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Review Article

Regulation of the Hurdles in Addition to the Obstacles Associated With the Eradication of Drug Resistant Tuberculosis Epidemic in India - Stress on the: National Tuberculosis Elimination Programme

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Abstract

India possesses a greater tuberculosis (TB) load in contrast to any other country, that accounts for a calculated 25% of the global load. Drug resistant tuberculosis (DR-TB) is a biggest public health difficulty in India. Massive alterations In the drug regimens is the requirements, for patients with DR-TB, that are mostly correlated with poor sticking to the treatment in addition to less than optimal treatment results in contrast to the drug sensitive tuberculosis. This hurdle of tackling DR-TB is key with regards to India, since India aids In greater than27% of global DR-TB patients. In the last few decades India has, become energetic with its fight against tuberculosis, with an execution of a revised National Strategic Plan (NSP) with the aim of eradication of TB by 2025. Nevertheless, for accomplishment of this aspiring objective, the requirement for India is to take a multistep strategy with regards to the DR-TB management. Inspite of consistent actions done via the National Tuberculosis Elimination Programme, considerable hurdles are faced by India in the context of DR-TB –care, specifically in peripheral, apart from resource restricted endemic areas. Here certain biggest short comings that are correlated with the escalation of the DR-TB epidemic in India as well as their influence.

Keywords: Tuberculosis; Epidemic; India; DR-TB; Diagnostics; MDR-TB Management

Introduction

India has been known to possess the maximum incidence of Tuberculosis (TB) as well as mortality besides keeps continuing to be possessing the number 1 status with regards to any country [1]. As per the India TB report 2020, a calculated 2. 69 million patients of TB manifestations in India which accounted for one fourth of all the global TB patients existed [2]. Subsequent to it getting initiated in 1997, the National Tuberculosis Elimination Program (NTEP) (previously the Revised National Tuberculosis Control Program) has attained significant success besides moving multiple steps forward via the policy alterations with the objective of attainment of reduction with regards to TB burden in India. The National Strategic Plan (NSP) constitutes the regulatory framework that has been laid down by the Indian government for showing the path to TB associated stakeholders in addition to crucial policy makers, central as well as state authorities along with other health bodies with regards to the total removal of TB. The biggest aim of NSPs is in collaboration with the World Health Organization (WHO) End Tuberculosis Strategy besides the United Nations (UN) Sustainable Development Goals (SDGs) for this total removal of TB. In the year

2017, India's revised NSP was projected (2017-2025) with a very high aim in addition to a goal believed to be a big challenge of total deletion of TB by 2025, that is 5 yrs prior to the 2030 target that was laid down by the UN-SDGs in addition to the WHO End Tuberculosis Strategy [2]. With regards to the attainment of the aim of the NSP, India needs a reduction of TB patients by 10% each yr in contrast to the global target of 2%. The revised NSP has given new advocates that is inclusive of escalation of a lot of rapid molecular diagnostic services with the idea of reduction of the burden of the drug resistance Tuberculosis (DR-TB) [2]. Inspite of important actions, there has been a slow reduction of incidence (1.8%) with a considerable escalation of the amount of drug resistant (DR) patients [2], that has been calculated to constitute 27% of the total world's patients [3]. A combination of India, China along with Russia account for greater than 50% of the multi drug resistant Tuberculosis (MDR) patients in the globe (Figure 1) [1].

Figure 1: Courtesy ref no4-Global incidence of MDR/RR-TB (in thousands). India has the highest incidence burden of MDR/RR-TB (135,000), followed by China (73,000) and Russia (56,000). MDR, multidrug-resistant; RR, rifampicin-resistant; TB, tuberclosis. Source from: World Health Organization. Tuberculosis; 2020 [1].

For the management of DR-TB, India initiated via the Programmatic Management of Drug Resistant Tuberculosis (PMDT, earlier Directly –observed Treatment Short Course (DOTS-Plus) that came under the 2007 NTEP Guidelines, that got liberated in 2010 as well as subsequent updates occurred in2017 as well as 2019 [5]. Standards for TB care were liberated in 2014, that were inclusive of Comprehensive Guidelines with regards to the treatment in addition to management of DR-TB [6]. The existent update with regards to services of PMDT, under the revision of NSP were inclusive of crucial policy revision in collaboration with WHO advocates for DR-TB care like Universal drug susceptibility testing (U-DST) with regards to assumed TB patients, escalation of cartridge based nucleic acid amplification tests (CB-NAAT), True NAT in addition to line probe assay (LPA) services, advisory Guidelines with regards to shorter/longer oral regimens for MDR along with rifampicin resistant (RR) patients besides centralization of DR-TB services with the idea of achievement of good access [5]. Inspite of important leaps in addition to a robust political will under the NSP, management in addition to treatment outcomes of DR-TB have continued to be less than ideal. Documentation from DR epidemiological surveys from various states in India have demonstrated a high Prevalence of MDR-TB in prior patients in receipt of treatment [7]. Various heterogenous factors have modulated the success of DR-TB management in India. Here briefly, certain maximum challenges/hurdles, besides what it implies with regards to correlation with causation of reduction in the escalation of TB epidemic in India is detailed.

Low Information as well as absence of Quality of Patients' Treatment in Private Sector

TB is a disease that needs notification. The word notification implies that once a diagnosis of TB is made it gets documented in the National surveillance system as well as to the WHO [8]. This notification was made compulsory by the Indian government in 2012, both for public in addition to private sector. The Ministry of health as well as Family Welfare gave another order as per which doctors, Pharmacists, chemists, along with laboratory staff might face jail in case of not informing with regards to TB patients. Inspite of these robust rules still India accounts for about25% of the unreported cases all over the globe [2]. As per WHO about 1 million TB cases from India do not get reported each year [1]. According to the notification results from various states of India pointed to the statement that this notification remains constantly high with regards to the public sector as compared to that from the private sector that continued to be subideal (Figure 2) [9]. The diagnosis in addition to treatment in the public sector, like the hospitals that get controlled by the states, remains low cost or free of cost for the TB cases, that get documented. Conversely the care of the TB cases, from the private sector, like the private clinics in addition to other private tertiary care hospitalsis not controlled by the NTEP, in view of poor notification rates. Furthermore, state correlated health insurance is not fully acceptable to the private hospitals in India. Although a lot of cost is incurred out of pocket with least insurance advantages, a biggest chunk of the presumed TB patients still come to get treated as well as take treatment from the private sector. In 2016, it was documented that practically 2/3rs of the cases with a label of TB diagnosis per year look for getting treatment in private sector in India [9]. During, 2020, itself about34% of the total calculated TB cases got documented via private sector which was a significant 40% escalation from the earlier yrs [2]. Additionally, approximately 50% of the relapsed patients, that had got notified by the public sector get treatment in the private sector prior to reaching the NTEP [10,11].

Figure 2: Courtesy ref no 4 - Notification rates (by percentage) from the public and private sectors in different Indian states. Source from: Arinaminpathy N., *et al*. Lancet Infect Dis 2016;16:1255-1260 [8].

Of the biggest causes of worst treatment results is the absence of quality regulation in addition to common utilization of treatment which had received approval with regards to NTEP by the private facilities. Under there vision by NSP, the Indian government brought out the Joint Effort to Eliminate Tuberculosis, that was a project which received funds from abroad with the idea of escalation of the quality of TB care that was attained by the patients in the private sector [2]. Inspite of important actions, the to-

tal success with regards to treatment for TB in 2018 was just 35% in the private sector as compared to79% in the public sector [2]. Greater political will in addition to endorsement from the policy makers besides stakeholders for the utilization of WHO/National-endorsed Guidelines for DR-TB care in the private sector will aid with regards to enhancement of the treatment results. Additionally, more actions are required for escalation of the utilization of National-online TB notification portal ''NIKSHAY'' by the private doctors in addition to health providers in urban, peri-urban as well as rural areas for escalation of DR-TB-surveillance, besides notification rates from these areas.

Restricted diagnostic ability for DR-TB in peripheral as well as areas in possession of restricted resources in India

Escalation of the diagnostic ability as well as fast estimation of DR-TB patients is key for the therapy of DR-TB patients in India. As per the WHO for the countries that possess a greater susceptibility of drug resistance, the generation of rapid estimationinvestigations in addition to enhancement of the management of DR-TB patients has achieved an urgent status [6]. The absence of rapid in addition to immediate diagnosis in an area with Restricted resources in India besides high endemicity exerts a maximum restraint with regards to DR-TB treatment. Secondary to that it is calculated that about 56% of MDR-TB cases keep remaining without diagnosis in India [12]. Delay, besides inefficient management can also be responsible for further spread of DR strains within the community. More recently, in these decades important generation of rapid molecular investigations for the diagnosis of DR-TB have been done. The list of the WHO approved CB-NAAT like GENE Xpert, Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) have aided for the diagnosis of DR-TB. GENE Xpert represents an automated real time-Polymerase Chain reaction (PCR) system in addition to is better for the simultaneous estimation of MTB complex, besides rifampicin resistant (RR) patients in under 2hrs as compared to the latest culture dependent methods that might take a lot of days/wks [13]. GENE Xpert, was believed to be the major aspect of (U-DST) Guidelines by NTEP for high risk groups for yielding a correct regimen TB patients. In India despite RR patients have been effectively considered an ambassador for MDR-TB [14], high economic pressure outside the public sector in addition to reduction in sensitivity of the assays in a smear negative cases are the major challenges with regards to the provisions of precise estimation of DR-TB as well as RR-TB in presumed -TB patients. In addition GENE Xpert usually fails to estimate the resistance that is outside the 81bp rifampicin resistance determining (RRDR) area of the rpoB gene thus it misses a big chunk of patients with mutations at separate areas [14].

With regards to tiding over these problems that are correlated with the reduction in sensitivity to the Xpert MTB/RIF assay, WHO in 2017 advocated replacement of the existent Xpert MTB/RIF cartridges with a next generation Xpert MTB/RIF assay (Xpert MTB/RIF Ultra) [15]. These expert Ultra cartridges are inclusive of a bigger chamber for aiding a greater volume as well as 2 MTB targets for the maximum diagnostic sensitivity in smear negative cases. Outcomes from studies that contrasted the diagnostic precision of Xpert MTB/RIF Ultra to Xpert MTB/RIF assay the observation was that the sensitivity of Ultra assay was 17% greater in smear negative samples as well as 12% greater in people who stay with HIV virus, thus with a 3.2% lesser specificity rates in contrast to Xpert MTB/RIF [16].

Other alternate methods to CB-NAAT systems are inclusive of commercial line probe assay (LPAs) like Genotype MTBDR Plus (Hains Life sciences, Nehren, Germany) that are further advocated by WHO in addition to possess extra benefits of escalation of sensitivity besides estimation of MDR (isoniazid as well asrifampicin) clinical samples [17]. Nevertheless, since their application is not feasible for sputum smear negative cases it significantly overcame their effectiveness with regards to MDR-TB in contrast to CB-NAAT. by WHO advocated the utilization of fast second line LPAs (MTBDRs1/Genotype MTBDRs 1ver 2.0) for the estimation of DR to fluoroquinolones as well as other second line drugs Plus in MDR-/RR) patients [18]. Despite, the outcomes of these investigations are key for placement of personalized oral regimens, they are usually believed to be secondary investigations to CB-NAAT for the corroboration of DR. Furthermore, irrespective of the benefits in addition to restrictions of both CB-NAAT as well as LPAs their nonavailability in maximum diagnostic centers, peripheral laboratories in addition to biggest private sector markets has resulted in low estimation rate of MDR-TB patients in India.

With regards to further escalation of, besides improvement of availability of CB-NAATsystems for the diagnosis of DR-TB in peripheral regions, an introduction of point of care (POC) system known as True Nat™ was done in India [19]. True Nat™ represents a native micro real time PCR test, that was generated by Molbio diagnostics/Bigtec Labs, India which provides higher sensitivity in

contrast to the usual GENE Xpert with regards to diagnosis of tuberculosis as well as pickup of RR (True Nat™ MTB/MTB-RIF-Dx). Additionally, True Nat™ provides the extra benefit of its, utilization intricately to the POC, besides for its operation is possible by the utilization of battery that makes its aid of particular, use in low resources in primary healthcare settings in least infrastructure along with resources. The Indian Council of Medical Research (ICMR) in July 2020 pointed that the WHO advocated the True Nat™ platforms as the first line test for the Original diagnosis of tuberculosis as well as the estimation of RR [20]. Whereas these generations have proved to be attractive, besides can significantly reinforce the diagnosis of DR-TB, the existent application of True Nat™ machines has been fixed to restriction of the investigations regions in just certain. Indian states. Furthermore, of the key gaps that has been the responsibility for the deterioration of the India's TB deletion targets is the absence of the diagnostic ability of the present CB-NAAT assay for pick up for DR-to second line drugs. This restriction is proved by the National statistical outcomes from 2019 that pointed to a greater case rate of DR-that is other than MDR (62%) (in view of greater manageability) in contrast to MDR documented in new (7%) in addition to cases that received earlier treatment (31%) (Figure 3) [2]. Secondary to this inspite of escalation of success of robustness of CB-NAAT s, only 44% of the calculated MDR patients got a diagnosis in India in 2019 [12]. During July 2020 the Foundation for Innovative New Diagnostics in addition to Cepheid Inc. gave the announcement of initiating the new Xpert MTB/XDR cartridges, that aid in inflated DR portrayal against a lot of drugs (isoniazid, ethionamide, fluoroquinolones, amikacin, kanamycin, capreomycin with a reversion time of 90minutes [21] shortcomings of the existent CB-NAAT systems they are still undergoing assessment by the WHO as well as it might consume significant time for connectivity with regards to (economical benefit evaluation in addition to infra structure) subsequent to introduction into the Indian market take treated.

Figure 3: Courtesy ref no 4 - (A) overall and (B) state-specific incidence data of DR/MDR-TB in new and previously treated cases. DR other than MDR includes mono-resistance to either rifampicin or isoniazid. DR, drug resistant; MDR, multidrug-resistance; TB, tuberculosis. Source from: Central TB Division, Ministry of Health and Family Welfare. India TB report 2020: national tuberculosis elimination programme annual report [2].

Shortcomings correlated with adhering to treatment as well a spublicizing New treatment guidelines of MDR-TB amongst health providers

Sticking to the treatment is key with regards to attainment of TB regulation in addition to elimination. Nevertheless, the length in addition to complicated nature of treatment protocols possess a negative influence on the patients regular adhering to these protocols, besides playing an important part in the generation of DR-TB. The standard TB treatment regimens for new patients need patients to consume the complicated combination of drugs for 2mths in the initiation phase that is followed by 4mths during the continuation phase [7]. In the context of DR-TB, there is escalation of time of treatment to 24-48mths as well as required a combination of second line drugs in addition to injections. Although these drug combinations are robust, they might possess robust adverse actions which can interfere with the patients continuously adher-

ing to treatment, hence cause less than ideal treatment results, besides escalation of the risk of mortality in addition to morbidity in contrast to the therapy for drug sensitive TB [22]. In view of this the success rate of MDR-TB treatment is about 48% in contrast to the Global success rate of 56% [13]. Investigators with regards to the reduction in drug toxicity besides the time period entailed has been a significant objective of the WHO's End Tuberculosis Strategy during the last 2 decades [1]. Two more robust drugs in possession of less toxicity like bed aquiline as well as delamanid got liberated [23]. The WHO issued its newer Guidelines in 2018 where they advocated a total oral regimen for MDR-TB, that got updated subsequently in 2020 where they gave encyclopaedic details with regards to management of DR-TB in developing countries that possess low resources [24]. This was inclusive of a shorter time duration (9-12mth) oral regimen with lesser concentration on injections that was inclusive of categorization listing of the second line drugs (A, B, C) for personalized therapy as per the Identification of the drug resistance. As per Indian context the existent guidelines with regards to DR-TB management that are in parallel with WHO advocate are inclusive of U-DST (Xpert MTB/RIF in addition to second line LPA for all the assumed. TB patients in addition to short duration MDR-TB regimen comprising of 9-12mths [25,26]. In the updated global guidelines there is a choice of utilization of a short duration regimen that are inclusive of injections or personalized long time oral regimens with the utilization of listed drugs (that includes bed aquiline).

Despite, appearance of being attractive, India 's National TB Programme is not bereft of any hurdles that are inclusive of i) execution ii) trainining besides iii) observation for side effects with the idea of National wide implementation of this Programme.

Additionally, India is loaded with a massive private sector market in addition to witness the issue of making the private care providers up to date with regards to the commonly altering global influencing for the DR-TB management. There is existence of lots of noninsured patients of TB (that get missed by the National TB Programme, as well as look for treatment from the private sector, that might not possess up to date knowledge with regards to treatment of TB or do not practice the existent PMDT Guidelines, for the DR-TB management. Moreover, whereas the MDR treatment regimen is free in public sector, the same does not hold true for the private sector where massive expenditure gets incurred. For the public sector lot of schemes are existent that are inclusive of a direct benefit transfer (DBT) schemes which gets directly transferred to the bank account of the recipient. One extra scheme is the Nikshay Poshan Yojana (a nutritional supplementation which gives incentives to the TB patients with regards to nutritional delivery the moment notification is done that is followed by the nutritional addition subsequent to the initiation of treatment via the therapy duration of as an anticipated reward. Besides that certain rewards are kept in the form of notification incentives to the private care providers or those that provide the information or notify the government via the ''NIKSHAY'' portal ii) incentives concerning the transport for from the trial/remote regions in addition to extra monetary or other support for those who are caring for the TB patients [2].

In the private sector whereas the Indian government's Pradhan Mantri Jan Arogya Yojana (Prime Minister's schemes) that gives restricted insurance with regards to the in patients treatment for those belonging to the economically poor areas, there is no cover of OPD cost, besides bad incentives with regards to TB correlated hospital admission. For attaining reduction in expenditure in private sector the NTEP is trying to get mixed private -public sector policy to get the maximum TB care via an Universal Access to Tuberculosis care. Whereas, certain pilot pogrammes in little states follow utilization of free medicines from the NTEP, robust ensuring policies or guidelines have not been laid by the TB Programme with regards to private distributors of free medicines, that can cause lot of cost which might prove to be disastrous. Documents pointed to an average expenditure of treatment of pulmonary MDR as well as DR-TB in private health setup settings varies amongst US5000$ along with -8000$ in contrast to US50-100$ for the therapy of drug sensitive TB which proves to be disastrous, massive expenditure on the family of the patients [27]. Absence of quality treatment in addition to massive expenditure in the non controlled private sector are the key causes for poor adherence of treatment besides bad treatment results for MDR-TB patients in India.

Despite, updated treatment regimens will aid in the enhancement of adherence of treatment in addition to reduction in the risks that are correlated with prolongation of the drug consumption. Significant upgrading of the TB health infra structure is the requirement for India to continuously keep being parallel with the fast alterations in the global perspectives for DR-TB treatment, in addition to incorporation of these alterations into National policy with regards to fast as well as timely spread these to the meaningful health providers.

Absence of studies with regards to molecular epidemiology as well as transfer dynamics for the MDR-TB in case of high endemic regions

Studies with regards to molecular epidemiology represent a key resource for getting insight in how it gets disseminated dynamics. With the escalation of the generation of DR-strains, enhancement of genomic studies are the requirements for estimation of the characteristics of MDR-TB patients in view of particular strains, in contrast to the continuous spread in rural as well as urban areas. The utilization of complicated genotyping approaches have got done widely with the aim of evaluation of epidemics, that implicated MDR-TB isolates [28]. These tools possess the utility for deciding the recent factors have the responsibility for the spread of MDR-TB-isolates, besides aiding in better regulation programme In the initiation of prevention of expansion of MDR-TB of the local or global population amounts. With the possession of cultural diversity in addition to heterogenous populations that are residing in rural as well as urban areas. Hence the anticipation of the exposure of the host to genetically variable types of Mycobacterium Tuberculosis genotypes. In these population dependent studies, isolates that share akin phenotypes, besides WHO advocated rapid, molecular laboratory investigations strategies like the Cepheids GENE Xpert as well as Hains LPAs yield little or just indirect knowledge with regards to drug sensitivity. During an observation study that was conducted in PD Hinduja hospital in Mumbai, of the MDR-TB patients that were recruited for a short time MDR-regimen, over 5% qualified that was dependent on the clinical properties in addition to the DST outcomes [29]. Of the different genetic investigations, next generation sequencing (NGS) has proved to be a strong diagnostic approach for the exhaustive characterization along with estimation of mutations in DR-strains [30]. As compared to rapid molecular assays, NGS assays, possess the capacity of provision of comprehensive, besides knowledge in details with regards to sequence for a lot of gene areas or whole-genomes of significance. These studies are of high significance with regards to public health, as they aid in programmes for estimation of population level risk factors for spread to prove altered public health approaches besides evaluation of the success of regulation methods. Although, benefits are there of NGS platforms, lot of hurdles are existent with regards to middle income countries like India due to cost prohibitions, requirements of staff that have been adequately trained in addition to absence of easy availability of data evaluation besides data storage solutions. With the idea of facilitation in addition to enhancement of anticipation of genetic resistance with regards to DR-TB along with amelioration of the challenges correlated with the evaluation of whole –genome sequencing results, the Comprehensive Resistance Prediction for Tuberculosis: that is an International Consortium Project (CRyPTIC) got floated in 2017. CRyPTIC introduction has been done as a collaboration project with the participation of MRC Newton Fund, Wellcome Trust in addition to Bill and Melinda Gates Foundation whose objective is provision of exhaustive statistical solutions for the potent isolation of genetic mutation patterns that are correlated with DR-strains all over the world [31]. The generation of CRyPTIC is oriented with the WHO End Tuberculosis Strategy goals with regards to provision of fast as well as moulded treatment approaches for the DR-cases through precise genetic anticipation programme. Encouragement of the public involvement, besides generation of association with various health associated institutions over the 4 continents. In India 2 Mumbai placed institutions, namely, PD Hinduja hospital, as well asMedical Research Center as well as Foundation of Medical Research are a part of CRyPTIC already. In coming future, the other public as well as private sector organization taking part in this CRyPTIC projects would aid further in the rationalization of drug regimens, besides reinforcement of the treatment results in MDR-TB specific patients.

Conclusions

Having reviewed the advances in diagnosis and Management of female Genital Tuberculosis, Comprehensively here we attempted to prohect this minireview with regards to in diagnosis and Management of drug resistant tuberculosis that has assumed epidemic proportions in India [32].

Inspite of the coordinated actions of the National Tuberculosis Elimination Programme, there is escalation of MDR-TB epidemic in India. Cooperative actions are required for supporting public-private partnership for escalation of notification date of the TB patients, besides enhancement of the quality of care with regards to DR-TB patients. The enhancement of reliability of diagnostic ability for both first in addition to second line anti TB drugs, total utilization of besides execution of the 2020 WHO treatment guidelines in National policy, besides the spread of those guidelines across the private sector would result will hasten the effectiveness of treatment as well as enhancement of treatment results. Isolation of different genotypes of Mycobacterium Tuberculosis besides studies

with regards to dynamics of spread, with the idea of Identification of the modulators of the transfer of MDR-TB might prove to be of utilization of for estimation of parameters for the generation along with strengthen the Programmatic management of drug resistant Tuberculosis in India.

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