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SHORT COMMUNICATION

First- and second-line drug resistance patterns among previously treated tuberculosis patients in India

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SUMMARY

Culture and drug susceptibility testing results of 2816 tuberculosis (TB) patients from across India who had failed repeated treatments from 2001 to 2004 were retrospectively analysed at the Tuberculosis Research Centre, Chennai. Of 1498 (53%) identified as having multidrug-resistant TB (MDR-TB), 671 (44.8%) were resistant to ⩾1 second-line drugs (SLDs): 490 (32.7%) to ethionamide, 245 (16.4%) to ofloxacin and 169 (11.3%) to kanamycin; 69 (4.6%) were extensively drug-resistant TB (XDR-TB). Although from a highly select and non-representative patient group, such high SLD resistance levels, including XDR-TB, among MDR-TB patients is of concern. The prevention of MDR/XDR-TB through quality DOTS services, however, remains the priority. In addition, rapid scale-up of quality programmatic management under the RNTCP is needed, with more control and rational use of SLDs outside the programme.

KEY WORDS: drug resistance; previously treated tuberculosis; India

ONE OF THE PRIMARY public health goals of the internationally recommended DOTS strategy, the basic package that underpins the World Health Organization (WHO) Stop TB Strategy, is to prevent the development of multidrug-resistant tuberculosis (MDR-TB, defined as resistance to both isoniazid [INH] and rifampicin [RMP]), which is difficult to cure and requires prolonged treatment with expensive and often toxic multidrug regimens.[1,2] The fourth report of the WHO/International Union Against Tuberculosis and Lung Disease Global Project on Anti-Tuberculosis Drug Resistance Surveillance estimated that almost 490 000 MDR-TB cases emerged in 2006, with 110 000 of these in India alone.[3] In 2006, extensively drug-resistant TB (XDR-TB) was defined as MDR-TB with additional resistance to any fluoroquinolone and at least one of the three injectable second-line drugs (SLDs)—capreomycin, kanamycin (KM) and amikacin.[4]

To date, limited representative drug resistance data are available from India, with no published representative data on SLD resistance or the estimated prevalence of XDR-TB.[3] Presented here is a retrospective analysis carried out on drug resistance patterns, including SLDs, among a highly select patient group from across India, whose sputum specimens were sent to the Tuberculosis Research Centre, Chennai, south India, during 2001 to 2004.

Sputum samples were received from 3173 patients, 75% of which originated from tertiary level government health institutions and hospitals. All specimens came from patients with a history of one or more previous courses of treatment, with many having chronic smear-positive pulmonary TB. The exact clinical history and the human immunodeficiency virus (HIV) status of patients were, however, not available for this retrospective evaluation.

Samples were processed for isolation of *Mycobacterium tuberculosis* on Löwenstein-Jensen media using standard methods. Isolates from 2816 (89%) patients were obtained and subjected to drug susceptibility testing (DST) for SLDs, namely KM, ethionamide (ETH) and ofloxacin (OFX), in addition to the first-line drugs (FLDs) INH, RMP and ethambutol (EMB) using the internationally recommended absolute concentration method, and streptomycin (SM) using the resistance ratio method.[5] Standard definitions for drug resistance were used.[5,6] All DST results were compared and assured by internal quality control (IQC) measures, and through proficiency testing (PT) for FLDs performed by the WHO Supranational Reference Laboratories (SNRL). The IQC DST result concordance

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Table 1 Type of resistance among isolates tested

Type of resistance, drug	Isolates *n*	%
Total number of strains tested	2816	100
Susceptible to all seven drugs	708	25.1
Any resistance		
INH	1902	67.5
RMP	1529	54.3
EMB	841	29.9
SM	1219	43.3
KM	184	6.5
ETH	692	24.6
OFX	272	9.7
Total	2108	74.9
Monoresistance		
INH	157	5.6
RMP	16	0.6
EMB	1	<0.1
SM	57	2.0
KM	2	0.1
ETH	94	3.3
OFX	8	0.3
Total	335	11.9
Number of drugs to which the patient is resistant		
1	335	11.9
2	428	15.2
3	496	17.6
4	459	16.3
5	257	9.1
6	92	3.3
7	41	1.5
Number of MDR-TB strains		
INH+RMP alone	355	12.6
INH+RMP + 1	561	19.9
INH+RMP + ⩾2	582	20.7
Total	1498	53.2

INH = isoniazid; RMP = rifampicin; EMB = ethambutol; SM = streptomycin; KM = kanamycin; ETH = ethionamide; OFX = ofloxacin; MDR-TB = multidrug-resistant tuberculosis.

and PT results from the SNRL over the past 10 years have always yielded excellent results.

Of the 2816 isolates with a DST result, 2108 (75%) showed resistance to one or more of the seven drugs tested (Table 1). Resistance either to any individual drug or in combination with other drugs was highest for INH (1902, 67%), followed by RMP (1529, 54%), SM (1219, 43%), EMB (841, 30%), ETH (692, 25%), OFX (272, 9.7%), and KM (184, 6.5%; Table 1).

Of the 2002 isolates that showed resistance to ⩾1 FLDs, 1040 (52%) isolates were resistant to ⩾1 SLDs (KM 181, ETH 597 and OFX 262). For the remaining 814 susceptible isolates, 108 (13%) isolates showed resistance to ⩾1 SLDs (ETH 95, OFX 10 and KM 3; Table 2).

In all, 1498 (53%) isolates showed resistance to at least INH and RMP (i.e., MDR-TB; Table 1), of which 671 (45%) were resistant to ⩾1 SLDs (ETH 490, 32.7%; OFX 245, 16.4%; KM 169, 11.3%; Table 3). XDR-TB was identified in 69 (4.6%) of the MDR-TB isolates.

Table 2 Cross-tabulation of patterns of resistance to first- and second-line drugs

Resistance to first-line drugs	*n*	Resistance to second-line drugs KM	ETH	OFX
Single				
INH	196	3	36	3
RMP	21	0	2	3
EMB	1	0	0	0
SM	65	0	8	0
Double				
INH+RMP	355	8	81	24
INH+EMB	32	0	5	1
INH+SM	136	8	37	5
RMP+EMB	3	0	0	0
RMP+SM	3	0	1	0
EMB+SM	2	0	0	1
Triple				
INH+RMP+EMB	176	11	64	25
INH+RMP+SM	385	36	115	46
INH+EMB+SM	40	0	16	1
RMP+EMB+SM	5	1	0	3
Quadruple				
INH+RMP+EMB+SM	582	114	230	150
Any resistance	2002	181	597	262
Susceptible to				
INH+RMP+EMB+SM	814	3	95	10
Total (%)	2816	184 (6.5)	692 (24.6)	272 (9.7)

KM = kanamycin; ETH = ethambutol; OFX = ofloxacin; INH = isoniazid; RMP = rifampicin; EMB = ethambutol; SM = streptomycin.

Table 3 Additional resistance to second-line drugs among MDR-TB patients (n = 1498)

	n	%
Single drug		
ETH	326	21.8
OFX	109	7.3
KM	58	3.9
Two drugs		
ETH+OFX	67	4.5
KM+ETH	42	2.8
KM+OFX	14	0.9
Three drugs		
KM+ETH+OFX	55	3.7
Total	671	44.8
XDR-TB		
MDR+KM+OFX (±ETH)	69	4.6

MDR-TB = multidrug-resistant tuberculosis; ETH = ethionamide; OFX = ofloxacin; KM = kanamycin; XDR-TB = extensively drug-resistant tuberculosis.

DISCUSSION

As the study group was a highly selective one, comprising mainly treatment failures and chronic cases, the 53% MDR-TB rate was not surprising. High levels of MDR-TB among previously treated patients can be due to poorly designed drug regimens, poor patient adherence to treatment and poor drug quality. However, in India, all anti-tuberculosis drugs, both FLDs and SLDs, are widely available and used, often irrationally, in the private and public sectors outside of the Revised National Tuberculosis Control Programme (RNTCP). In 2006, 75% of FLDs and virtually 100%

of SLDs sold by manufacturers were procured and used outside the RNTCP, most likely under suboptimal management conditions.[7]

Of great concern is the observed resistance to OFX (16.4%) and KM (11.3%), and XDR-TB (4.6%). This information assumes significance, as resistance to SLDs, especially XDR-TB, is associated with worse outcomes than MDR-TB.[8,9] Although the data presented here are likely to be a poor reflection of the SLD DST patterns among RNTCP's Category II cases, the potential presence of 1–2 SLD non-XDR-TB drug resistance and/or XDR-TB, which may or may not respond to the standardised RNTCP Category IV regimen,* is a matter of great concern. A recent study in South Africa raised the concern of those MDR-TB cases that were resistant to a single marker of XDR-TB (either OFX or KM), as being at great risk of developing XDR-TB if not managed appropriately.[10]

A substantial proportion of the RNTCP Category II retreatment cases are not from previous treatment under RNTCP, but rather from the private sector and other areas of the public sector that are offering non-RNTCP, non-DOTS treatment, which often may have included a fluoroquinolone.[11] The fact that, under poor management practices, TB isolates can develop OFX resistance within 1 week, makes this widespread availability and misuse of fluoroquinolones a matter of great concern.[12] High levels of fluoroquinolone resistance have already been documented among TB and MDR-TB cases in Mumbai, India.[13] The authors postulated that this is due to widespread, poor usage of fluoroquinolones in the treatment of both TB and other infections in the community.

Although the percentages of MDR-TB in India seen from available data look relatively low (0.5–3.3% in new smear-positive pulmonary TB cases and 12–17% in previously treated cases), these translate into huge absolute numbers of MDR-TB cases—recently estimated at ≈110 000.[3] Although the focus of the RNTCP is to sustain the basic DOTS activities to prevent the emergence of drug resistance, it is scaling up services to manage those MDR-TB cases that already exist. The RNTCP is currently diagnosing and managing MDR-TB cases in eight states with a standardised Category IV treatment regimen, as per WHO management guidelines.[2,14] The RNTCP plans to expand services for MDR-TB cases in a phased manner and, by 2012, to screen all smear-positive previously treated patients at the time of enrolment into the RNTCP Category II retreatment regimen, in addition to those who appear to be failing Category II treatment.

As the RNTCP expands its diagnostic and treatment services for MDR-TB cases, there will be a potential threat to the standardised Category IV treatment regimen if such high levels of SLD resistance are present in enrolled patients. There is therefore an urgent need for more control and rational use of the widely available quinolones and other SLDs outside of the RNTCP, by both the public and private health sectors in India. In general, new SLD regimens and better rapid diagnostic tests are needed for effective detection and treatment of MDR-/XDR-TB.

* 6 (or 9) months of KM+ETH+CYC+OFX+PZA+EMB followed by 18 months of ETH+CYC+OFX+EMB. CYC = cycloserine; PZA = pyrazinamide.

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RÉSUMÉ

On a analysé au Centre de Recherche de la Tuberculose à Chennai les résultats des cultures et des tests de sensibilité des années 2001–2004 chez 2816 patients tuberculeux provenant de l'ensemble de l'Inde et chez qui des traitements répétés avaient échoué. Une tuberculose multirésistante (TB-MDR) a été identifiée chez 1498 d'entre eux (53%). Chez 671 (44,8%) de ceux-ci, une résistance à ⩾1 médicament de deuxième ligne (SLD) a été trouvée, chez 490 (32,7%) une résistance à l'éthionamide, chez 245 (16,4%) à l'ofloxacine et chez 169 (11,3%) à la kanamycine, et chez 69 (4,6%) on a mis en évidence une ultrarésistance (TB-XDR). Bien qu'existant dans un groupe de patients fortement sélectionnés et non représentatifs, des taux aussi élevés de résistance aux SLD (y compris TB-XDR) sont préoccupants. La prévention de la TB-MDR et -XDR grâce à des services DOTS de qualité reste néanmoins prioritaire. Par ailleurs, une augmentation rapide de la qualité de la gestion du programme sous le RNTCP est nécessaire, ainsi qu'une utilisation plus surveillée et plus rationnelle des SLD en dehors du programme.

RESUMEN

Se analizaron en forma retrospectiva los resultados de los cultivos y los antibiogramas realizados entre el 2001 y el 2004 en el Centro de Investigación sobre Tuberculosis de Chennai en 2816 pacientes tuberculosos con fracasos en tratamientos repetidos, provenientes de toda la India. Se detectaron 1498 casos (53%) de tuberculosis multidrogorresistente (TB-MDR). De estos, 671 (44,8%) fueron resistentes a uno o varios medicamentos antituberculosos de segunda línea (SLD) y 490 aislados (32,7%) fueron resistentes a etionamida, 245 (16,4%) a ofloxacino y 169 (11,3%) a kanamicina. Se encontraron 69 casos (4,6%) de tuberculosis extensamente drogorresistente (TB-XDR). Si bien estos pacientes pertenecen a un grupo muy seleccionado y no son representativos de la población general, esta frecuencia de resistencia a los SLD y de TB-XDR en los pacientes con TB-MDR es preocupante. No obstante la prevención de la TB-MDR y XDR en los servicios de alta calidad de DOTS, sigue siendo una prioridad. Además, un aumento rápido de la cualidad de la gerencia del programa debajo el RNTCP es necesario, así como una utilización más controlada y racional de los SLD fuera del programa.