] of 266 women) than those in the multidose group (253 [95·5%] of 265; p=0·007). However, when re-examining our data to remove those who had sex with any partner during follow-up and who did not adhere to their medication, we still found that multidose remained superior (37 [20·8%] of 179 women in the multidose group *vs* 16 [9·8%] of 164 in the single-dose group; relative risk 1·70, 95% CI 1·11–2·59; p=0·005]. Earlier data suggest that most repeat infections were due to treatment failure and not reinfection.[6] Sexual activity with an untreated partner could be driving high re-infection rates post-treatment, though it is unlikely that this occurrence explains the consistent finding of multidose superiority.

We agree that the high rate of test-of-cure positives, even among those receiving multidose metronidazole (not explained by organism in-susceptibility), is concerning and a better understanding of factors that interfere with metronidazole treatment and development of more efficacious low-cost treatments for trichomoniasis are needed.

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