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

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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 modelling suggests that an effective vaccination strategy will be required to achieve the ambitious targets described in the SDGs 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% CI, 2.1 to 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 is 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 is likely to be necessary before this vaccine is licensed and deployed. Whilst three-year efficacy data of 49% 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 *et al* in Cape Town reported in this journal provide a useful demonstration of the potential for human experimental medicine studies in this space.

Here, Davids *et al* have established a human experimental medicine of bronchoscopic installation of either purified protein derivative (PPD) or 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
*M. 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 et al recruited subjects within a spectrum of pre-existing mycobacterial exposure, from asymptomatic household contacts who were interferon gamma 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 bronchoalveolar lavage fluid collected prior to installation of PPD/BCG, together with a repeat lavage taken three 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+ interferon gamma+ 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 compartmentalisation 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 utilised 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 utilised 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, non-human 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 time point 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 et al is that the bronchoscopic installation of BCG or PPD does not mimic the natural route of infection. Aerosol delivery is increasingly being used in non-human 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; NCT03912207). Further work in humans and non-human primates, ideally in parallel studies, will allow us to determine the best approach to exploit the full potential of this model.

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 et al is an important step in establishing a lung controlled human infection model for TB. Further studies which 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.
References


2. WHO. Global Plan to Stop TB. 2016.


