Tuberculosis: A Global Overview

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Together with HIV/AIDS and malaria, tuberculosis (TB) is recognised as one of the most important threats to human health. There are around 9 million new cases of TB every year, resulting in up to 2 million deaths. Key issues in combating global TB include the emergence of strains of *Mycobacterium tuberculosis* that are resistant to available drugs, synergy with the HIV pandemic, and a historical shortage of funding for both research and disease control (1). In 2006, the Global Partnership to Stop TB launched a 10-year plan designed to address the aims set out in the UN Millennium Development Goals. The Global Plan to Stop TB envisages saving 14 million lives by effective treatment of 50 million people, and aims to cut the global burden of TB in half by the year 2015 (2).

A central element of the Global Plan is the need to develop improved tools for TB control; it is projected that even the most efficient implementation of current control strategies will fail to meet the Millennium Development Goals in many parts of Africa. The Plan advocates investment of $9 billion in research and development for new tools. A series of initiatives have been put in place to promote the R&D goals (Figure 1). These include three public-private foundations directed towards development of new vaccines (the Aeras Global TB Vaccine Foundation (3), new drugs (the Global Alliance for TB Drug Development (4), and new diagnostics (FIND, the Foundation for Innovative Diagnostics (5). International consortia addressing complementary research efforts are supported by funds from the Bill & Melinda Gates Foundation, the European Union, the National Institutes of Health, and other national funding agencies.

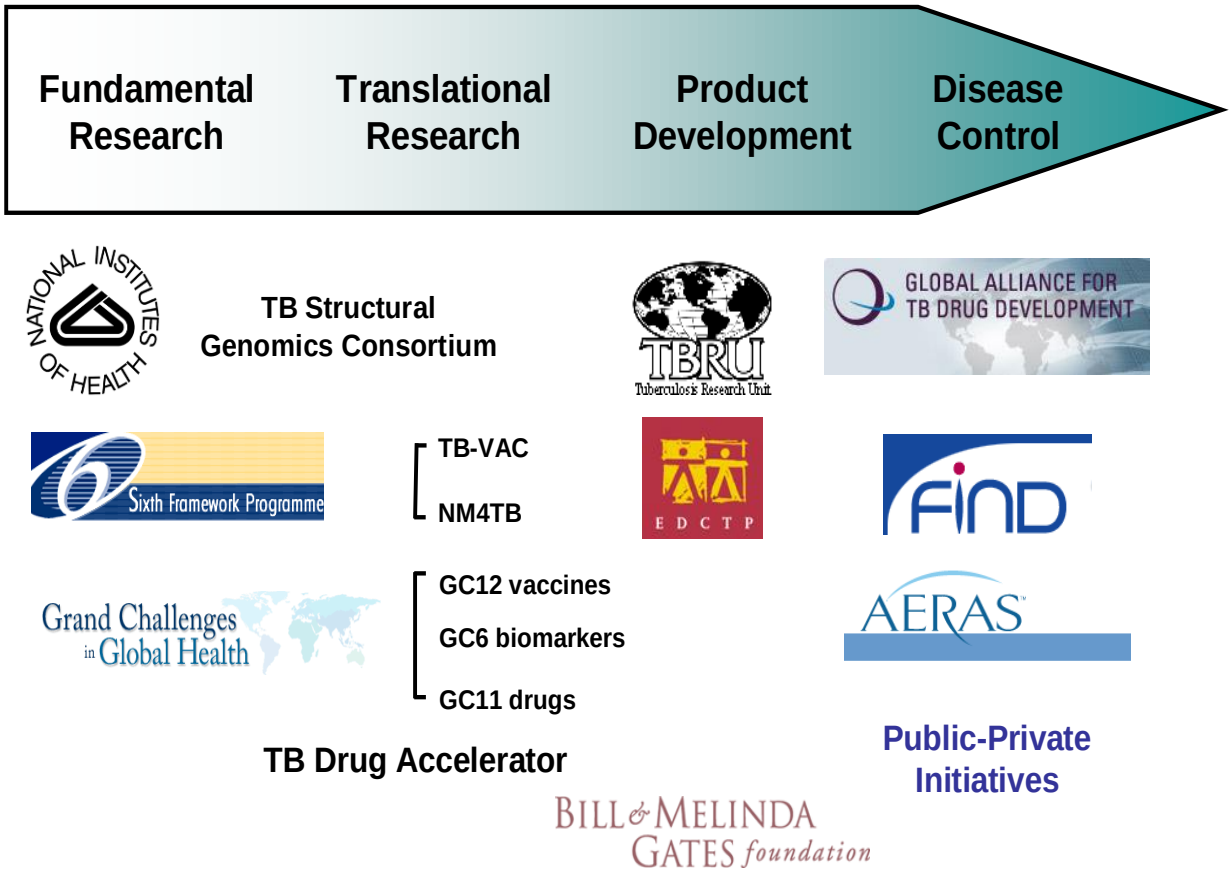

Figure 1: **A series of major initiatives have been put in place to address the R&D challenges involved in produced the new drugs, diagnostics and vaccines required for improved control of TB.**

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Vaccines: The aim of the Global Plan is to have a safe, effective vaccine available at reasonable cost by 2015. To achieve this goal, it is anticipated that around 20 vaccine candidates will enter clinical trials over the next decade. After Phase I evaluation of safety, and Phase II assessment of immunogenicity, the four best candidates will be assessed for protective efficacy in Phase III trials. The budget required to support the TB vaccine programme – including clinical trials, underpinning research, and maintenance of BCG vaccination – is approximately $3 billion over the next decade.

To date, clinical trials have been initiated for six candidates (6). Four of these are designed to boost the immune response established by neonatal BCG vaccination. These include two purified protein preparations delivered along with an adjuvant, and two viral vectors carrying genes for major *M. tuberculosis* antigens. Two further candidates were produced by modifying BCG strains to enhance their immunogenicity.

Drugs: Two strategies are being pursued for TB drug development (7). The first is based on a search for compounds with properties similar to those of existing drugs. These compounds inhibit biochemical functions essential for mycobacterial growth, and will replace drugs that have become ineffective in treatment of resistant organisms. In addition to controlling drug-resistant disease, it is anticipated that, using appropriate drug combinations, standard treatment times can be progressively reduced from the current 6-month minimum to 4 months or less.

A second strategy is to target non-replicating bacterial sub-populations that are able to persist during treatment with standard drugs and are thought to underlie the need for prolonged therapy. It is anticipated that drugs which kill non-replicating *M. tuberculosis* will allow a radical reduction in treatment times for cure of active disease, and may also be effective in rapid elimination of bacteria in individuals with latent infection. Research underpinning this strategy focuses on the need for a better understanding of the physiology of *M. tuberculosis* within human lesions. This is being addressed by analysing whole genome transcriptional profiles of *M. tuberculosis* in freshly resected tissue samples from individuals with active and latent infection. Targets shown to be essential for bacterial survival are then entered into high-throughput screens for drug discovery.

Global, regional, local: Global initiatives to combat TB have the advantage of attracting major funding opportunities and of bringing together the efforts of international experts. A potential drawback is that there may be differences in the problems that need to be addressed in different countries, and there may therefore be limitations in one-size-fits-all global solutions.

There is growing interest, for example, in possible differences between the strains of *M. tuberculosis* prevalent in different parts of the world (8). *M. tuberculosis* lineages can be viewed in terms of "ancient" and "modern" strains that may have adapted to succeed in lower and higher density human populations respectively. Differences in host-pathogen biology associated with different lineages may result in different epidemiological patterns that may affect the relative effectiveness of different control measures. Africa is characterised by the greatest diversity in terms of *M. tuberculosis* lineages.

Differences amongst human populations also have an impact on the epidemiology of TB. Age-related patterns of disease differ between Africa and Asia for example, with the peak incidence seen in young adults in most African countries displaced towards older age groups in Asia (9). There is an increased incidence of TB amongst older men in Tanzania and Nigeria, which is not seen in Kenya and South Africa: such differences may result from a combination of social and environmental influences. A high incidence of extra-pulmonary TB is seen in Ethiopia, but not in neighbouring Kenya (9). One factor that might influence this difference could be exposure to bovine TB through infected milk or meat.

Bovine TB in the global framework: The potential contribution of bovine TB to human disease was fiercely debated at the First British Congress of Tuberculosis in London in 1901. Robert Koch expressed a strong opinion that humans could not contract disease from the products of infected cattle and that control of bovine TB was irrelevant in addressing human disease. This position was equally strongly opposed by other experts, including Sir John McFadyean, Principal of the Royal Veterinary College in London, triggering a series of investigations over the next few years. While Koch maintained his viewpoint, he was opposed by the majority of scientists attending the International Tuberculosis Congress in Washington in 1908, paving the way for introduction of pasteurisation of milk, and test-and-slaughter policies to clear herds of infected animals. As a result, bovine TB is now rigorously controlled in all high-income countries. Retrospective estimates suggest that, prior to introduction of these control measures, as much as one third of human TB in the UK might have been caused by infection from cattle.

Bovine TB does not feature in the Global Plan to Stop TB. Should it? Do R&D efforts towards improved tools for human TB offer prospects for better control of bovine TB? Would this in turn have a beneficial impact on human disease? Britain spends almost £100 million per year in efforts to control bovine TB; there is no programme to control bovine TB in Ethiopia. Is there a case, from the perspective of human health or animal welfare, to try and control TB in Ethiopian cattle?

While these are straightforward questions, with potentially important implications, we lack the baseline data required to provide them with a sensible answer. We have sparse anecdotal data on the prevalence of TB in Ethiopian cattle; there are indications that prevalence is related to farming conditions and to cattle breed. We have no information about the strains of *M. bovis* that are present in Ethiopia; are there African lineages of *M. bovis* analogous to the African lineages of *M. tuberculosis*? Does *M. bovis* make an important contribution to human TB in Ethiopia, particularly to the high incidence of extrapulmonary disease?

The Wellcome Trust programme to study Bovine TB in Developing Countries attempts to address these questions within the framework of an economic evaluation of the potential impact of disease control in Ethiopia. The aim of the Stakeholders Meeting is to set this study within the wider context of farmers, veterinarians, health care professionals and government officials as a means of bringing attention to this neglected area.

References

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