# Accelerating TB vaccine development by “planning for success”: The MTBVAC phase 2b clinical trial to prevent TB in African adolescents and adults

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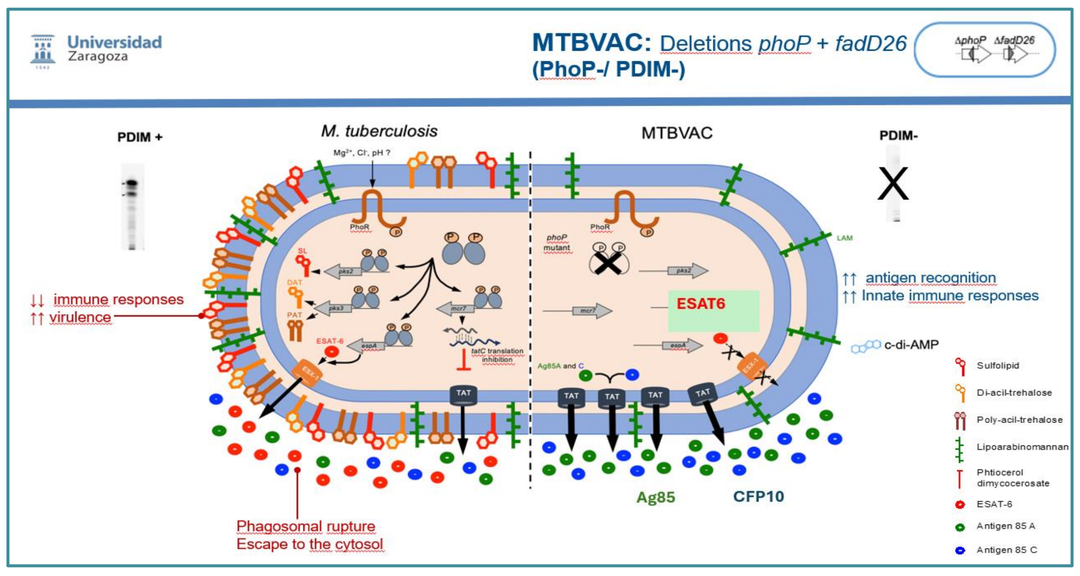
## Background

Accelerating the development of TB vaccines represents an important WHO goal. Opportunities may exist within the traditional vaccine development pathway to realize a goal of accelerating the path leading to regulatory assessment for marketing approval. In this discussion we use the development of MTBVAC, a live, rationally attenuated vaccine derived from a virulent clinical isolate of Mycobacterium tuberculosis (Mtb), as a case study in creating the potential for accelerating TB vaccine development. A phase 2b (ph2b) trial of MTBVAC’s ability to prevent TB in IGRA+, HIV- persons in South Africa, Kenya and Tanzania is being planned (NCT06272812). This presentation will discuss strategies by which a ph2b trial such as this can be reimagined to “plan for success” and accelerate TB vaccine development, potentially saving resources, time, and lives.

## MTBVAC schematic

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## Discussion

MTBVAC represents the only live, attenuated candidate in the TB vaccine pipeline directly derived from a clinical Mtb isolate. MTBVAC is being developed along two clinical pathways: preventing TB disease in infants, and in adolescents and adults (A/A). The initial ph1 trials involving adults were conducted in 2013 and 2015 (NCT02013245, NCT02729571). These were followed by a ph1b/2a safety, immunogenicity, and dose-finding trial in 144 IGRA+ and IGRA-, HIV- persons ages 18-60 (NCT02933281). A ph2a trial evaluating the safety and immunogenicity of MTBVAC in A/A living with and without HIV in South Africa is ongoing (NCT05947890).

A ph2b trial of MTBVAC to prevent TB in 4,300 IGRA+, HIV- A/A ages 14-45 in TB endemic regions of sub-Saharan Africa is scheduled to begin in Q3 2024 (the IMAGINE trial; NCT06272812). The assumptions used in calculating the sample size included a LL 95% CI of ≥0 % with a point estimate of vaccine efficacy varying between 60-70 %; the final analysis will be triggered when 35 pulmonary TB cases have occurred. As designed, the IMAGINE trial will provide data in 2029 to permit a go-no go decision for a phase 3 registration trial. Because this trial will be using the same, commercially-ready product as that being used in a phase 3 trial in infants (NCT04975178), we have an opportunity to submit phase 2b data for registration consideration should these data warrant such a submission. This opportunity requires discussions with relevant regulatory authorities to establish acceptable statistical targets for efficacy and meeting requirements for establishing safety. Including populations needed to ensure access to a licensed product – in this case, IGRA-negatives – is also important. Risking additional investments in this trial, such as in support of an IGRA-negative cohort, may permit data submission for licensure at study conclusion in 2029, if supported by sufficiently robust efficacy data.

## Conclusion

While an acceleration strategy incurs risk of additional investment, the approach, if successful, could reduce the development of a TB vaccine such as MTBVAC by 7 or more years, potentially saving hundreds of millions of dollars in development costs and thousands of lives. This approach may serve as a model by which the development of future TB vaccines may be accelerated.

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