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Viewpoint

Too little too late: Waiting for TB to come

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ABSTRACT

There is a new paradigm that preventing tuberculosis (TB) and addressing the reservoir of latent TB infection in combination with curing all TB cases is essential to accelerate the decline of TB rates and ending TB by 2050. However, complacency and incremental change eludes radical policy transformation needed to meet global targets. This essay explores current attitudes, policy disparities between high and lower burden settings, and what changes are needed to remove the obstacles to progress.

Achieving TB elimination requires a direct attack on the reservoir of latent infection, with a drug or a vaccine (or both) that is effective against established infection. For instance, if just 8% of people infected with M. tuberculosis are fully and permanently protected each year, incidence would fall to 90 per million by 2050 with no other intervention.[1] – Chris Dye

Imagine a garden with patches of dandelion weed. Would you pull the weeds only after it has developed its classic fluffy seed head with half of it blown in the wind? Or, would you use a comprehensive approach and pull all dandelion weeds out, those that have bloomed or seeded and those not yet bloomed? The scenario is similar to a comprehensive disease control strategy, but until this year tuberculosis (TB) control has been nothing more than passive case finding of those who are ill enough to have symptoms and have already spread TB, each to at least 10 people. This secures TB's future in society.

1. Policy disparities: low-intermediate vs. high burden countries

Tuberculosis (TB) is a curable and preventable disease, yet the ancient scourge continues to persist and grow in drug-resistant strength. Today, the global cure rate of drug resistant TB is no better than sunshine, fresh air and grandmother's chicken soup. Airborne transmission of multi-drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB) go unchecked from the shameful fraction of cases that are passively detected. Yet, we forget or ignore that acquired drug resistance can be prevented if those with latent TB infection (LTBI) never get the disease.

Preventive treatment of LTBI is a proven strategy that has maximum benefit when targeting the screening and treatment to those at highest risk of progression, especially in congregate or geo-hotspots and yet, prevention is not recommended for at-risk groups in high burden settings. Paradoxically, the WHO

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launched guidelines on the management of LTBI in 2015 for 115 countries with a TB incidence of less than 100 cases per 100,000 population.[2] Ironically, TB prevention would make a much bigger impact in high-burden settings and yet India, a country that contributes the most in the world, is left out.

The WHO also recommends comprehensive contact screening and prevention in low and intermediate burden countries,[2] yet high burden settings like India rely on limited testing and prevention to those living with HIV or pediatric contacts under 5. This sliver of prevention is too small to make any impact on case rate decline. Further, this pick and choose approach confuses healthcare workers performing this duty as well as the very people exposed to active TB. It provides a perception that those not screened for LTBI are not valued, or are invulnerable from acquiring TB. Even worse, it implies that TB is somehow a weak pathogen that can be easily controlled with limited measures.

Paradoxically, screening and prevention of persons living with diabetes, the largest contributing cause of TB in India and countries outside of Africa, has a negative recommendation from the WHO despite poorer active treatment response, higher relapse, and death rates compared to persons without diabetes.[3,4] Persons with diabetes living in high-TB burden settings do not have a right to know their TB infection status, thereby missing the opportunity of TB prevention, and to stop smoking and gain better control their blood glucose through medication, weight loss, diet and exercise.

Despite a modern artillery of studies on TB risk factors and epidemiologic tools that include genotyping, cloud-based surveillance and geo-mapping, local TB programs of high burden countries do not target populations for active case finding and prevention. Instead, high-burden programs ignore the profiles of their own cases and like robots, use global recommendations that prohibit TB screening, active case finding and prevention except to persons living with HIV or contacts under age 5.

Despite effective methods that use combined symptom screening and TB testing as a non-stigmatizing means to find subclinical and symptomatic cases as well as LTBI, active case finding study pilots focus on poorly sensitive methods such as isolated symptom review as triggers for sputum collection or chest X-ray.[5] Mass chest X-ray (CXR) screening can be effective in finding active TB; however, non-TB findings can be costly and stigmatizing to work up while LTBI, the seedbed, is totally neglected.

Finally, preventive treatment has been reduced from a daily 9–12 month isoniazid (INH) regimen to a 12-dose once a week INH-rifapentine (3HP) 3-month regimen.[2] With equivalent efficacy to 9 months of INH, a better safety profile and significantly better adherence rates, the 3HP regimen is rapidly replacing INH as the regimen of choice in US TB programs. Additionally, for more than a decade, more accurate Food and Drug Administration (FDA)-approved blood tests have been available. Like the tuberculin skin test, interferon gamma release assays (IGRAs) are aids to diagnose TB's carrier state. Unlike the skin test, IGRAs are not impacted by prior Bacillus Calmette–Guérin (BCG) vaccination or most non-tuberculous mycobacterial bacilli, and they require only one patient visit instead of two to get a result.[6] In large prospective LTBI prevalence trials in China and Vietnam comparing an IGRA to tuberculin skin tests (TST) head to head, a profound reduction in LTBI rates and a statistically significant higher progression rate were found with the IGRA.[7–9]

2. Distorted reality

While treatment of active TB cuts the line of transmission, it has no impact on the seeds of infection that have already fallen, ensuring the fate of future TB disease. Hence, ''waiting for TB to come'' is an innocent assault on the very principles of disease control by allowing an airborne pathogen to fester and spread until consumption brings them to death or the doctor. ''Even if TB transmission is interrupted completely in 2015, reactivation and relapse of old infections would still generate more than 100 cases per million population in 2050.''[1]

It is also illogical to not prevent disease in individuals and families who are living on the margins of society, who cannot afford to be sick while barely having enough for the minimum necessities of food and shelter. From a non-public health viewpoint, passive case finding undermines our Hippocratic oath of doing no harm as it encourages advanced disease and decreases the chance of cure while increasing morbidity and mortality. From a public health perspective, it is illogical to not actively pursue disease diagnosis and prevention among those patients with known risks that are causing syndemics, or surges in rates of disease.

Business as usual is not working. India provides 25% of the world's 10.4 million TB cases and despite the decline in deaths from TB in India, it contributes one third of the 1.4 million global TB deaths annually.[10] Pediatric TB rates remain high and serve as a sentinel for transmission. Drug resistant strains and incurable drug resistance continue to grow and spread, becoming part of the seedbed of tomorrow's disease. Yet, most Indian providers wait for TB to come. They do not understand the importance of the LTBI reservoir or how to diagnose it. They believe that if LTBI is treated, patients will get infected again so there is ''no use''. It is also misunderstood that treatment of LTBI could cause drug resistance. India's annual infection rate is estimated at 1.5%, hardly a high chance for general reinfection, and the bacilli burden in LTBI is much too small to harbor wild drug resistant mutants required for drug resistance to emerge. A WHO systematic review showed no evidence of acquired resistance from LTBI treatment.[2] Finally, there is a perception that LTBI treatment toxicity is similar to active TB treatment which is utterly false.

It is now clear that a comprehensive strategy of active case finding, effective treatment of all cases and attacking the reservoir of LTBI with preventive treatment is essential to achieving TB elimination. The WHO includes TB prevention in their strategic pillars to the End TB Strategy and multiple modeling studies confirm the need to address LTBI in order accelerate the decline of TB.[1,11,12] The new National Strategic Plan for Tuberculosis Elimination of the Revised National TB Control Program (RNTCP) acknowledges that scaling up TB preventive therapy is important to meet the goals of ending TB in India; yet disappointingly, it only expands screening and prevention to a mere sliver of persons with LTBI: individuals with silicosis, individuals on immunosuppressive drugs and high-risk adult contacts that are not well defined. According to

a WHO modeling study, the critical mass for accelerating the decline to end TB by 2050 is effectively treating 14% of those with LTBI along with effectively treating all TB cases.[1] This amounts to approximately 73 million persons of the estimated 40 percent of the Indian population with LTBI. This is a huge number but one that can be used to estimate the true cost of eliminating TB in India.

3. Changing the passive mindset to true action and change

It is unimaginable to have approached severe acute respiratory syndrome (SARS) or Ebola with the "wait until sick" TB approach. Why should it be any different for TB? The complacency of our TB community is mind boggling since TB kills someone every 18 seconds, more people globally every year than any other infectious agent. Our obstacles to a true call to action mimic the stealth slow nature of the TB pathogen itself. Its timescale from infection to disease is variable, unpredictable and long. It could be decades before disease emerges. Instead of thinking of it as a time bomb or land mine, we behave on a slow time scale by acting incrementally, repeating studies and collecting evidence as if time itself will solve the problem. Our obsession on the affordability and cost-effectiveness of interventions make us forget the unrelenting toll and cost caused by TB's kill rate, pervasiveness, individual financial impact, lifelong morbidity and acquired drug resistance. How can we not afford to prevent TB? We must accept the fact that if we truly want to achieve the goal of eliminating TB it will be expensive. It will cost billions, but how is that different to other investments in that price range such as the Indian space program that is considered a bargain with an annual budget in 2014 of 1.2 billion USD.

A comprehensive TB control and prevention approach will require new champions who will boldly take on human rights and TB prevention as the new paradigm and demand that advocacy, mass education, educational and treatment centers of excellence, and adequate program funding are prioritized. Rapid scale up and investment in TB programs are needed from local, provincial, national and international funders. Surveillance systems and bidirectional data sharing between national and local programs need to be enhanced to target and determine interventions and track their progress.[13]

A shift from dullness and complacency to action will require looking in the mirror of truth. "Waiting for TB to come" is neither a convenient or affordable option. It is a rationed approach and not a logical disease control choice. Let's not kid ourselves: our goal of TB elimination by 2050 is but a pipe dream without aggressively draining the infection reservoir of LTBI. We have a choice to rise up and prevent TB now or just stay with business as usual, preoccupied with the usual excuses. . .while waiting for TB to come.

Conflicts of interest

The author has none to declare.

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