New developments on interferon-gamma release assays for tuberculosis diagnosis

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To diagnose or exclude tuberculosis can be challenging because of the varied clinical signs and the limitations of diagnostic tests. Tuberculosis diagnosis has evolved from autopsies and histology to radiography and microbiological tests, with culture as the ultimate gold standard. Interferon-γ release assays (IGRAs) measure T-cell responses to *Mycobacterium tuberculosis*-specific antigens. Although IGRAs have an established role for detection of latent tuberculosis, their use for suspected active tuberculosis is discouraged because a positive test result does not differentiate active from latent tuberculosis, whereas a negative result does not exclude active tuberculosis because of the suboptimal sensitivity. In *The Lancet Infectious Diseases*, Hilary Whitworth and colleagues[1] report a prospective study among patients with suspected tuberculosis in the UK, comparing both existing IGRAs (QuantiFERON-TB Gold and TSPOT.*TB*) with two novel second-generation IGRAs. Second generation IGRAs were developed from TSPOT.*TB* with additional antigen Rv3615c, or without ESAT-6 but including Rv3615c and Rv3879c.

In this well designed multicentre study, the sensitivity of second-generation IGRAs for culture-confirmed or probable active tuberculosis, diagnosed in 363 (43%) of 845 patients, was higher than that of TSPOT.*TB* (89·2% [95% CI 85·2–92·2] *vs* 81·4% [76·6–85·3]), whereas the specificity was lower (80·0% [75·6–83·8] *vs* 86·2% [82·3–89·4]). For unexplained reasons, QuantiFERON did below par, in disagreement with comparable sensitivity of QuantiFERON and TSPOT.*TB* in a meta-analysis[2] and a large comparative study.[3] The authors indicate second-generation IGRAs as rule-out tests in case of a negative test result or as complementary to molecular tests in case of a positive result. The similar high sensitivity of ESAT-6-free second-generation IGRA is an indication of the potential of this assay as an adjuvant diagnostic in association with possible future ESAT-6-containing vaccines.

The trend towards higher sensitivity of second-generation IGRAs represents the first advancement in this field since the introduction of IGRAs. The sensitivity meets the requirement for a triage test, as described by WHO in a high-priority target product profile.[4] However, the target groups in that report are patients with suspected tuberculosis in medium or high incidence regions, and the envisioned triage test should be a simple field-friendly test, providing results within 30 min at a maximal cost of US$2,[4] none of which apply to the reported second-generation IGRA. In low-endemic countries, such as the UK, a triage test has low priority, but a complementary role to microbiological tests could be of practical value.

The lower specificity of second-generation IGRAs compared with clinically available IGRAs could be an asset rather than a limitation because false-positive responses were most probably explained by improved detection of latent tuberculosis. This assumption was corroborated by the higher specificity of second-generation IGRAs among participants without previous exposure or other risk factors. This trade-off is analogous to the higher sensitivity of Xpert MTB/RIF Ultra, compared with its predecessor Xpert MTB/RIF, at the cost of a lower specificity in sputum samples due to the detection of DNA of dead bacilli.[5] In both settings, so-called false-positive test results occur because the assays do not differentiate between two different stages of tuberculosis.

However, the observed results in the study by Whitworth and colleagues[1] cannot be generalised to all patients with suspected tuberculosis. First, individuals with previous tuberculosis (n=99) were excluded. Second, indeterminate test results, possibly reflecting an impaired immune status, and borderline results were excluded from the analysis, as were data from participants in the clinically indeterminate category. Finally, indeterminate results were frequent and the sensitivity of second-generation IGRAs was low (70·6%) among HIV-infected patients.

Tuberculosis is now recognised as a spectrum of conditions, rather than a dichotomy.[6] With IGRAs being poor predictors of development of active tuberculosis,[7] a test for incipient tuberculosis is on the most-wanted diagnostics list.[8,9] Assessment of the stage of infection could be achieved through testing responses to stage-specific antigens, such as latency antigens, resuscitation promoting factors, and replication associated antigens.[10] Other possible targets are cytokines other than interferon-γ,[11] specific T-cell populations, or host biomarkers, such as prognostic correlates of risk

based on mRNA expression signatures, which are now being evaluated for prediction of active tuberculosis.[12]

In conclusion, the second-generation IGRAs represent two promising new twigs on the IGRA branch, with a high sensitivity in a selected population in the UK. They merit further study in various settings to assess their diagnostic potential for latent, incipient, active tuberculosis, or all.

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We declare no competing interests.

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Enhancing immune responses to oral vaccines: still an enigma

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In *The Lancet Infectious Diseases*, James A Church and colleagues[1] report the results of a systematic review and meta-analysis of studies on attempts to enhance the immune responses to oral vaccines, especially infants given oral polio vaccine (OPV) and oral rotavirus vaccine. The suboptimal immune responses to these oral vaccines in Africa and Asia has long been recognised, and it would seem there should be a reasonable explanation and a simple intervention that could improve effectiveness. This review, however, concludes that there are no simple solutions that could be applied generally for oral vaccines.

OPV was highly successful in eliminating polio from North America and it was assumed that the vaccine would have a similar outcome in low-income countries. Unfortunately, this was not the case in India and other low-income countries.[2] More doses of vaccine were required to achieve similar response rates to those in North America, and cases of polio continued to occur even in areas of high OPV coverage.

Similarly, rotavirus vaccines, which were highly efficacious in North and South America,[3,4] showed lower efficacy in Africa[5] and Asia.[6] Now that the vaccines are used routinely, their effectiveness is confirmed, but at a lower rate in lower-income countries.[7] Clearly, even with the lower efficacy, these vaccines provide a major public health benefit because the disease burden is so high; however, if there was a way to improve immunogenicity, these vaccines would be even more powerful.

Many reasonable theories have been suggested as to why children in low-income countries have a weaker response to oral vaccines than do those in high-income countries.[8] The most common suggestions relate to interference by maternal antibody in serum or breast milk, intestinal parasitic infestations, micronutrient (especially zinc or vitamin A) or macronutrient malnutrition, concurrent enterovirus infection, and intestinal mucosal enteropathy. Considering the young age at immunisation, some of these explanations seem more likely than others. For example, parasitic infestations, micronutrient deficiencies, or even enteropathy would seem to be uncommon at this young age. Nevertheless, considering these potential mechanisms, controlled clinical trials have attempted to improve the immune responses to these vaccines. In short, Church and colleagues found that there was no general strategy that seems to substantially improve the serological responses to these oral vaccines. Of those tested, some would have been difficult to implement, such as avoiding breastfeeding for a few