Connecting the DOTS: Spectre of a Public Health Iatrogenesis?

Rajib Dasgupta, I Ghanashyam
Center of Social Medicine and Community Health, Jawaharlal Nehru University, \textsuperscript{1}Chief Medical Officer (TB), Municipal Corporation of Delhi, New Delhi, India

Introduction

Significant but not surprising: Totally Drug-Resistant TB (TDR-TB) was recently reported from Mumbai, India.\textsuperscript{(1)} Despite the nation-wide implementation of the DOTS-strategy based Revised National Tuberculosis Control Program (RNTCP), the rising number of Multi-drug-resistant TB (MDR-TB) patients and those with sputum positive for AFB after 12 months of Category-IV treatment [suspected Extensively Drug-Resistant TB (XDR-TB)] is ominous; they were all treated Category I/II (or both) patients.\textsuperscript{(2)}

That all’s not well is not unknown. The mortality trend (2000-2009) reported 66,345 deaths from Pulmonary Tuberculosis in 2009, up from 10,463 deaths in 2000. Death rates (per 100,000) from TB in adults thus increased five-fold, while 100\% coverage of the country with RNTCP was attained too [Graph 1].\textsuperscript{(3)}

Experiences from Tamil Nadu (a state with one of the most responsive public health systems) portend grave messages. Among a cohort of successfully treated smear-positive cases, 15\% had died after 2-3 years and 19\% of the remaining was bacteriologically positive.\textsuperscript{(4)} Default occurring during the critical intensive phase (IP) was about 15\%; similar was the experience in Nicaragua, Spain, Turkey and Russia (specifically reported high cure, low default but high death rates among smear-positive patients).\textsuperscript{(5)} Six-fold excess mortality (than the general population) was reported from among a cohort of 2,674 patients treated at Chest Clinics of the Chennai Municipal Corporation and followed up for 600 days.\textsuperscript{(6)} Panic buttons are yet to be pressed.

Negative sputum bacteriology is the hallmark of patients successfully completing treatment in the RNTCP. Recurrence of disease after completion of treatment is increasingly being reported as is the prevalence of higher drug resistance among them (than among new cases). A study in Hong Kong found the intermittent regimen to be strongly associated with recurrence; poor adherence (particularly, during IP) emerged as an important factor.\textsuperscript{(7)} Default during IP is critical to the program not achieving its desired success. A report from Pakistan indicated halving the default on switching from an intermittent to a daily regimen.\textsuperscript{(8)}

Clinicians point to the perils of lack of individualized regimens (a tactic to ensure adherence) in national TB programs; the choice of a regimen is thus critical, varying somewhat globally. India is the only high burden country with a thrice-weekly regimen implemented nationally.\textsuperscript{(9)} A Cochrane review could not confirm whether the intermittent regimen is as efficacious as a daily regimen.\textsuperscript{(10)} Intermittent therapy may be an effective regimen in controlled program environments; it may not have been a wise choice in a strikingly diverse India. A systematic review found that patients with INH resistance treated with a thrice-weekly regimen during IP had significantly higher risks of failure and acquired drug resistance (compared to daily dosing). With INH resistance in India currently estimated to be about 15-18\%, a daily regimen in the IP is strongly indicated; Bangladesh implements a daily regimen during the continuation phase (CP) as well.\textsuperscript{(11)} Quality-assured fixed dose combinations (FDCs) are programmatically critical; India is again conspicuous as the only high-
burden country that neither uses nor has a plan for FDCs.

The WHO, in its current guidelines, strongly recommended daily therapy in both HIV-positive as well as negative populations. Other than a marginal increase in INH and ethambutol, dosage of drugs used in the thrice weekly RNTCP regimen during IP is little different than the daily regimen. The total exposure to anti-tuberculous drugs is thus less than half in case of intermittent regimens (3 days vs. 7 days per week) and made worse with problems of adherence (missed doses) during IP.

In a cryptic and stunningly blunt statement Giovanni Migliori, Director of the World Health Organization (WHO) Collaborating Centre for Tuberculosis and Lung Diseases summarized the situation: “Resistance is man-made, caused by exposure to the wrong treatment, the wrong regimen, the wrong treatment duration”. The rising phenomenon of recurring and resistant forms of TB in India is seemingly attributable to the intermittent regimen and problems of adherence during the intensive phase leading to missed doses (an unintended consequence of the ‘Directly Observed’ strategy). Despite the overwhelmingly acknowledged success of the DOTS strategy, TB remains the single largest killer (on account of communicable causes) among adults in India (and China). A five-fold rise in deaths rates is a serious matter; but inaction more so.

In a high-burden country as India, it is inexplicable why the intermittent regimen was opted for, and never critically reviewed. The current WHO guidelines, based on “strong/high grade evidence” recommends “wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy”; also noting that rates of acquired drug resistance were higher among patients receiving three times weekly dosing throughout therapy than among patients who received daily drug administration throughout treatment. The Indian Journal of Tuberculosis in a recent editorial contested the WHO recommendation of daily regimen (in non-HIV patients) by invoking the achievement of a high cure rate of 85% and cautioned about the potentials of: (i) lower adverse effects in alternate day regimen; (ii) providers opting out on account of excess workload, and, (iii) high dropout rates. This probably signals the folly of ‘conventional wisdom’ at play, ignoring these patently warning signals.

Will TDR-TB turn out to be the proverbial nemesis of the RNTCP in India? We are perhaps witnessing a form of massive public health iatrogenesis, distinct from clinical iatrogenesis. This has significant public health ethics concerns, perhaps of hitherto unforeseen dimensions. The emerging evidence merits some serious introspection.

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