Need for more TB vaccine field sites

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Efforts to control the tuberculosis (TB) epidemic have been challenged by both the geographical overlap with the HIV pandemic, and the emergence of multi- and extensively drug-resistant strains of *Mycobacterium tuberculosis*. There is, therefore, an urgent global need for an improved vaccine. However, the development of an improved vaccine is scientifically and logistically challenging. Immunological correlates or biomarkers of protection are not known and there is no perfect preclinical animal model with which to predict success in humans. Indeed, vaccine development in general is time-consuming and costly. One of the many road-blocks to the development of new TB vaccines is the availability of field sites that are suitable for large-scale Phase IIb/III efficacy testing. Because disease incidence is low, even though prevalence is high, Phase IIb efficacy trials involve several thousand subjects, and require lengthy follow-up. Phase III licensure trials will need to be even larger, and are likely to require the involvement of multiple field sites. There is currently inadequate capacity within high-burden TB countries to conduct these essential trials. We need to invest now to expand current capacity if we are to reduce the time taken to develop new vaccines.

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There are strong scientific reasons why new TB vaccines should be evaluated in many different countries and continents. It is known that the efficacy of *M. bovis* bacille Calmette-Guérin (BCG), the currently available vaccine, varies widely with geographical latitude\(^1\). Part of the explanation for this may lie in differing levels of exposure to environmental mycobacteria (EM) within and between countries\(^2\). Host genetics, helminthic exposure and nutritional factors also vary across countries and between continents, and may contribute to the variability in efficacy of BCG. Finally, exposure to *M. tuberculosis* will also vary considerably across and between high-burden countries, and this may impact on the protective efficacy of new vaccines. Hence, we need to be confident that a new TB vaccine is effective in all TB endemic countries throughout the world, and it is therefore essential that such vaccines are evaluated in as many different settings as possible.

To expand TB vaccine trial capacity throughout the world, a substantial amount of funding is required, but this is about more than just funding.

Regulatory capacity

To ensure the integrity of clinical trial data, on which new vaccines and drugs are licensed, there are many standards and systems in place which must be rigorously adhered to. Clinical trials must be conducted according to the International Committee on Harmonisation guidelines for Good Clinical Practice (ICH-GCP). All clinical trial protocols must be reviewed and approved by the relevant regulatory and ethical authorities, and often this can require review by multiple agencies throughout the world. Regulatory capacity within the developing world is a substantial bottleneck for the conduct of clinical trials. Many countries within sub-Saharan Africa do not have any such Competent Authority that is capable of reviewing and approving clinical trial protocols. Outside of Africa, the situation is better, but far from optimal. Turnaround time for regulatory review and trial approval can be considerable and this can lead to significant delays in product development. In addition, the expertise necessary to review some of the more complex protocols and products in development is often lacking. The World Health Organisation (WHO) has established a network of regulators across the developing world, the Developing Countries Vaccine Regulators Network (DCVRN), with the aim of linking this network to expertise within UK and US regulatory agencies\(^3\). Ultimately, regulatory capacity within the developing world will need to expand considerably, if it is not to become a rate-limiting step in the licensure of a new TB vaccine.
Laboratory procedures and systems

Another vital aspect of clinical trial conduct is to have validated systems in place for such things as sample processing, safety, microbiological and immunological laboratory evaluation. If the trial endpoint is TB disease, then it is essential that the methods used to diagnose TB are clearly defined, validated, rigorous and reproducible. This potentially requires considerable investment in training and local health infrastructure. Laboratory accreditation and compliance with Good Laboratory Practice standards is required. Independent trial monitoring to ensure integrity of data and safety of subjects is also an essential part of ICH-GCP. All new vaccines must be manufactured under Good Manufacturing Practice conditions in order to be fit for human use. Systems and structures for safety review and reporting to both the regulatory and ethical authorities are essential for the safety of study subjects and the integrity of the data.

Epidemiological studies

Reliable epidemiological data is essential in order to determine the sample size needed to obtain a certain level of vaccine efficacy. Often this necessitates conducting large scale epidemiological studies at potential clinical trial sites. Such studies provide a useful way of building teams, networks and local acceptability prior to large scale clinical trials.

Skills and training

Conducting clinical trials is very different from doing basic research, and a detailed understanding of the many processes involved is essential. Clinical trials are not intrinsically difficult. However, the science and discipline of clinical trials conduct is a field in itself for which specialised training programmes are needed. The mindset needed is different from that of scientists and clinical doctors. Committed staff with administrative ability, willingness to engage with bureaucracy, attention to detail, and stamina are needed.

Additional field sites must be developed and established throughout in places like India, China, and South East Asia. Currently, these countries are significantly under-represented and there are compelling scientific and logistical reasons for the need to correct this. Substantial funding, directed at building this capacity, is required. Much of this funding will need to come from public sources. An excellent example of the type of facilities and infrastructure required is the site on the Western Cape in South Africa, where the Aeras Global TB Foundation has worked with the South African TB Vaccine Initiative (SATVI) to establish a world class TB vaccine trial site. This model must be reproduced elsewhere in the world if we are to achieve the goal of the development of a new TB vaccine and reduce the burden of mortality and morbidity attributable to this terrible disease.

References