Controlled Human Infection Models: Is it Really Feasible to Give People Tuberculosis?

Tuberculosis (TB) is currently responsible for more deaths per annum than any other pathogen (1). Despite modest gains in control in recent years, the rate of progress is too slow. Data from mathematical modeling suggest that an effective vaccination strategy will be required to achieve the ambitious targets described in the Sustainable Development Goals and the Stop TB Partnership's Global Plan to End TB (2). The recent results from the M72/AS01e efficacy trial give us some cause for optimism (3). The M72/AS01e protein/adjuvant vaccine candidate achieved 49.7% efficacy (95% confidence interval, 2.1–74.2%) in preventing TB disease in *Mycobacterium tuberculosis* (*M.tb*) latently infected subjects. This is a landmark result for the field and provides proof of concept that it is possible to protect against TB disease with vaccination. However, more data are needed, in particular on how effective this vaccine is in protecting against TB disease in those uninfected with *M.tb*. The confidence intervals in this trial are wide, and further efficacy data are likely to be necessary before this vaccine is licensed and deployed. Although 3-year efficacy of 50% is better than anything else achieved to date, we should not rest on our laurels: a more effective vaccine would be better.

Two key challenges in TB vaccine development are the lack of predictive preclinical animal models and the absence of validated immunological correlates of protection. In other fields where vaccine development is complex, such as malaria, the use of controlled human infection models has complemented preclinical and human immunology studies and facilitated vaccine development (4). There are obvious challenges with the development of a controlled human infection model for TB. It would not be ethical to deliberately infect healthy subjects with virulent *M.tb*. However, there are alternative approaches, and the work conducted by Davids and colleagues (pp. 1277–1291) in Cape Town reported in this issue of the *Journal* provides a useful demonstration of the potential for human experimental medicine studies in this space (5).

Davids and colleagues have established a human experimental medicine of bronchoscopic installation of either purified protein derivative (PPD) or bacillus Calmette-Guérin (BCG) (5). BCG is the only licensed vaccine against TB and confers highly variable efficacy against pulmonary disease (6). As BCG is a live attenuated strain of *Mycobacterium bovis*, it provides a potential surrogate human challenge agent for use in a controlled human infection model. This work builds on earlier work in which PPD delivered intrabronchially resulted in an influx of Th1 $CD4^+$ T cells 48 hours later (7). Davids and colleagues recruited subjects within a spectrum of preexisting mycobacterial exposure, from asymptomatic household contacts who were IFN-γ release assay negative, through to subjects with multiple previous, fully treated episodes of microbiologically proven TB disease. Importantly, the incidence of adverse events in this study was low and the intervention appeared to be safe. All adverse events were mild and managed in an outpatient setting. The authors go on to use the BAL fluid collected before installation of PPD/BCG, together with a repeat lavage taken 3 days after installation, to interrogate the host immune response. They demonstrate alterations in innate cells and total IgG at the highest BCG dose administered and an increased frequency of $CD4^+$ IFN-γ^+ T cells after the highest dose of PPD. Furthermore, the authors also show differential gene expression and a dysregulated protein response after BCG and PPD installation. These BAL-specific responses were not detected in the peripheral blood, suggesting considerable compartmentalization of the response.

These novel findings are important and provide proof of concept of the feasibility of this human challenge model approach within the field of TB. They also demonstrate how important human immunological data can be derived from such an approach. The utility of such a model for vaccine evaluation, as a tool to complement preclinical animal studies and conventional human immunogenicity studies, now needs evaluation. Storage of immune correlate samples from such studies can then be used to interrogate putative immune correlates, which can be subsequently validated in field efficacy studies. The biological validation of controlled human infection models is ultimately by comparison with field efficacy studies. However, preclinical animal models can be used to demonstrate a comparable vaccine effect with a BCG challenge model to that seen with a virulent *M.tb* infection model. A BCG vaccine effect comparable in magnitude to that detected after virulent *M.tb*/*M. bovis* challenge was detected using an intradermal BCG infection model in mice, nonhuman primates, and cattle (8–10).

A further opportunity with a controlled human challenge model is to use it to interrogate and understand the immunobiology of a defined point in mycobacterial infection. Such studies would complement studies in the field where the timing of infection cannot be precisely determined. Using new-generation transcriptomic and proteomic approaches, together with detailed sampling of the respiratory mucosa as well as peripheral blood, allows an unprecedented definition of the host immune response that could yield insights that facilitate vaccine design and development.

One limitation of the approach taken by Davids and colleagues is that the bronchoscopic installation of BCG or PPD does not mimic the natural route of infection. Aerosol delivery is increasingly being used in nonhuman primate challenge studies to better mimic the natural route of infection, and is currently being evaluated in clinical studies as well (11) (clinicaltrials.gov NCT02709278 and NCT03912207). Further work in humans and nonhuman primates, ideally in parallel studies, will allow us to determine the best approach to exploit the full potential of this model.

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In a field as complex as TB, and where a vaccine is so urgently needed, new tools with which to facilitate vaccine development are to be welcomed. The study by Davids and colleagues is an important step in establishing a lung controlled human infection model for TB. Further studies that evaluate novel candidate vaccines are now needed to determine the utility of this and other models. Iatrogenically infecting healthy human subjects with mycobacteria, providing we "do no harm," may yet prove a useful tool to facilitate the development of an effective vaccine for this devastating pathogen. ■

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References

1. WHO. Global tuberculosis report. 2019 [accessed 2019 Dec 3]. Available from: https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1.
2. WHO. Global plan to stop TB. 2016 [accessed 2019 Dec 3]. Available from: http://www.stoptb.org/assets/documents/global/plan/GlobalPlanToEndTB_TheParadigmShift_2016-2020_StopTBPartnership.pdf.
3. Tait DR, Hatherill M, Van Der Meeren O, Ginsberg AM, Van Brakel E, Salaun B, *et al*. Final analysis of a trial of M72/AS01$_E$ vaccine to prevent tuberculosis. *N Engl J Med* 2019;381:2429–2439.
4. Stanisic DI, McCarthy JS, Good MF. Controlled human malaria infection: applications, advances, and challenges. *Infect Immun* 2017;86:e00479-17.
5. Davids M, Pooran A, Hermann C, Mottay L, Thompson F, Cardenas J, *et al*. A human lung challenge model to evaluate the safety and immunogenicity of PPD and live bacillus Calmette-Guérin. *Am J Respir Crit Care Med* 2020;201:1277–1291.
6. Mangtani P, Abubakar I, Ariti C, Beynon R, Pimpin L, Fine PE, *et al*. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. *Clin Infect Dis* 2014;58:470–480.
7. Silver RF, Zukowski L, Kotake S, Li Q, Pozuelo F, Krywiak A, *et al*. Recruitment of antigen-specific Th1-like responses to the human lung following bronchoscopic segmental challenge with purified protein derivative of Mycobacterium tuberculosis. *Am J Respir Cell Mol Biol* 2003;29:117–123.
8. Minassian AM, Ronan EO, Poyntz H, Hill AV, McShane H. Preclinical development of an *in vivo* BCG challenge model for testing candidate TB vaccine efficacy. *PLoS One* 2011;6:e19840.
9. Harris SA, White A, Stockdale L, Tanner R, Sibley L, Sarfas C, *et al*. Development of a non-human primate BCG infection model for the evaluation of candidate tuberculosis vaccines. *Tuberculosis (Edinb)* 2018;108:99–105.
10. Villarreal-Ramos B, Berg S, Chamberlain L, McShane H, Hewinson RG, Clifford D, *et al*. Development of a BCG challenge model for the testing of vaccine candidates against tuberculosis in cattle. *Vaccine* 2014;32:5645–5649.
11. Sibley L, Dennis M, Sarfas C, White A, Clark S, Gleeson F, *et al*. Route of delivery to the airway influences the distribution of pulmonary disease but not the outcome of Mycobacterium tuberculosis infection in rhesus macaques. *Tuberculosis (Edinb)* 2016;96:141–149.