

First National Anti-Tuberculosis Drug Resistance Survey (NDRS) from India - An Eye Opener

Gyanshankar P. Mishra^{1*}, Jasmin D. Mulani²

¹Department of Respiratory Medicine, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India

²Department of Biochemistry, Government Medical College, Nagpur, Maharashtra, India

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*Correspondence:

Dr. Gyanshankar P. Mishra, Associate Professor, Dept. of Respiratory Medicine, Indira Gandhi Government Medical College, C.A. Road, Nagpur, Maharashtra, India- 440018;

Telephone No: 91-9850349074;

Email: gpmishra81@gmail.com

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Abstract

Recently the report of the first National Anti-Tuberculosis Drug Resistance Survey (NDRS) from India was released on the occasion of World TB Day this year, i.e., 24th March 2018. The salient features were as follows: 1. MDR-TB is 6.19% (CI 5.54–6.90%) among all TB patients with 2.84% (CI 2.27–3.50%) among new and 11.60% (CI 10.21–13.15%) among previously treated TB patients. 2. Among MDR-TB patients, additional resistance to any fluoroquinolones was 21.82% (17.33–26.87%), and 3.58% (1.8–6.32%) to any second-line injectable drugs. 3. Among MDR-TB patients, additional resistance to at least one drug from each of the two classes, i.e., fluoroquinolone and second-line injectable drugs (XDR-TB) was 1.3% (0.36–3.30%). 4. Any first- or second line drug resistance among all TB patients is 28.0% (CI 26.77– 29.29%) with 22.54% (CI 21.10–24.10%) among new and 36.82% (CI 34.64–39.04%) among previously treated TB patients. 5. Any isoniazid resistance is 11.06% (CI 9.97–12.22%) and 25.09% (CI 23.1–27.11%) among new and previously treated TB patients, respectively. 6. Any pyrazinamide resistance is 6.95% (CI 6.07–7.91%) and 8.77% (7.53–10.13%) among new and previously treated TB patients, respectively. The current article reviews the findings of the survey along with their practical implications in the present-day clinical scenario.

Introduction

Recently the report of the first National Anti-Tuberculosis Drug Resistance Survey (NDRS) from India was released on the occasion of World TB Day this year, i.e., 24th March 2018¹. The survey represents the largest ever NDRS conducted by any country in the world and the first ever survey having drug susceptibility testing (DST) for 13 anti-TB drugs using the automated liquid culture system, mycobacteria growth indicator tube (MGIT) 960. A total of 5280, sputum smear-positive pulmonary TB (Tuberculosis) patients (3240 new and 2040 previously treated) diagnosed at designated microscopy centres were enrolled in the survey. The salient results of the survey are shown in Table 1.

Discussion

The key finding of this study was the proportion of Multi-Drug Resistant TB (MDR-TB) among new and retreatment TB cases were 2.84% and 11.60% respectively. Monoresistance to rifampicin was not observed among new TB patients, thereby indicating that rifampicin resistance was always accompanied by isoniazid resistance. These figures are below the recently released global estimates of 3.6% of new cases and 17% of retreatment cases having MDR/RR (Rifampicin Resistance) TB². A possible reason for this could be the non-inclusion of TB patients visiting private sector

Table 1. Salient results of the first National Anti- Tuberculosis Drug Resistance Survey (NDRS) from India.

Sr. No.	Salient Results
1	MDR-TB is 6.19% (CI 5.54–6.90%) among all TB patients with 2.84% (CI 2.27–3.50%) among new and 11.60% (CI 10.21–13.15%) among previously treated TB patients.
2	Among MDR-TB patients, additional resistance to any fluoroquinolones was 21.82% (17.33–26.87%), and 3.58% (1.8–6.32%) to any second-line injectable drugs.
3	Among MDR-TB patients, additional resistance to at least one drug from each of the two classes, i.e. fluoroquinolone and second-line injectable drugs (XDR-TB) was 1.3% (0.36–3.30%).
4	Any first- or second line drug resistance among all TB patients is 28.0% (CI 26.77–29.29%) with 22.54% (CI 21.10–24.10%) among new and 36.82% (CI 34.64–39.04%) among previously treated TB patients.
5	Any isoniazid resistance is 11.06% (CI 9.97–12.22%) and 25.09% (CI 23.1–27.11%) among new and previously treated TB patients, respectively.
6	Any pyrazinamide resistance is 6.95% (CI 6.07–7.91%) and 8.77% (7.53–10.13%) among new and previously treated TB patients, respectively.

in the current study. A major proportion of TB patients in India visit the private sector and the quality of TB care in the private sector has been shown to be suboptimal with wide variations in knowledge and adherence to guidelines, thereby increasing the risk of development of drug resistance^{3,4}. Also, the survey only included patients with smear positive pulmonary TB, excluding smear-negative pulmonary TB and extrapulmonary TB, as well as patients from jails and prisons^{1,5}. Among MDR TB patients, additional resistance to fluoroquinolones (Pre-XDR (Pre-Extensively Drug-Resistant TB) with fluoroquinolone resistance) was seen in 21.82% patients. This high proportion of resistance to fluoroquinolones necessitates that empirical use of fluoroquinolones in respiratory ailments should be discouraged. Also, previously it has been shown that high rates of treatment failure and deaths are associated with fluoroquinolone resistance in the Indian cohort of MDR-TB patients⁶. This finding limits the potential benefit of short course regime for MDR-TB patients which has currently been introduced in the country, as known resistance to fluoroquinolones is one of the exclusion criteria for the regime⁷. The proportion of INH resistance was 11.06% and 25.09%, among new and previously treated TB patients, respectively. Considering this, the current recommendation of INH chemoprophylaxis for TB needs to be relooked at. It has been shown previously that aggressive community-wide IPT (INH Prophylaxis therapy) can have an impressive impact on reductions of drug-sensitive disease, but at the cost of increasing the selective pressure for resistance⁸. This finding is however in sync with recent recommendation to shift to treatment regimens for drug-sensitive TB where Ethambutol is a part of the regime throughout the treatment along with INH and Rifampicin, thus preventing possible amplification of Rifampicin resistance which could have happened in absence of Ethambutol in the regime⁹.

The individual state-wise data shows Maharashtra to have the highest proportion of MDR-TB in new TB patients (7.72%), above than the national figure of 2.8%. Similarly, Uttarakhand had the highest proportion of MDR TB in

previously treated TB patients (20%), above the national figure of 11.62%. As per the survey, the distribution of MDR among the States that participated suggests areas for focus action. Strategies to map TB hotspots in the country are urgently required as they could be a possible causative factor for increased figures from a particular state even though the TB management in the rest of the state could be at par with the national standards. E.g. Previously the first case reports of TDR-TB (Total Drug Resistant TB) from India came from Mumbai in Maharashtra state and the current DRS survey shows Maharashtra as the state with highest proportion of MDR-TB in new TB patients^{1,10}. The current survey showed that the highest proportion of primary MDR TB was in Maharashtra. It may be stated here that if India is the ground zero for global tuberculosis (TB) epidemic, then Mumbai, the capital of Maharashtra is the ground zero for India's epidemic of drug resistant TB¹¹. Mumbai has seen an increasing trend of drug resistant TB in the last two decades¹². Mumbai accounts for the highest proportion of drug resistant TB patients in Maharashtra and recent reports indicate that the menace of drug-resistant TB grew by 36% in the city in last three years¹³. In a recent study from Western Maharashtra, the proportion of initial drug resistant TB was found to be an alarming 31.25%¹⁴. In another study from Mumbai over an extended timeline (2005-2013), the authors found a six-fold increase in the absolute number of MDR-TB cases between the first 3-year period (2005–2007) and the last 3-year period (2011–2013), as well as the trend towards increasingly advanced patterns of resistance¹⁵. The relatively high rate of primary MDR-TB cases could be due to the identification of the undiagnosed resistance cases in the community. Thus, these findings may imply the need for intensifying active TB case finding using community-based health extension workers and this could help in timely identification of undiagnosed resistant strains¹⁶. On the other hand, Uttarakhand had the highest proportion of secondary drug resistant TB patients. Secondary resistance may reflect poor implementation of Directly Observed Treatment Short course (DOTS) programme and should be taken as a serious challenge in the TB control programme¹⁶. Interestingly as per

the state wise TB case notification data for 2017 it is evident that Uttarakhand accounted for highest proportion of TB patients who had a history of previous anti TB treatment, a factor which could be important in contributing to the high numbers of secondary drug resistant TB patients in the state¹⁷.

Even though there was no age limitation, children (0-14 years) contributed 1.7% of the total population¹. This proportion could have increased by usage of induced sputum, gastric aspirate and CBNAAT (Cartridge based Nucleic Acid Amplification Test) to define “microbiologically confirmed TB” as is currently being advocated in the recent RNTCP (Revised National Tuberculosis Control Programme) guidelines in India⁹. There was a low proportion of female TB patients (27.99%) in the study¹. This may highlight the fact that women are less likely to seek medical advice for early symptoms than males. This may be due to socio-cultural reasons associated with TB-related stigmas, a factor which needs to be addressed with urgency^{18,19}. The RNTCP needs to focus on raising the disease awareness in the female population. A notable limitation of the survey was absence of TB patients from the private sector¹. It has been shown recently that about 2.2 million tuberculosis cases in India might have been treated in the private sector in 2014, which is two to three times higher than the current assumption³. This finding has revealed the hidden numbers, signifying the alarming magnitude of the problem unaccounted for in the official figures²⁰. These patients visiting the private sector are important as the standard of TB care in private sector in India still has a lot to be desired. It has been shown that factors for drug resistance were present in 68% of anti-TB prescriptions from the private sector in India²¹. Apart from this, the lack of a reporting, monitoring or tracing mechanism of patients all these years has augmented the problem of absence of concrete data on drug resistance in the patients visiting the private sector. With compulsory notification of TB patients as mandated recently, these issues may have had their solution³. The inclusion of these TB patients visiting the private sector may present future NDRS surveys with a different result profile.

The key recommendations of the NDRS survey are: a. Setting up and strengthening drug resistance surveillance including using state of art next-generation sequencing. b. Moving rapidly towards universal DST and appropriately DST guided treatment. c. Strengthening epidemiologic intelligence for specific interventions based on local epidemiological profile¹. These recommendations if followed with intent have the potential to positively change the present-day scenario of drug-resistant TB in India.

Conclusion

The findings of the NDRS survey are an eye opener for

us. The future strategies in line with NSP (National Strategic Plan) (2017-2025) in India need to strongly consider the trends of drug resistance showcased by the survey. The capacity building of drug resistance diagnostics combined with compulsory notification of all TB patients may see future DRS surveys depicting an increased magnitude of the problem of drug-resistant TB in India and the policymakers should be aware of this possible trend in the coming years.

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