



## Commentary

## A new step toward tuberculosis vaccine?

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Understanding the role of the immune system in controlling tuberculosis (TB) infection is pivotal to reach the goal of full elimination of the disease by 2050, as highlighted by World Health Organization (WHO) [1]. TB diagnosis in children is particularly challenging, especially in limited resource settings, and studies which aim to identify target population to address efforts are crucial. Host's characteristics in determining disease control and its severity are increasingly studied, with the main aim to identify biomarkers of TB "resistance", especially in the pediatric age.

Basu Roy et al. recently published on EBioMedicine a study on a cohort of Gambian pairs of children ( $n = 58$ ) exposed to the same index case with different infection status (infected and uninfected). This study emphasizes the importance that a discordant infection status could be related to the unique characteristics of the individual to inhibit mycobacterial growth [2]. The selection process of included children and the elimination of possible confounding factors give strength to what can be considered as an important milestone surrounding this fundamental topic [2]. Using a mycobacterial growth inhibition assay, bacterial growth was evaluated at baseline and at 96 h and a quantitative analysis of IL-1 $\alpha$ , IL-1 $\beta$ , IL-10, IFN- $\gamma$  and TNF- $\alpha$  was performed [2]. The used test, an autoluminescent BCG growth monitoring in whole blood, has been described by the same groups of authors in a recent publication [3]. It permits, with a small amount of blood (225  $\mu$ l) to obtain serial measurements (after 1 h and at 24, 48, 72 and 96 h) with the quantification of luminescence related to bacterial colony forming units (CFUs) [3].

While mycobacterial control was superior in uninfected children at one hour, suggesting the role of both adaptive and innate immune response, on the other hand, children with mycobacterial infection showed a superior control at 96 h with a greater role of adaptive responses [2]. Regarding cytokine production, uninfected children

produced less BCG-specific interferon gamma compared to infected children, mirroring the infection status [2]. Moreover, infected children were statistically significant older than uninfected, with a longer smear-positive index case exposure. Historically, the most important role regarding tuberculosis immunity has been attributed to T-cell-mediated response, with CD4+ T cells playing a crucial role both for the control of infection and the tissue damage during TB infection [4,5]. Together with adaptive immune response, innate immune cells are crucial for TB infection control [4,5]. Nevertheless, unanswered questions remain. In fact, as stated by the authors, the complete knowledge of immune response to TB is still lacking and consequently, the way to find an effective vaccine is still far away. It is well known that the only available vaccine, the Bacillus Calmette-Guèrin (BCG), used for the first time in 1921, confers a significant protection against TB meningitis and miliary tuberculosis, especially in children under 5 years of age, with a different level of protection against pulmonary TB, ranging from 0 to 80% [6]. In addition, BCG scarring has been associated with a lower morbidity and mortality compared to children not having a scar [7,8]. Up to now, several new TB vaccines are in the pipeline with incomplete results regarding safety and efficacy in the pediatric age [9]. Mechanisms required for mycobacterial killing are still under investigation and large studies in different populations are needed to help vaccine development. Intriguing results provided by this study, using a tool which helps to understand the *in vivo* interactions between the host and the *Mycobacterium spp*, pave the way for new studies regarding TB vaccine development with a direct applicability in the clinical practice.

## Contributors

CT and LG both conceived and wrote the manuscript. LG approved the final version.

## Declaration of Interests

The authors have nothing to declare.

## References

- [1] World Health Organization. WHO targets elimination of TB in over 30 countries. Available at: <https://www.who.int/mediacentre/news/releases/2014/tb-elimination/en/>. Accessed on: 3 July 2020.
- [2] Basu Roy R, Sambou B, Sissoko M, et al. Protection against mycobacterial infection: a case-control study of pairs of Gambian children with discordant infection status despite matched TB exposure. EBioMedicine 2020. doi: 10.1016/j.ebiom.2020.102891.

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- [3] Basu Roy R, Sambou B, Uhiá I, et al. An auto-luminescent fluorescent BCG whole blood assay to enable evaluation of paediatric mycobacterial responses using minimal blood volumes. *Front Pediatr* 2019;7:151.
- [4] de Martino M, Galli L, Chiappini E. Reflections on the immunology of tuberculosis: will we ever unravel the skein? *BMC Infect Dis* 2014;14(Suppl 1):S1.
- [5] de Martino M, Lodi L, Galli L, Chiappini E. Immune response to mycobacterium tuberculosis: a narrative review. *Front Pediatr* 2019;7:350.
- [6] Colditz GA, Brewer TF, Berkey CS, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA* 1994;271:698–702.
- [7] Benn CS, Roth A, Garly ML, et al. BCG scarring and improved child survival: a combined analysis of studies of BCG scarring. *J Intern Med* 2020;10: 1111.
- [8] Funch KM, Thysen SM, Rodrigues A, et al. Determinants of BCG scarification among children in rural Guinea-Bissau: a prospective cohort study. *Hum Vaccin Immunother* 2018;14:2434–42.
- [9] Schragger LK, Vekemens J, Drager N, et al. The status of tuberculosis vaccine development. *Lancet Infect Dis* 2020;20:e28–37.