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Editorial

Is There Any Hope for Preventing Replacement of All Drug Sensitive Tuberculosis Cases by Drug Resistant Tuberculosis?

Tuberculosis (TB) is a bacterial disease caused by *Mycobacterium tuberculosis* that can be treated effectively with a combination of anti-TB drugs. However, the use and misuse of anti-TB drugs, such as using a wrong drug, or not completing the course of treatment, may result in developing drug resistance known as acquired drug resistance. Tuberculosis occurs worldwide and remains an important cause of morbidity and mortality in many countries including India.

In India, there was an estimated 2.8 million new cases of TB causing death to 0.48 million people in 2015.[1] The TB cascade of care in Indian public sector carried by the Indian Council of Medical Research (ICMR), World Health Organization (WHO) and Harvard Medical School estimates 2.7 million cases of TB in India. Number of TB patients registered in India for the treatment in 2014 was 1.4 million and 0.38 million were notified from private clinics and hospitals between June 2014 and December 2015. Over a million of patients are missing and how they are treated, government has no information.[2] In India, prevalence of multi-drug resistant TB (MDR-TB) among new and previously treated patients was 2.5% and 16%, respectively.[1] It is estimated that 130,000 cases of MDR-TB/rifampicin resistant TB (RR-TB) emerge every year, of which 79000 were among notified cases of TB in 2015. Out of these 79000 MDR-TB/RR-TB cases, only 28876 (36%) were diagnosed and 26988 (34%) were started on anti-TB therapy with a success rate of 46%.[1] Also around 21% of MDR-TB cases are resistant to flouroquinolones and 30% cases of MDR-TB are resistant to either flouroquinolones or second-line injectables.[3] Since 2011, there have been a rising instance of extensively drug resistant TB (XDR-TB) in India and this has become a serious emerging threat to public health. According to the data reported on XDR-TB from India, it varied from 1.5% to 11% of MDR-TB cases.[4-7] It is estimated that in India, about 8000 XDR-TB cases emerge every year.[8] In 2015, 3048 cases of XDR-TB were diagnosed and 2130 cases put on treatment with a success rate of 31%.

Now there has been reports of TB having resistance to additional drugs beyond XDR-TB.[3] Even there has been a case where resistance to both bedaquiline and delamanid in the same patient has been reported.[9] This spread of resistance has raised the possibility of programmatically incurable TB for which there is not enough effective drugs to form an effective curable regimen. This would halt the progress made in recent years to control TB in India. Dheda and colleagues[3] have now sounded even greater alarm regarding drug resistant TB (DR-TB) pandemic on a global scale and described that every year strains of DR-TB will emerge that will be more transmissible, more difficult to treat and more widespread in the community. A new study[10] using a compartmental model to forecast the increase of MDR-TB and XDR-TB cases by 2040 in four countries (India, the Philippines, Russia and South Africa) with an already high burden of TB. The model predicted an increase in percentage of MDR-TB to 12.4% in India by 2040 compared to 7.9% in 2000. The study also predicted percentage of XDR-TB among incident MDR-TB will reach to 8.9% in India by 2040, indicating that India could witness an alarming spike in cases of MDR-TB, XDR-TB and incurable TB in the next two decades.

It is suggested in modelling analysis[11] and recently shown in kwazulu-Natal, South Africa[12] that most new MDR-TB and XDR-TB cases now reflect transmission in communities between man to man rather than acquiring during treatment. While better access to treatment programmes will reduce all type of DR-TB, these alone will not eradicate the problem as current efforts may not be enough to reverse the spike. Practice for the management of individual patients in a setting with high TB burden is not sufficient to prevent the emergence of all types of DR-TB. So a big question arise "Is there any hope for preventing the eventual replacement of all drug sensitive TB cases by MDR-TB, XDR-TB and incurable TB?"

There is an urgent need to dramatically step-up efforts to break the cycle of transmission and to rapidly find and treat all TB cases. It requires research into additional control measures to control the spread of MDR-TB, XDR-TB and incurable TB. These measures may include early detection, reducing the number of patients who do not complete the treatment and providing tailored treatment regimen depending on drug susceptibility test. We cannot focus solely on curing people with TB and MDR-TB and XDR-TB, if we want to halt the epidemic. Even if we prevent the development of new MDR-TB and XDR-TB cases, there are enough current cases to keep the epidemic going. MDR-TB, XDR-TB and incurable TB will

continue to be an increasingly dangerous threat so long as resistant strains spread through the air from one person to another. We must prevent the spread of all TB cases from person to person by strengthening infection control measures, focusing on household, health centers and communities and by developing more effective diagnostic tests to rapidly and accurately detect MDR-TB and XDR-TB. Diagnostic capacity for MDR-TB and XDR-TB in the form of expert MTB/RIF scale up[13] and improving susceptibility testing for second-line drug by genotype MTBDRsl assay (second-line Line probe assay)[14] is more accurate, more reliable and more widespread than ever before.

The Year 2016 heralded first time in history that treatment regimen for MDR-TB of less than one year duration was recommended on a global scale.[15] If this regimen's effectiveness is proven in larger trials, the global incidence of MDR-TB could fall by 20% or more.[16] Further, preliminary evidence suggests that a six-month all oral regimens using newer drugs for XDR-TB might achieve very high rates of treatment success.[17] Target regimen profile for improved treatment of drug susceptible and DR-TB has been developed and disseminated,[18] providing a road-map to the treatment regimen that could rival the tolerability and efficacy of current first-line treatment. Additional tools like point of care test, preventive therapy using novel drugs are on the very near horizon. Deeper understanding of the epidemic of DR-TB should be dealt with renewed financial commitment and multi-faceted response may result in nation-wide drop in the incidence of MDR-TB and XDR-TB cases. Such reversal has been demonstrated in low-burden countries, like USA[19] and even in high burden countries, like Estonia[20], Kwazulu-Natal[21], South Africa[21] and an equivalent success rate as high as 89% has been achieved in resource-constrained countries, like *Niger*.[22]

In conclusion, while MDR-TB, XDR-TB and incurable TB continued to evolve, the response to this growing threat has not been an idle one. It is upto us to respond, as our tools for the diagnosis and treatment continues to improve, there is no reason to believe that we cannot produce similar results more broadly and MDR-TB and XDR-TB epidemic can be reversed completely. Given that MDR-TB and XDR-TB is now a transmitted disease, we cannot control it simply by improving our diagnosis and treatment of drug susceptible cases. What is needed now is a stronger commitment by the governments of high burden countries to use existing and emerging tools as a part of comprehensive and targeted response to MDR-TB and XDR-TB and it should also be matched by appropriate financial help.

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