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EDITORIAL

Can India End TB? Of Course

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In spite of India's proud heritage of having conquered smallpox and poliomyelitis, the challenge of overcoming the highest burden of tuberculosis (TB) of any country in the world may seem unsurmountable. India's extreme population density, especially among the very poor, makes control of TB a uniquely difficult challenge. Control of TB in India is further complicated by the presence of the second highest burden of multiple drug resistant (MDR) and extremely drug resistant (XDR)-TB. Nevertheless, the country is making important progress toward control, as evidenced by recent national statistics [1, 2]. Elements are already in place upon which India can build to achieve the World Health Organization goal to "End TB" (http://www.who.int/tb/post2015_strategy/en/).

Tuberculosis control is organized under the Revised National Tuberculosis Control Program (RNTCP) (2), which receives funding from the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and is designed according to the guidance of the World Health Organization (WHO). The design includes a network of Tuberculosis Units at the District and Taluka level which manage diagnostic testing by Designated Microscopy Centers (DMC) and anti-TB treatment (ATT) drug distribution and patient management. In 2014, the RNTCP provided ATT to 1,416,014 people with active TB [2], a remarkable accomplishment. The work of the RNTCP is benefitted by the efforts of the National Rural Health Mission (http://nrhm.gov.in/), which provides medical and preventive care to rural populations, including assistance with diagnosis and management of TB in many cases. The emergence of the National Urban Health Mission (http://nrhm.gov.in/nhm/nuhm.html) may augment TB control efforts among the urban poor. Approximately half of patients with TB in India are treated by private physicians, outside the purview of the RNTCP, and this effort is viewed as an important component of TB control [2]. Partnerships between government and non-governmental organizations (NGOs) contribute to control efforts in important ways, as exemplified by the Partnership for Tuberculosis Care and Control in India (http://tbpartnershipindia.org/). Despite standardized treatment being nationally operational, the RNTCP exercises flexibility in approach by which it adapts to opportunities as it continues to make progress.

The statistics reported by the RNTCP demonstrate its success as well as its opportunities to improve. In 2014, the success rate for primary treatment of TB within the RNTCP was estimated to be 88-90%, implying that more than 1 million people were successfully treated for TB. By the end of 2015 there were 30 laboratories in place qualified to perform culture-based drug sensitivity testing (DST), and 46 laboratories performing molecular testing for drug sensitivity using the Line Probe Assay (LPA) [2]. There is ongoing rapid dissemination of cartridge-based nucleic acid

amplification testing (CB-NAAT), which allows for rapid diagnosis of both active TB and the presence of rifampicin-resistant infection (rifampicin resistance is usually accompanied by isoniazid resistance, and serves as a marker for the presence of MDR infection [3]). Limitation of availability of DST has been part of the rationale for treating primary TB with first line drugs; with data indicating that only 2-3% of cases nationally are MDR/XDR infections [2]. As molecular DST becomes more widely available, it seems likely that there will be evolution of treatment practices to address patient needs.

Major opportunities exist to reduce transmission of TB, including MDR TB, by reducing the numbers of those who are most infectious and interrupting transmission of MDR TB by those already infected. The apparent laudatory success of primary treatment of TB in the RNTCP obscures the significance of treatment non-success. Non-success includes those who fail treatment and those who default on treatment or fail to complete for other reasons. In addition, approximately 10% of patients who convert to smear negative on treatment eventually relapse. Relapse has been seen to be associated with periods of treatment non-compliance during primary therapy [4]. Patients who are non-successes on primary treatment or who relapse and reinitiate treatment have extremely poor outcomes: the treatment success rate is only about 71% with mortality estimated to be 7-9%. Since 23% of patients on treatment in the RNTCP are retreatment cases, there are a very large number of patients who spend many months without being effectively treated and develop progressively advanced disease. As disease progresses, it is likely that these patients become increasingly infectious. Some of these patients fail primary therapy because of drug resistance of primary infection, the frequency of which is not currently known. However, only about 15-17% of retreatment cases are found to have MDR TB, meaning that treatment failure is likely the result of non-compliance with prescribed regimen in most cases. Reasons for non-compliance are multiple, including drug side effects, stigma associated with being on treatment for TB, concurrent HIV infection, and alcohol use disorder (AUD)[5]. Successfully addressing these challenges is difficult, but can be achieved. A major challenge and opportunity for the RNTCP is to develop innovative approaches to early recognition of incipient treatment failure and effective techniques for intervention. As the RNTCP moves from directly observed therapy short course (DOTS) to daily therapy in an effort to increase effectiveness of primary therapy, maintaining contact with patients will continue to be important, as will developing methods for recognition of problem cases and effective interventions.

It is unclear what proportion of patients with drug-resistant TB develop resistance de novo while on inadequate treatment and what proportion of patients develop it as primary infections. It is safe to assume that some develop MDR/XDR TB as primary infections, since the organisms have established transmission within the population. It may well be that most cases of MDR/XDR TB develop as primary infections, as has been observed in countries with lesser burdens of TB. Alarmingly high rates of MDR TB identified in some patient cohorts point to primary transmission being the major source of new infections [6-9].

Reduction in transmission of MDR and XDR TB

will be critical to stemming the tide of this epidemic. Certainly, increased use of molecular DST will result in more patients receiving second line treatment earlier in the course of infection, and effective early treatment will reduce transmission. However, increasing early diagnosis will also increase demand for second line drugs that are in short supply, expensive, and toxic (meaning that intensive followup is needed for effective patient management). The burden of need for treatment of MDR and XDR TB can best be addressed by primary prevention. Currently, contact tracing for TB in India is mainly focused on household transmission. Reported results of contact tracing indicated that 0-6.9% of household members has active disease, and only some of those are "concurrently infected". Only the concurrently infected cases may have been the sources of infection transmission to the index cases [10-11]. It is clear that contact tracing limited to patients' households misses more than 90% of cases that were the sources of TB transmission to the index cases, and these individuals may remain untreated and continuing to transmit for some period of time. Failure to identify these cases is particularly important with respect to MDR/XDR TB. Effective contact tracing requires dedicated effort of trained public health workers, is costly, and is time consuming. Effective contact investigation of a single case requires multiple visits with the case and investigation of coworkers and social contacts. Conducting effective contact tracing regarding MDR/XDR TB will further increase the demand for treatment of such patients in the short term, but should significantly reduce numbers of new cases in the medium and long term.

It is too soon to know whether India has truly begun to reduce the rates of new TB infections in its populace, but it is clear that success in that regard is in the offing. The standardized approach of RNTCP operations, while essential, may at first appear to be somewhat of a barrier to change. The adaptability of the RNTCP over the past two years has been impressive in response to changing needs and opportunities. Leadership that continues to evolve to meet the changing needs of the national epidemic will be essential to the achievement of the ultimate goal of ending TB. Development of new program elements that address the social and health factors that lead to primary treatment failure and adopting the goal of ending transmission of MDR/XDR TB should greatly accelerate progress toward ultimate success.

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