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EDITORIAL

New tools for achieving tuberculosis control: progress and reflexion

WITH ITS HIGH DISEASE BURDEN and mortality, tuberculosis (TB) remains a global health emergency.[1] The history of the dramatic decline of TB, which plagued Europe in the past, has taught us that improvements in socio-economic factors are crucial for curtailing the epidemic, and that these formidable drivers will need to be tackled in parallel with newer advances in technology and science for global control of the disease.[2] The Stop TB Partnership, established by the World Health Organization (WHO) in 2000, has three working groups, for diagnostics, drugs and vaccines, focused on new tool development to achieve TB control. It has been a decade since the formation of the Partnership, and the time appears to be ripe to take stock of the progress and reflect on the future. Since the launch of the Global Plan to Stop TB in 2006,[3] increased, although not optimal, investment for the development of new tools has led to the generation of several promising technologies and a number of potentially high-quality product candidates.[4–6] A surge in research activities has also taken place, with fruitful results. With newer tools, a revised Global Plan to Stop TB (2011–2015)[7] is now available, and the direction is set with renewed intensity in care and control efforts.

A number of important new developments in diagnostics give hope for the future of TB control.[8] New WHO-endorsed tools (also due to the joint efforts of the Foundation for Innovative New Diagnostics) include molecular line-probe assays for the diagnosis of drug-resistant TB, particularly multidrug-resistant TB (MDR-TB), and an assay for the rapid detection and speciation of mycobacteria. Advances in sputum microscopy diagnosis and phenotypic methods of drug susceptibility testing, such as the microscopic observation drug susceptibility assay, are also underway. Other diagnostic tools are in development, such as the breath analyser screening test, loop-mediated isothermal amplification and phage-based tests for rapid TB disease detection, with or without concomitant assessment of bacillary drug susceptibility. A quite significant recent development has been that of a commercially available tool that rapidly detects the presence of *Mycobacterium tuberculosis*, alongside its drug susceptibility, especially to rifampicin.[9,10] This apparently robust test requires minimal manual skill/expertise, and is readily applicable at the point of care. The test holds some promise for revolutionising routine TB diagnostics in areas with high endemicity of disease and a significant MDR-TB problem. However, it still has some rate-limiting steps that are largely rooted in infrastructure and resource limitations in these areas.[11] As it is clear that the availability of new diagnostic tools does not necessarily ensure their adoption and use, the translation of policy into practice requires a thorough understanding of the barriers to implementation, as well as approaches to overcoming the obstacles. Furthermore, the two populations most vulnerable to TB, infants and children and people living with human immunodeficiency virus (HIV) infection, are either unable to produce sputum specimens or are likely to produce paucibacillary specimens, respectively. As a result, they might still have access to TB diagnostics of suboptimal performance.[11]

Regarding the development of new TB drugs, there is now a coordinated portfolio of promising compounds on the horizon.[5,12] The 11 new drugs currently in clinical development might lead to two newly approved drugs by 2015. Of these 11 agents, three are in Phase I (safety) trials, six are in Phase II (early bactericidal activity and bacteriological conversion) trials, and two in Phase III (efficacy) trials. There are also at least five candidates in preclinical development. The diarylquinolines, the nitroimidazoles and the newer fluoroquinolones appear to hold the greatest promise for clinical use in treating TB in the near future. Other potentially useful compounds might include the ethylenediamines and the oxazolidinones. Despite this encouraging progress, the global drug pipeline is still insufficient to meet needs. One of the main challenges in TB drug development is the lack of a global clinical trial capacity to conduct late-stage clinical trials to support the registration of these new compounds in clinical development. Capacity building, infrastructure development and training of local expertise in developing countries should become an essential component of any investment in testing newer drugs as well as diagnostics and vaccines.[13]

Research in TB vaccine development has also accelerated. There has been increased investment and development in relevant research over the past 5 years, resulting in strengthening of the pipeline of vaccine candidates, and furnishing of information on overall vaccine development.[6] The only TB vaccine available for use today, bacille Calmette-Guérin (BCG), was developed about 90 years ago, and its protective efficacy clearly leaves room for improvement. There is an urgent need for modern, safe and effective TB vaccines to prevent all forms of disease, in all age groups and among people with HIV infection. New vaccines are urgently needed if the goal of substantially reducing the incidence of TB is to be achieved by 2050.[3,7]

As of 2009, 12 TB vaccine candidates have entered clinical trials. Of these, nine are still being tested: five are in Phase I, two are in Phase II and two are Phase IIb (proof-of-concept) trials. At least six TB vaccine candidates are in preclinical development. The most promising candidates include recombinant forms of BCG, other live mycobacterial vaccines and vaccines based on genetic attenuation of *M. tuberculosis*.

Despite increased scientific activity, progress in the discovery of new TB biomarkers for monitoring disease activity, cure and relapse has been slow.[4] In an attempt to identify new biomarkers, several ambitious projects are now using highly multiplex assays to compare gene expression among TB patients, healthy persons with latent infection due to *M. tuberculosis*, and healthy controls with no exposure to the tubercle bacillus.[14–17] It is now thought that multiple biomarkers, when combined, may perform substantially better than any single marker, and a small number of studies have suggested better specificity and predictive value by measuring multiple parameters using techniques of proteomics, transcriptomics and metabolomics.

The past decade has witnessed a renaissance of scientific activities and funder investment in the development of new TB drugs, diagnostics, biomarkers and vaccines. An exciting and important portfolio of more efficient and accurate diagnostics, more efficacious drugs and probably also vaccines, has been endorsed by the Stop TB Partnership, and the increasing number of clinical trials on the potential candidates, particularly in the high-TB burden areas, reflects substantial progress towards attaining the targets of the Global Stop TB Plan, which, whilst ambitious, now seem realisable.

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