Emerging challenges for IGRAs in tuberculosis diagnosis

José Domínguez

Institut d'Investigació Germans Trias i Pujol. CIBER Enfermedades Respiratorias. Universitat Autònoma de Barcelona. Badalona.

Correspondencia:
José A. Dominguez
E-mail: jadominguez@igtp.cat

Enf Emerg 2026;25(3):163-164
doi: 10.18176/enfemerg.0046

In 2024, tuberculosis (TB) affected an estimated 10.7 million people worldwide, of whom approximately 10% were children, and caused 1.23 million deaths[1]. TB is closely associated with poverty and social vulnerability, highlighting the need for a Global Health approach to protect populations from cross-border health threats through early identification of cases and rapid public health responses. Despite continued progress, TB remains a significant public health challenge in Spain, where approximately 3,800 new cases were reported in 2024. Particular attention is required for vulnerable groups, including close contacts of TB patients, immunocompromised individuals, and people living with HIV. Across the WHO European Region, the estimated incidence rate remains 22 cases per 100,000 inhabitants.

Despite major advances in diagnostics and treatment, TB continues to represent a substantial global health threat. Effective TB control requires both the rapid identification of active disease and the timely detection and treatment of tuberculosis infection (TBI). It is estimated that approximately 1.7 billion individuals worldwide exhibit immunological evidence of exposure to *Mycobacterium tuberculosis* (Mtb) without clinical manifestations of active disease[2].

Traditionally, the diagnosis of TBI has relied on the tuberculin skin test (TST). More than two decades ago, interferon-gamma release assays (IGRAs) emerged as an alternative method for detecting cellular immune responses against Mtb-specific antigens. These in vitro assays stimulate peripheral blood cells with RD1 antigens, such as ESAT-6 and CFP-10, overcoming several limitations associated with the TST. Over the past twenty years, numerous studies have demonstrated the utility of IGRAs in contact investigations and in assessing TB infection across diverse populations, including children, healthcare workers, and immunocompromised individuals[3-5].

Although neither TST nor IGRAs can reliably distinguish latent infection from active disease, nor accurately identify individuals at highest risk of progression from infection to active TB, both methods have provided invaluable support for the diagnosis and management of TBI.

However, recent advances in our understanding of host-pathogen interactions, together with the need to decentralize diagnostic services, the development of novel in vivo diagnostic approaches, and the emergence of new TB vaccines, challenge the current role of IGRAs and warrant a critical reassessment of their future utility.

The concept of Mtb infection has evolved substantially in recent years. It is now widely recognized that TBI encompasses a spectrum of biological states, rather than a simple dichotomy between infection and disease, each requiring distinct diagnostic and therapeutic approaches[6]. This evolving framework also includes a growing recognition of post-TB lung disease and the need for improved strategies to prevent, diagnose, and manage its long-term consequences. Novel approaches based on the characterization of host immune responses are expected to play a key role in defining the different stages within the TB infection-disease spectrum.

Furthermore, although current diagnostic tools are effective, their implementation remains limited by cost, laboratory infrastructure requirements, and restricted decentralization, particularly in resource-limited and peripheral settings. The development of accurate, affordable, and portable diagnostic tools for TBI has the potential to significantly expand access to testing and contribute to reducing the global TB burden.

At the same time, the development of novel TB vaccines based on attenuated Mtb strains, such as MTBVAC, introduces new diagnostic challenges. Unlike BCG vaccine, MTBVAC contains the RD1 region, which are currently used in commercial IGRAs. Consequently, existing IGRAs may lose their ability to discriminate between vaccinated and naturally infected individuals in populations where such vaccines are implemented[7].

In parallel, new skin tests based on RD1 Mtb-specific antigens have recently been developed[8]. These next-generation skin tests offer diagnostic performance comparable to that of IGRAs while retaining some of the operational advantages of in vivo testing, although they continue to present limitations inherent to skin-based assays.

In summary, the rapidly evolving landscape of TBI, diagnostics, and vaccination strategies requires a thorough reassessment

of the role of IGRAs. Revisiting their applications, limitations, and future integration with emerging technologies will be essential to ensure that diagnostic strategies remain aligned with the next generation of TB control and elimination efforts.

Acknowledgments

This article is based on work supported by a grant the Instituto de Salud Carlos III (PI22/01834) integrated in the Plan Nacional I+D+I and co-founded by the ISCIII Subdireccion General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER) and CERCA Programme/Generalitat de Catalunya; and from the European Union's Horizon Europe Research and Innovation Programme under the Marie Skłodowska-Curie Actions Staff Exchanges project TB-SPECTRUM (Grant agreement no. 101236673).

Bibliography

1. Word Health Organization (WHO). Global Tuberculosis Report 2024.
2. Houben RMGJ, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLoS Med*. 2016;13(10):e1002152. doi: 10.1371/journal.pmed.1002152.
3. Latorre I, Mínguez S, Carrascosa J-M, Naves J, Villar-Hernández R, Muriel B, *et al*. Immune-mediated inflammatory diseases differently affect IGRAs' accuracy for latent tuberculosis infection diagnosis in clinical practice. *PLoS One*. 2017;12(12):e0189202. doi: 10.1371/journal.pone.0189202.
4. de Souza-Galvão ML, Latorre I, Altet-Gómez N, Jiménez MA, Milá C, Solsona J, *et al*. Correlation between tuberculin skin test and IGRAs with risk factors for the spread of infection in close contacts with sputum smear positive in pulmonary tuberculosis. *BMC Infect Dis*. 2014;14:258. doi: 10.1186/1471-2334-14-258.
5. Díez N, Giner E, Latorre I, Lacoma A, Roig J, Mialdea I, *et al*. Use of Interferon-gamma release assays to calculate the annual risk of tuberculosis infection. *Pediatr Infect Dis J*. 2015;34:219-21. doi: 10.1097/INF.0000000000000514.
6. Esmail H, Macpherson L, Coussens AK, Houben RMGJ. Mind the gap - Managing tuberculosis across the disease spectrum. *EBioMedicine*. 2022;78:103928. doi: 10.1016/j.ebiom.2022.103928.
7. Tameris M, Rozot V, Imbratta C, Geldenhuys H, Mendelsohn SC, Kany Luabeya AK, *et al*; MTBVAC 202 study team. Safety, reactogenicity, and immunogenicity of MTBVAC in infants: a phase 2a randomised, double-blind, dose-defining trial in a TB endemic setting. *EBioMedicine*. 2025;114:105628. doi: 10.1016/j.ebiom.2025.105628.
8. Krutikov M, Faust L, Nikolayevskyy V, Hamada Y, Gupta RK, Cirillo D, *et al*. The diagnostic performance of novel skin-based in-vivo tests for tuberculosis infection compared with purified protein derivative tuberculin skin tests and blood-based in vitro interferon-γ release assays: a systematic review and meta-analysis. *Lancet Infect Dis*. 2022;250-64. doi: 10.1016/S1473-3099(21)00261-9.