What are the TB Program & Vaccine Approaches to Control Global TB?

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Tuberculosis Evolution, Epidemiology & World Situation

The fact that over one-quarter of humanity has latent Mycobacterium tuberculosis infection attests to the vast evolutionary success of the etiologic agent of tuberculosis (TB). Over a life-time, 7 to 10% of non-immune compromised people with latent infection will progress to TB disease as the result. This provides a continuum of transmission to naïve persons, in whom TB disease develops at its greatest rate in the first 1-2 years after infection. M. tuberculosis, a member of M. tuberculosis complex (MTBC), diversifies through gene deletion as a means to further adapt to humans (and non-human primates). Genetic analysis of MTBC suggests temporal co-existence of M. tuberculosis with hominids over the last 2 to 3 million years that further attest to the success of M. tuberculosis, a success probably grounded in the tubercle bacilli’s adaptation to the host [1].

WHO estimates 8.8 million incident TB cases for 2010, of which 1.1 million TB cases were associated with HIV infection and approximately 650,000 multidrug-resistant (MDR) cases out of 12 million prevalent cases [2]. This large burden of TB results in (i) 1.1 million deaths per year, (ii) transmission of infection to over 180 million naïve person per year (based on the likelihood that one index case may infect up to 20 contacts), (iii) the expansion of the pool of drug-resistant (DR) TB because of poor or incomplete treatment as indicated by the finding that many TB programs do not achieve the WHO benchmark of 85% treatment success of new smear-positive case. To meet this challenge, WHO and resource rich countries, through Stop TB, Expand TB, Global Fund, PEPFAR, and other initiatives, have pledged significant resources and technical assistance to build capacity to control TB in predominately resource poor countries or countries undergoing political and economic disruption. However, the contributions from donor and country meet significant challenges. Many ministries of health have insufficient capacity to provide in-country governance so that the funds are utilized in accordance to stated objectives. Country plans have clear objectives but some do not delineate measurable targets and an operational implementation strategy. TB programs are not adequately staffed to find and treat all patients and contacts, lack a system to monitor and evaluate performance, and personnel trained in epidemiological methods to gather and analyze surveillance data in order to provide polices and implementation plans. Many countries lack an appropriate laboratory network with culture and drug susceptibility testing capacity for diagnosing DR TB. Similarly, the newer Xpert MTB/RIF molecular assay is out of reach for many countries, even at the national reference laboratory.

Country Response and the Need for Technical Assistance

Given these challenges, could these weaknesses be overcome? We argue for the following approaches that are consistent with WHO guidance: 1) universal symptom screening at health centers, 2) active case finding, 3) supervised directly observed therapy (DOT), and 4) technical assistance in these areas as well as direct assistance to national TB programs to strengthen human capacity and improve systems for resource planning, mobilization, and management.

For universal symptom screening for TB at health centers, one must simultaneously screen for HIV infection, since TB is the earliest and most common opportunistic infection in persons living with HIV/AIDS (PLHIV). Importantly, HIV also alters the symptoms of TB, such that, in an immune competent person, a cough for 2 weeks or more in duration has a high sensitivity of detecting active TB, while in PLHIV, cough alone misses significant numbers [3,4]. However, the addition of fever, weight loss and night sweats to the symptom screening questions can greatly increase the sensitivity to detect TB in PLHIV [3,4]. Unfortunately, 10% to 40% who come to medical attention at some community health centers are lost to follow-up because of inconsistent symptom screening at all steps of healthcare delivery, as well as delays in laboratory testing and reporting of results. Adding to this at many peripheral health centers is the lack of more sensitive diagnostic tools to better diagnosis TB other than light microscopy, such as, by rapid molecular method, culture with DR testing and chest X-ray that remain unavailable.

Self-referral because of a perceived illness is the primary approach to identify patients with TB in many resource poor countries. Unfortunately, many patients often delayed seeking medical evaluation because they do not perceive an illness, or have first sought care from traditional medicine practitioners. To overcome the delay, WHO recommends active case finding to identify TB cases who otherwise may remain unrecognized [3]. Active case finding should include close contact tracing and targeted screening in high prevalence locale [3].

Data supporting active case detection approach comes also from the screening Haitians for TB in resident visa applicants to the USA. The screening process is rigorous including chest X-ray of persons age 15 or older (and TST positive in age <15) and sputum TB smear and culture for all individuals with an abnormal chest X-ray. Partial data from a 2 year period (2010, 2011), suggest the prevalence of active TB was 188 per 100,000 (16,501 screened, preliminary data, personal communication). This latter data strongly suggest that there is considerable under-recognition of TB and active screening even in a more limited form (by symptoms) could yield many more cases of TB. To achieve greater treatment success and reduce development of DR TB, a higher level of supervised DOT may prove to be crucial. Importantly, the performance of spot checks in the community could greatly augment the trained “accompagnateur” and potentially further improve treatment success. Lastly, as part of DOT, food supplementation should be considered because many of the patients are malnourished and food appears to decrease medication intolerance and to enhance compliance to medication. These comments are observation-based and should be tested by operational research as part of program implementation.

To more rapidly build capacity of national TB programs, technical
assistance from donor countries or programs should be utilized when available to assist in a country’s TB control efforts. Moreover, where there is in-country PEPFAR program, personnel and resources from this program could be leveraged to assist TB clinical program in the same health center or a nearby center since TB transmission is a health threat to all PLHIV.

**Finding an Effective TB Vaccine: Can we Alter Host Immune Response to M. tuberculosis?**

Investment in vaccine discovery is largely financed by countries with resources. This investment in the long term can minimize TB in these countries as the global burden of TB is reduced. Current effort towards a prevention vaccine is very challenging given that the whole genome live vaccine approach appears to be of limited effectiveness. This is evident by the low efficacy of the Bacillus Calmette Guerin (BCG) vaccine and that cure of active TB following treatment does not protect against re-infection and disease [5]. These lines of data argue for the need to take a different approach to induce cell-mediated response that is protective. To uncover such new vaccine targets, two approaches may yield new targets. They include *M. tuberculosis* gene discovery through screening for immune inhibitors induced by *M. tuberculosis* and comparative computational analysis of *M. tuberculosis* sublineage genomes associated with distinct ethnic/racial groups or regions.

The accumulated data from studies of lung immune response suggest a prominent down-regulatory immune response in active TB [6]. Through a series of comparative studies of lung immune response of TB cases at the time of diagnosis and patients with other infectious lung diseases and volunteers, our group and others have found that TB cases expressed significantly higher levels of mediators that counteract Th1 helper 1 (Th1)-type and innate immunity critical for containment of *M. tuberculosis*. Despite the concomitant heightened levels of Th1-type mediators, they are rendered ineffectual by high levels of intracellular Th1-receptor inhibitors (e.g., Suppressor of Cytokine Signaling (SOCS), Interleukin Receptor-Associated Kinase (IRAK)-M) and extracellular (e.g., Interleukin (IL)-10) immune suppressors. These modulators are a direct response to *M. tuberculosis* as many suppressive factors declined to the levels of controls by 30 days of anti-TB treatment while most Th1-type and innate immune mediators rose above the pretreatment levels [5]. Parallel laboratory studies and monitoring of lung alveolar macrophage effector, nitric oxide synthase-2 (shown critical for killing *M. tuberculosis*), support the supposition that *M. tuberculosis* actively promotes down-modulatory mediators to counteract Th1-type/innate immunity as an immunopathological strategy [5]. These studies highlight the potential application of immune mediators as surrogate markers for TB diagnosis, treatment response or vaccine response monitoring [6].

Although as yet unproven, the removal of *M. tuberculosis* specific gene promoting the expression of down-modulatory immune response could be an approach to enhance BCG vaccine effectiveness. Such an approach could utilize transposon/phage mediated *M. tuberculosis* gene disruption. Such a characterized gene-disrupted strain bank is available [7]. These specific gene disrupted strains along with wild-type *M. tuberculosis* can be monitored in vitro for induction/over-expression of down-modulatory genes (e.g., IL-10, SOCS) by *M. tuberculosis* but not by transposon/phage-gene disrupted strain[s]. Taking a similar approach we have knocked out a MTBC specific gene, cpf32. In prior studies of cpf32, it is reported that it is immunogenic and is recognized by antibodies produced by patients with active TB [8,9]. Importantly, *M. tuberculosis* cpf32 gene knock-out results in a significantly lower induction of IL-10 and SOCS genes that are probably involved in counteracting Th1-type and innate immunity critical for containment of *M. tuberculosis* [Ho JL, personal communication, unpublished data]. Therefore, pursuing a gene-disruption approach in *M. tuberculosis* and in the BCG vaccine may improve BCG vaccine effectiveness.

A second approach to vaccine discovery may be through comparative computational analysis of sublineage genomes associated with distinct ethnic/racial groups or regions. *M. tuberculosis* has undergone clonal evolution into divergent lineages typically through gene deletion that are associated with specific geographic regions and possibly with distinct human ethnic populations [10,11]. Recent reports have suggested that genetic variation [differential loss] between *M. tuberculosis* lineages may translate into measurable biological differences. Lineage-specific differences in rate of growth, ability to induce or evade immune responses, pathogenicity, and expression of virulence factors have been observed previously in vitro and/or in animal studies [12]. Lineage-specific differences in transmissibility and the resulting clinical manifestations of human TB have been previously suggested [12]. Limited studies suggest that lineage-specific *M. tuberculosis* demonstrated differences in host ethnic preference are beginning to emerge [11,13]. More recently, in a study, conducted in New York City that compared the RDRio *M. tuberculosis* sublineage to other lineages, the authors reported that RDRio strains were associated with heightened transmission as shown by: (i) a higher cluster proportion compared to other prevalent lineages, (ii) a higher secondary case rate, (iii) and cases in children. Moreover, RDRio strains were significantly associated with US-born Black or Hispanic race and birth in Latin American and Caribbean countries [12]. The RDRio sublineage is clonal in origin and was derived from a large chromosomal deletion that involved 10 genes including two proline-proline-glutamic acid (PPE) mycobacterium family genes known to be recognized by host immunity [14,15]. Shedding the two PPE genes may allow RDRio strains to delay immune control and gain a foothold as a survival strategy. Given prior reports and the finding of *M. tuberculosis* RDRio sublineage in an ethnically and racially diverse human population of New York City, cumulatively suggest a comparative computational analysis of sublineage genomes could uncover loci that when restored or over-expressed in BCG may improve host control of *M. tuberculosis*. Such an approach was conducted in conjunction with the development of a new method to study HIV variants between USA and Haiti in order to characterize genetic divergence among isolates. This new method uses existing population genetic methods but combines population genetic statistical methods with codon analysis to reveal putative amino acid sites evolving to better understand HIV response to host selection pressures [16]. This computational approach may provide information on epitopes under selective pressure, as well as putative functional domains [17].

The PPE genes are suspected to be strongly associated with antigenic and genetic variability as well as virulence [18,19]. PPE genes and specifically proline-glutamic acid (PE)-domain of 1818c have been shown to induce a preferential Th1 cellular immune response while other genes or PGRS (polymorphic GC-rich-repetitive sequence)-domain of 1818c to induce a Th2 antibody response [17,20-22]. Therefore, the protective efficacy whereby one or more of these genes or over-expressed in BCG may improve host control of *M. tuberculosis*. Such an approach was conducted in conjunction with the development of a new method to study HIV variants between USA and Haiti in order to characterize genetic divergence among isolates. This new method uses existing population genetic methods but combines population genetic statistical methods with codon analysis to reveal putative amino acid sites evolving to better understand HIV response to host selection pressures [16]. This computational approach may provide information on epitopes under selective pressure, as well as putative functional domains [17].
Summary

Control of such an ancient pathogen will require concerted global public health effort directed at strategies that will identify the most unrecognized TB cases. In addition, potentially taking new but untested approaches may lead to discovery of new targets for a TB vaccine. Through the removal of M. tuberculosis genes that induce a down-modulatory immune response or over-expression of M. tuberculosis gene that redirect host Th-1 cellular immunity may improve BCG or other whole genome live-vaccines.

Footnote

The opinions expressed in the editorial are solely that of the author and does not represent the Centers for Disease Control and Prevention (CDC), DHHS, US Government. For a comprehensive discussion on the elimination of TB in the United States of America and globally, see review cited in [23].

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References