World TB Day 2014: Reach the three million: a TB test, treatment and cure for all

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Tuberculosis (TB) is a disease of poverty and social exclusion with a global impact. It is these underlying truths that are captured in the theme of World TB Day 2014 ‘Reach the three million: a TB test, treatment and cure for all’. Of the 9 million cases of tuberculosis each year, one-third do not have access to the necessary TB services to treat them and prevent dissemination of the disease in their communities. The StopTB Partnership is calling for ‘a global effort to find, treat and cure the three million’ and thus eliminate TB as a public health problem.1 So is the scientific community making sufficient progress to realise this target?

Early diagnosis is a cornerstone of management of the individual, we know that as the disease progresses and the bacterial load and severity of disease increase, the likelihood of a poor outcome is exacerbated.2 It is important to distinguish between diagnosis of tuberculosis and detection which is confirmation of the presence of mycobacteria. Diagnosis for the 3 million (and many more) is largely dependent on the clinical expertise of the healthcare worker, with minimal input from technology. Whereas detection requires input from microbiological services and the principal tool in this area is sputum smear microscopy. A sputum sample with no evidence of acid fast bacilli is the accepted predictor of low risk of transmission, and so early application is critical in the management pathway. With improvements such as the auramine stain and LED fluorescent microscopy, the smear remains a cost effective component of TB screening programmes.3 The emergence of multi and now extensively drug resistant tuberculosis (MDRTB and XDRTB), has accentuated the need for prompt confirmation of drug susceptibility and this is where molecular tools have potential impact. The WHO supported roll out of GeneXpert (Cepheid, Sunnyvale, USA) in resource poor settings is going ahead and we are seeing change in practice, but it is too soon to determine the public health impact of this innovation.4 The challenge for microbiology is not to get drawn into ‘one size fits all’ solution. In many settings the low technology, low cost and rapid screening of smears serves to break the chain of transmission of drug sensitive tuberculosis. Whereas, in areas of high endemicity of drug resistant tuberculosis, such as South Africa, an equally fast indication of drug resistance is essential.

Diagnosis leads to treatment. TB is curable but treatment regimens are long, toxic and complex to deliver. Following the stakeholders meeting in Cape Town in 20005 there has been a major effort to open up the drug development pipeline. There are two aspects to this, firstly new agents and secondly clinical trials. There is a new enthusiasm for exploring new compounds with action against TB and the publication of the whole genome of Mycobacterium tuberculosis allowed the interrogation of its biochemistry, opening the door for medicinal chemists to contribute their expertise. The development of MDRTB has led us to reconsider compounds previously excluded as too toxic or too difficult to administer; these drugs, such as PAS and thioridazene, are now being re-visited or forming the basis of fresh iterations of chemical screening programmes.6 After 30 years of no new drugs for TB treatment, two phase 3 trials (RIFAQUIN and OFLATUB) reported in 2013 and a third (REMoxTB) is expected to report at the time of this Editorial. These studies have shaken things up. They each have potential to make improvements in TB treatment. However, it could be argued that their real benefit lies in the development of a network of facilities capable of undertaking TB clinical trials, as exemplified by the Global Alliance for TB Drug Development and the EDCTP funded PanACEA consortium, and their contribution to the active debate about how to efficiently deliver clinical trials that have a real impact on individuals and populations. We are now looking outside the world of TB and to, for example, cancer trial methodology for innovations such as the multi-arm multi-stage (MAMS) approach.7 A significant challenge here is to convert the results of studies undertaken, with the aim of full regulatory approval, into the rather more complex environment of programmatic delivery.

The host-pathogen interaction for M. tuberculosis is manifest in the pathology of tuberculosis and has proven to be a fruitful area of immunological research. This, together with the (variable) success of BCG vaccination, has led us to the reasonable expectation of a vaccine for control of tuberculosis. There has been much innovation as the auramine stain and LED fluorescent microscopy, the smear remains a cost effective component of TB screening programmes. The WHO supported roll out of GeneXpert (Cepheid, Sunnyvale, USA) in resource poor settings is going ahead and we are seeing change in practice, but it is too soon to determine the public health impact of this innovation. The challenge for microbiology is not to get drawn into ‘one size fits all’ solution. In many settings the low technology, low cost and rapid screening of smears serves to break the chain of transmission of drug sensitive tuberculosis. Whereas, in areas of high endemicity of drug resistant tuberculosis, such as South Africa, an equally fast indication of drug resistance is essential.

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that we may be able to define a host response signature to tuberculosis.\textsuperscript{10} If successful, this approach may allow us to select those patients for whom a shorter course of therapy is adequate. From the UK MRC studies it was clear that as many as 80\% of patients would be cured with a 4 month regimen; the difficulty was that they could not be identified in advance or during treatment. A host response biomarker may well enable us to address this issue.

\textit{M. tuberculosis} is a fascinating organism with many features of its biology that are distinct from other bacteria. For this reason the TB research community has become rather insular, not necessarily drawing on the experience from the wider bacteriology community. This was further exacerbated by the apparent fall in incidence of TB through the 1960’s and 70’s. Complacency is the term that comes to mind. Despite the commitment of groups such as those led by Mitchison and Grossett, there has been very little innovation in detection and diagnosis, and no new drug introduced to first line treatment after the 1960’s.\textsuperscript{11} The declaration by WHO of TB as a global health emergency alerted us to the need for new ideas and new tools to meet this challenge. Twenty years down the line, we have rolled out new diagnostics and a new drugs pipeline that flows with the first phase 3 trials reporting at about the time of this Editorial. Similarly innovation in vaccine design and application moves forward and importantly our understanding of operational and behavioural aspects of controlling tuberculosis increases. However, we must not become complacent again. \textit{M. tuberculosis} is not just an academic challenge and as long as the 3 million exist, we need to focus all our knowledge to achieve a TB test, treatment and cure for all.

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\textbf{References}