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Detection and treatment of subclinical tuberculosis

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SUMMARY

Reduction of active disease by preventive therapy has the potential to make an important contribution towards the goal of tuberculosis (TB) elimination. This report summarises discussions amongst a *Working* Group convened to consider areas of research that will be important in optimising the design and delivery of preventative therapies. The Working Group met in Cape Town on 26th February 2012, following presentation of results from the GC11 *Grand Challenges in Global Health* project to discover drugs for latent TB.

1. The 2050 elimination goal

The *Stop TB Partnership* has set the goal of tuberculosis elimination (defined as an annual incidence of fewer than one case per million individuals) by 2050.[1] Although this is an ambitious goal in the context of global trends over recent decades, the required rate of decline is broadly in line with successful TB control achieved in post-second world war Europe and North America. The current global control strategy is guided by *Millennium Development Goal 6*, which is to reduce the incidence of cases by 2015, and the *Stop TB Partnership* target of halving 1990 prevalence and mortality rates by 2015. Historically, control efforts have prioritised identification and treatment of all cases of active TB, but this has been insufficient to interrupt transmission and there is a need to combine the existing approach with new interventions that will reduce the development of infectious cases by vaccination and preventive therapy.[2] The framework chosen by the United Nations to replace the *Millennium Development Goals* after 2015 will be critical for TB control.[3]

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Research is an essential driver towards TB elimination,[4] and the aim of the present document is to outline a research strategy that will optimise the impact of therapeutic intervention during the phase of infection prior to development of clinical TB.

Latent tuberculosis infection (LTBI) is currently defined by immunological sensitisation to *Mycobacterium tuberculosis* antigens in the absence of clinical symptoms of disease. The relationship of the immune response to the continued presence of live bacilli is unclear. This description is applicable to one third of the global population and encompasses a diverse spectrum of individuals at widely differing risk of developing active TB.[5] While the broad concept of a clinically "latent" phase of infection provides the rationale underlying preventive therapy, effective implementation will depend on stratification of individuals on the basis of disease risk rather than the presence or absence of an immune response. We propose to use the term "subclinical tuberculosis" to denote at-risk populations who would receive the greatest benefit from preventive therapy.

There is extensive evidence that preventive therapy can reduce the incidence of future disease, and current WHO guidelines strongly recommend that HIV-infected persons in whom active TB has been excluded should receive isoniazid for at least 6 months, and preferably 9 months, as part of a comprehensive package of HIV care.[6] Addition of rifapentine allows an important reduction to a three-month treatment schedule[7] in HIV-negative individuals, though the risk of reinfection imposes an obvious limitation on the utility of preventive therapy in areas with high rates of transmission.[8] Current preventive therapy involves prolonged treatment of large populations in order to prevent a relatively small number of cases. For tractable integration into global strategies for TB control, we need short, safe preventive treatments targeted at high-risk populations.

The overall strategic requirements are:

- Strategies to identify groups with subclinical TB at high risk of developing symptomatic infectious disease
- Short, simple therapeutic regimens to treat subclinical TB and prevent the development of active disease
- Integration of preventive therapy with pre- and post-exposure vaccination strategies

2. Widening the diagnostic net

The effectiveness of current control efforts is limited by incomplete recruitment of infectious cases, thereby limiting their impact on TB transmission. Prevalence surveys have shown that an important proportion of infectious individuals with bacteriologically positive sputum do not experience symptoms of sufficient severity to prompt health-seeking behaviour.[9–11] In the context of HIV co-infection in high burden settings, the prevalence of asymptomatic culture-positive TB can be as high as 8.5%.[12] Improved recruitment of prevalent cases will require expansion of the diagnostic net by increased social awareness of early symptoms as well as the incorporation of more flexible diagnostic tests into health care programmes.

Three broad criteria can be proposed as potential early markers of disease risk. The first is bacterial load. Potential biomarkers include detection of bacterial components in systemic fluids, detection of antibodies, and detection of *M. tuberculosis*-specific T cell responses based on novel phenotypic markers. These strategies are being explored in the context of definitive diagnosis of active disease, but may have alternative application as indicators of future risk. A second approach could be based on molecular markers of early pathology; for example, metabolic or proteomic disturbances related to lung damage. Blood-based transcriptional profiling offers a novel approach with potential application in this context.[13,14] The third could be novel imaging modalities that reflect bacterial load and early disease activity, which may provide important tools to track host–pathogen interactions and to discover biomarkers for different stages of infection.[5] With an increasing knowledge of systems immunology, it may be possible to identify immunological biomarkers that are precursors of future pathology.[15,16] In order to achieve the desired levels of specificity it may be necessary to combine multiple biomarkers, using mathematical modelling approaches to determine the potential utility of combining tests with lower levels of sensitivity and specificity in point-of-care tests. Finally, we should anticipate that, as the prevalence of infection declines as TB control moves towards the elimination goal, we may need to translate increasingly sophisticated diagnostic tools from research into practical application.

In summary, in order to identify individuals who would receive maximum benefit from preventive therapy, we need to identify novel biomarkers, or combinations thereof, that provide information about:

- Bacterial load
- Early pathology
- Phenotypic state of antigen-specific T cells

3. Bacterial physiology

An intuitive expectation is that clearance of the small numbers of bacteria present prior to disease onset should require less extensive treatment than active disease. The need for prolonged preventive therapy is thought to reflect either sequestration of bacteria in sites of low drug penetration, or transient periods of persistence involving a physiological state that confers phenotypic tolerance.[5] Phenotypic tolerance can be induced in a variety of *in vitro* culture systems in which bacterial replication is inhibited by starvation, oxygen deprivation, or other means, and it is likely that such systems are broadly reflective of the *in vivo* situation. Stochastic persisters that express a drug-tolerant phenotype independent of environmental signals have also been observed within an otherwise logarithmically-growing population *in vitro*, although their relevance to *in vivo* infection is unclear.[17,18] Non-replicating persistence under oxygen-starved conditions has been well-characterised, and the observation that metronidazole – a drug that has *in vitro* activity only under hypoxic conditions – can be applied successfully as preventive therapy in a nonhuman primate model[19] provides compelling evidence that hypoxia contributes to latent TB. Phenotypic tolerance is also observed during active disease, and the distinction between subclinical infection and active TB is best viewed as a quantitative difference in distribution of bacterial phenotype and load rather than as a strict qualitative difference between replicating and non-replicating states.[5] A consequence of this line of reasoning is that the targeting of phenotypically tolerant populations is of equal importance for improved preventive therapy and for shortening regimens applied in the treatment of active disease.

While technical advances, particularly in the area of transcriptomics, have allowed characterisation of *M. tuberculosis* in mouse tissues and in human sputum,[20,21] there is very little information about the physiological state of bacteria within human lesions. Studies of mycobacteria isolated directly from human sputum surprisingly revealed that the organisms are phenotypically and transcriptionally similar to bacteria adapted to hypoxia *in vitro*.[20] This conflicts with the conventional view of the origin of sputum-borne bacilli as emerging from rapidly replicating bacterial populations at the cavity surface. Also contrary to conventional wisdom, in sputum (and lesions including cavities) the bacilli are