High prevalence of DR-TB (drug-resistant tuberculosis): An Indicator of public health negligence

Rida Masood, Iyad Naeem Muhammad*, Tuba Siddiqui, Madiha Mushtaque and Asma Irshad
Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi, Pakistan

Abstract: Tuberculosis (TB) is among the 10 most common worldwide causes of mortality. In Pakistan, estimated 510,000 tuberculosis patients had been diagnosed with an occurrence of 276/100,000. As per most recent global TB report 2018, Pakistan is amongst the 30 countries high TB with drug-resistant *Mycobacterium tuberculosis* particularly MDR (multi-drug resistant strains). A retrospective study had been designed using DR-TB patients' records from January 2013 to the December 2017 year from a public sector hospital in Karachi. Overall 315 drug-resistant tuberculosis patient's data had been incorporated in the study. All data had been analyzed using SPSS version 16 software. Chi-square test had been used to analyze the data with CI (confidence interval) 95% and level of significance 5%. The study result showed that 64.1% MDR patients, 27.9% MTB rifampicin resistance, 4.8% mono-drug resistant , XDR(1.6%), 1% poly-drug resistant and only 0.6% are MDR suspects showing no association of DR-TB with gender (p-value 0.787), age group (p-value 0.757), treatment outcomes (p-value 0.549), year of registration(p-value 0.206), first line treatment history(p-value 0.643) with a 95% confidence interval. The drug resistance TB cases have been periodically rising every year. Early identification is required to reduce the percent mortality and inhibit the disease transmission.

Keywords: *Mycobacterium tuberculosis*, drug-resistant tuberculosis (DR-TB), first-line and second-line anti-tuberculosis treatment.

INTRODUCTION

Tuberculosis (TB) continues to be a worldwide public health issue of severe extent demanding urgent attention. Present worldwide efforts to prevent and control tuberculosis have 3 distinct but coinciding extents: economic, humanitarian and public health. Worldwide, TB is among the 10th utmost common causes of mortality. (Pakistan Observer, 2017)

DR-TB is a persistent threat. In 2016, there had been 600,000 new cases of RR-TB (Rifampicin resistance tuberculosis, which is the most effective first-line anti-tubercular drug) of which 490,000 cases had MDR-TB. Nearly 47% of drug-resistant tuberculosis cases were in China, the Russian Federation, and India. (World Health Organization, 2017b)

Above 2 billion individuals, (equivalent to one-third of the population of the world) suffer from M. tuberculosis bacilli. 1 in 10 TB patients progresses to active tuberculosis. Each year around 1.8 million individuals demises because of tuberculosis, which equals 4,500 demises/day, a majority of which occur in immensely populated areas, such as China, Pakistan, Bangladesh, Indonesia and India where the 48% of new tuberculosis cases occur. (Dye, 2006). In Pakistan, around 297,000 tuberculosis cases are reported per year. Multidrug-resistant tuberculosis (MDR-TB) is a type of tuberculosis categorized by the resistance of two or more effective first-line anti-tubercular medicine particularly isoniazid and rifampicin. Internationally, approximately 440,000 MDR-TB cases emerge each year which equals 3.6% of overall new tuberculosis patients. As per WHO, Pakistan is among the 27 countries with a huge problem of multi-drug resistant tuberculosis. MDR-TB occurs in 35% of formerly treated TB patients and 2%-3.2% of recently diagnosed (Javaid *et al*., 2008). Treatment success rates in MDR-TB are less compared to DS-TB (drug-susceptible tuberculosis). (Rao *et al*., 2009), (World Health Organization, 2010)

A study conducted on 50,000 tuberculosis cases in thirty-five countries, International Union against Tuberculosis and Lung Diseases, CDC (Centers for Disease Control and Prevention), and WHO noticed that in Russia, Estonia, India, Latvia, Argentina, Ivory Coast, and The Dominican Republic, *M. tuberculosis bacilli* were resistant to the most potent first-line anti-tubercular drugs i.e. rifampicin and isoniazid. One-third of the countries investigated had multi-drug resistant tuberculosis level ranging between 2 to 14%. (World Health Organization, 2000). According to another study (World Health Organization, 2000) among 64,104 tuberculosis cases from fifty-eight geographical locations, DR-TB (drug-resistant tuberculosis) was found between 2.9-40.8%. The occurrence of DR-TB was directly linked to the proportion of registered earlier cured cases and inversely

*Corresponding author: e-mail: iyanaeem@uok.edu.pk

linked to the proportion of tuberculosis cases cured under DOTS.

The development of resistance to anti-tubercular drugs and mostly MDR-TB is an important public health issue and a bottle neck like in effective tuberculosis control. (Toman, 1979) (Grover and Takkar, 2008)

MATERIALS AND METHODS

Research design

A retrospective observational study had been designed using DR-TB patients' records from 2013 to 2017 year from a teaching, tertiary care government hospital in Karachi.(Goodhand *et al*., 2012) The entire bioethics requirement has been approved from Bioethical Institutional Review Board Committee (IRB) of hospital.

Setting

New and direct observed therapy, short course DOTS treated patients having DR-TB via established regimen by world health organization. The treatment regimen was decided on the individual basis subject to clinical conditions. A drug-resistant tuberculosis patient offers MTB-rifampicin drug resistance, MDR, mono drug resistance, XDR and poly-drug resistance.

Mono-resistance-TB

Tuberculosis in which M. tuberculosis offers resistance to only one first-line anti-tubercular drug.

Poly-resistance-TB

Mycobacterium carries resistance to more than one first-line anti-tubercular drug, excluding isoniazid and rifampicin both.

Multidrug resistance (MDR)

Mycobacterium tuberculosis which carries resistance to most effective first-line anti-tubercular drugs i.e. rifampicin and isoniazid.

Extensive drug resistance (XDR)

A very uncommon type of MDR-TB in which *Mycobacterium tuberculosis* bacteria offers resistance to isoniazid and rifampicin but also to any fluoroquinolone and one of three second-line anti-tubercular injectable drugs i.e. capreomycin, kanamycin and amikacin.

TB- Rifampicin resistance (RR)

Resistance to rifampicin is identified via phenotype and genotype methods. Rifampicin resistance might be with or without the resistance other anti-tubercular drugs. Rifampicin resistance resides presents either in MDR-TB, XDR-TB, mono-resistance tuberculosis and poly-resistance tuberculosis. (World Health Organization, 2017a)

Population

The population comprised of all drug-resistant tuberculosis patients from a government hospital from the period of January 2013 to December 2017 in Karachi

Inclusion criteria

- New and direct observed therapy treatment, short course (DOTS) treated cases of DR-TB
- No restriction of age limit

Exclusion criteria

- Drug-susceptible tuberculosis

Collection of data

Overall, 315 drug-resistant tuberculosis patients' data had been included in the study. Patient treatment cards, together with TB register had been reviewed so as to record patient characteristics along with treatment outcomes. Through standard definitions, a record was prepared for the TB category and final treatment result. Death has been explained because of any reason while treatment continued with anti-tuberculosis drugs.

Following data had been collected

1. Patient age and gender
2. Year of registration of patient in the hospital
3. Treatment outcomes
4. Type of DR-TB
5. First line Tuberculosis drug treatment history and outcomes
6. Second line tuberculosis drug treatment history and outcomes
7. Site of DR-TB
8. DST (drug-susceptibility testing of first-line and second-line anti-tubercular drugs)

STATISTICAL ANALYSIS

An explanatory and methodical approach was followed to investigate the clinical administration and outcomes. The data was assessed via SPSS v16 software which was subsequently sorted to get the appropriate frequencies, statistics, cross tables, bar graph/diagram plotted etc. (for more understanding). Chi-square test utilized to evaluate the data with 95% CI (confidence interval) and 5% level of significance.

RESULT

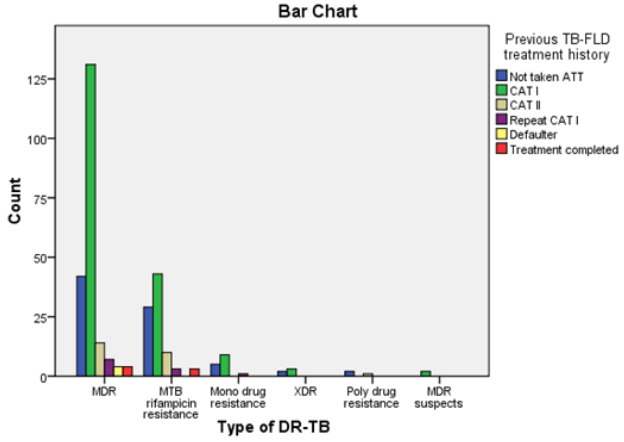

Fig. 1: History of previous first-line drug therapy given to DR-TB patients.

Table 1: Year-wise registration of Type of DR-TB patient

		Year of registration					Total
		2013	2014	2015	2016	2017	
Type of DR-TB	MDR	11	40	55	54	42	202
	MTB Rifampicin Resistance	2	14	28	12	32	88
	Mono drug resistance	0	1	3	4	7	15
	XDR	0	1	1	2	1	5
	Poly drug resistance	0	0	1	2	0	3
	MDR suspects	0	1	0	0	1	2
Total		13	57	88	74	83	315

Table 2: Age-wise distribution of DR-TB patients

Year of registration			Age Group							Total
			5-14 yrs	15-24 yrs	25-34 yrs	35-44 yrs	45-54 yrs	55-64 yrs	65+ yrs	
2013	Type of DR-TB	MDR	2	4	2	2	0	1		11
		MTB rifampicin resistance	1	0	0	0	1	0		2
	Total		3	4	2	2	1	1		13
2014	Type of DR-TB	MDR	3	12	12	7	4	2	0	40
		MTB rifampicin resistance	1	3	2	2	1	4	1	14
		Mono drug resistance	0	1	0	0	0	0	0	1
		XDR	0	0	1	0	0	0	0	1
		MDR suspects	0	0	0	1	0	0	0	1
	Total		4	16	15	10	5	6	1	57
2015	Type of DR-TB	MDR	3	23	10	6	4	4	5	55
		MTB rifampicin resistance	0	13	5	3	2	4	1	28
		Mono drug resistance	0	1	1	1	0	0	0	3
		XDR	0	0	1	0	0	0	0	1
		Poly drug resistance	0	1	0	0	0	0	0	1
	Total		3	38	17	10	6	8	6	88
2016	Type of DR-TB	MDR	3	21	12	9	4	5	0	54
		MTB rifampicin resistance	2	4	2	2	0	1	1	12
		Mono drug resistance	0	2	1	0	0	1	0	4
		XDR	0	0	0	0	0	1	1	2
		Poly drug resistance	0	2	0	0	0	0	0	2
	Total		5	29	15	11	4	8	2	74
2017	Type of DR-TB	MDR	0	14	12	9	4	2	1	42
		MTB rifampicin resistance	2	10	4	6	6	2	2	32
		Mono drug resistance	0	1	0	3	2	0	1	7
		XDR	0	1	0	0	0	0	0	1
		MDR suspects	0	1	0	0	0	0	0	1
	Total		2	27	16	18	12	4	4	83

DISCUSSION

DR-TB is one of the constantly puzzling hazards. In 2016, 600,000 new cases of RR-TB (rifampicin resistance tuberculosis) were registered which (rifampicin) is an efficient first-line anti-tubercular drugs. Out of 600,000 new cases 490,000 had multi-drug resistant tuberculosis. Almost half of the drug-resistant tuberculosis cases i.e. 47% were observed in the Russian Federation, India, and China. (World Health Organization, 2017b)

Globally in 2016, an estimated 19% (9.8-27%, Confidence Interval: 95%) of formerly treated cases and 4.1% (CI: 95% [confidence interval] 2.8-5.3%) new cases had drug-resistant tuberculosis (MDR/RR-TB). (World Health Organization, 2017b).

Around thirty-five countries have introduced short treatment regimens for RR-TB or MDR-TB. Efforts to upsurge therapeutic outcomes for extensive and multi-drug resistant tuberculosis, eighty-nine countries had begun utilizing bedaquiline however delamanid was

prescribed by fifty-four countries from June 2017. (World Health Organization, 2017b).

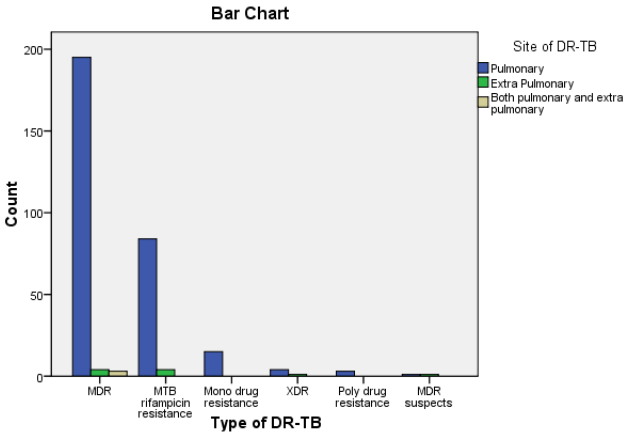

Fig. 2: Site of DR-TB of DR-TB patients

In current study, number of drug-resistance tuberculosis patients has been increase every year as shown in table 1, and most commonly occurred in 15-44 years age group as shown in table 2.The rate of successful management for MDR-TB can be ≈ 70-90% (Sampathkumar, 2008). Approximately, sixty percent mortality rate has been witnessed among MDR-TB (Irfan *et al*., 2006) in contrast, the low percent mortality was found in HIV infections (Seung *et al*., 2009). A study by Khurram *et al*., in 2011 observed the 10% cure rate in MDR-TB patients while 40% had died, defaulted and treatment failure were 30% and 20% respectively (Khurram *et al*., 2011) In all, present study found the cure rate of (110/315, 34.9%) among multi-drug resistant-TB, however, 42/315 (13.3%) patients were died and 10/315 (3.2%) were treatment failed. Moreover, 15 (4.8%) patients were non-complaint, 9 (2.9%) patients had completed their treatment, 30 (9.5%) patient had failed to evaluate as well as 99 (31.4%) patients had still undergone treatment from 2013 till 2017 as shown in table 5. An investigation conducted in Pakistan, found the resistance among isolates of MDR-TB i.e. 80% against pyrazinamide and streptomycin and 66% against ethambutol. However, some researchers observed increasing resistance towards quinolones (ciprofloxacin and ofloxacin) due to excessive and inappropriate usage of these quinolones. (Khurram *et al*., 2011). Another study identified resistance towards ethambutol and pyrazinamide to be 17.61% and 10.79%, respectively. However, the drug sensitivity data for 2nd-line antibiotics were not available in MDR-TB patients (Saeed *et al*., 2009). Another research in 2006, documented the presence of 38% cases of MDR-TB that were found resistant to 6 Ist-line anti-tuberculous agents, 20%, 25% and 12% cases showed resistance toward 5, 4 and 3 first-line anti-tuberculosis agents respectively. Nevertheless, the 2nd-line antibiotics sensitivity data were also not recorded in the work (Javaid and Ziaullah, 2006). The current investigation reported, 36 (11.4%) to be resistant to HRZE, 76 (24.1%) resistant to HR, 29 (9.2%) resistant to HRZES, 10 (3.2%) resistant to HRZS, 12 (3.8%) resistant to HRS, 10 (3.2%) resistant to HRE, 26 (8.3%) resistant to HRZ, 106 (33.7%) resistant to R, 5 (1.6%) resistant to HRES, 1 (0.3%) resistant to H and 1 (0.3%) resistant to R respectively (table 6).

The current investigation reported, resistance profile to 2nd-line anti-tuberculous agents were 13 (4.1%) to FQ and Eto, 1 (0.3%) resistance to Am and Km, 24 (7.6%) resistant to Eto, 64 (20.3%) resistance to FQ, 2 (0.6%) resistance to Km, Cm, Am and Ofx, 1 (0.3%) resistance to Am, Cm, Km, Ofx and Lzd, 1 (0.3%) Km, Am and Ofx, 2 (0.6%) Am, Cm. Furthermore, upto 207 (65.4%) showed no resistance to second-line drugs as shown in table 7.

Kruk *et al*., (2008) had reported 6-30% default cases (Kruk *et al*., 2008). The causes of drug intolerance to 2nd-line treatment include: clinical failure of rapid improvement and increasing expenses of diagnostic test and treatment. However, the expenses incurred on current study i.e. diagnostics/treatment were funded by governmental/ non-governmental organizations. Nevertheless, the non-respondents of MDR-TB have severe consequences. Additionally, the disease progression may cause serious complications that may even lead to patient's death. Furthermore, these non-respondents may help in the spread of disease. The current research most frequently observed DR-TB during the age of 15-24 years (table 2). Male DR-TB patients contributed 133/315 as shown in table 3.

More than 50% of DR-TB patients hailed from low socio-economic, illiteracy, and over-populated groups. A previous study revealed 95% of patients were treated for TB earlier and incomplete tubercular therapy compliance whereby 65.5% patients. (Khurram, 2009). In contrast, the present work determined 25.4% DR-TB patients who were not previously treated with any ATT while rest 74.6 % were treated with ATT previously. Among them, 59.7% and 7.9% had previously been treated with CAT I and II respectively. Furthermore, CAT I therapy was repeated in 3.5% of patients, defaulters were 1.3% and only 2.2% had completed the treatment course as shown in fig. 1.

Upto 92% of DR-TB patients were not treated with any 2nd line agent previously; in-contrast only 7.9% patients had been treated with second-line drugs (table 4). The treatment cost of patients of the MDR-TB patient in the advanced world is approx. £60,000 which is around 10663685.36 Pakistani Rupees or US $100,000 (Zumla and Grange, 2001); hence, management of patients (priorities etc.) of DR-TB at government hospitals is enormously challenging in resource-limited situations. In order to control and prevent the spread and development of MDR-TB, one should focus on effective treatment of drug-susceptible tuberculosis. (Khurram *et al*., 2011).

Table 3: Gender wise distribution of DR-TB patients

Year of registration			Gender Of Patients		Total
			Male	Female	
2013	Type of DR-TB	MDR	5	6	11
		MTB rifampicin resistance	0	2	2
	Total		5	8	13
2014	Type of DR-TB	MDR	18	22	40
		MTB rifampicin resistance	4	10	14
		Mono drug resistance	0	1	1
		XDR	0	1	1
		MDR suspects	0	1	1
	Total		22	35	57
2015	Type of DR-TB	MDR	20	35	55
		MTB rifampicin resistance	8	20	28
		Mono drug resistance	1	2	3
		XDR	0	1	1
		Poly drug resistance	0	1	1
	Total		29	59	88
2016	Type of DR-TB	MDR	23	31	54
		MTB rifampicin resistance	6	6	12
		Mono drug resistance	1	3	4
		XDR	2	0	2
		Poly drug resistance	1	1	2
	Total		33	41	74
2017	Type of DR-TB	MDR	19	23	42
		MTB rifampicin resistance	22	10	32
		Mono drug resistance	3	4	7
		XDR	0	1	1
		MDR suspects	0	1	1
	Total		44	39	83

Table 4: Previous second-line treatment history administered to DR-TB patients

		Previously received SLD		Total
		No	Yes	
Type of DR-TB	MDR	184	18	202
	MTB rifampicin resistance	85	3	88
	Mono drug resistance	15	0	15
	XDR	4	1	5
	Poly drug resistance	2	1	3
	MDR suspects	0	2	2
Total		290	25	315

Table 5: Treatment outcome of DR-TB patients

		Treatment outcome							Total
		Cured	Died	Failed	Non-compliant	Completed	Not evaluated	Still under Treatment	
Type of DR-TB	MDR	73	28	8	8	8	20	57	202
	MTB rifampicin resistance	33	12	1	5	1	7	29	88
	Mono drug resistance	3	0	0	1	0	2	9	15
	XDR	0	1	1	1	0	1	1	5
	Poly drug resistance	1	0	0	0	0	0	2	3
	MDR suspects	0	1	0	0	0	0	1	2
Total		110	42	10	15	9	30	99	315

Table 6: Drug susceptibility testing of first-line anti-tubercular drugs

		Year of registration					Total
		2013	2014	2015	2016	2017	
Resistance to first-line drugs	MDR suspect	0	1	0	0	1	2
	HRZE	1	8	9	14	4	36
	HR	1	6	18	25	26	76
	HRZES	4	12	7	3	3	29
	HRZS	2	1	5	1	1	10
	HRS	2	4	5	1	0	12
	HRE	1	2	2	1	4	10
	HRZ	0	4	6	11	5	26
	R	2	16	32	17	39	106
	HRES	0	3	2	0	0	5
	H	0	0	1	0	0	1
	RS	0	0	1	0	0	1
	RZ	0	0	0	1	0	1
Total		13	57	88	74	83	315

Where H= Isoniazid; R= Rifampicin; Z= Pyrazinamide; E= Ethambutol; S= Streptomycin

Table 7: Drug susceptibility testing of second-line anti-tubercular drugs

		Year of registration					Total
		2013	2014	2015	2016	2017	
Resistance to second-line drugs	No resistance	8	38	56	41	64	207
	FQ, Eto	0	0	7	4	2	13
	KM, Am	1	0	0	0	0	1
	Eto	0	4	6	10	4	24
	FQ	4	14	18	16	12	64
	Km, Cm, Am, Ofx	0	1	0	0	1	2
	Am, Cm, Km, Ofx, Lzd	0	0	1	0	0	1
	Km, Am, Ofx	0	0	0	1	0	1
	Am, Cm	0	0	0	2	0	2
Total		13	57	88	74	83	315

Where FQ= Fluoroquinolones; Eto= Ethionamide; Km= Kanamycin; Am= Amikacin; Cm= Capreomycin; Ofx= Ofloxacin; Lzd= linezolid

Table 8: Chi square test for association

Association of DR-TB with	Chi-square	p-value	CI	α-value	Remarks
Gender	2.433	0.787	95%	0.05	No
Age group	24.388	0.757	95%	0.05	No
Treatment outcome	28.407	0.549	95%	0.05	No
Year of registration	24.881	0.206	95%	0.05	No
FLD-treatment history	21.875	0.643	95%	0.05	No
SLD treatment history	30.868	0.000	95%	0.05	Yes
Site of DR-TB	22.564	0.012	95%	0.05	Yes
Treatment outcome	28.407	0.549	95%	0.05	No

This study recorded 64.1 % MDR patients, 27.9% MTB rifampicin resistant, 4.8% mono-drug resistant, XDR (1.6%), 1% poly-drug resistant and only 0.6% are MDR suspects as shown in fig. 3. Out of 315 patients, 195 patients suffering from pulmonary multi-drug resistant tuberculosis whereas only 4 patients suffering from extra pulmonary multi-drug resistant tuberculosis, 84 patients were diagnosed with rifampicin resistance pulmonary tuberculosis and 4 patients with rifampicin resistance extra-pulmonary tuberculosis, 15 patients showed Mono drug resistant pulmonary tuberculosis, 4 patients were XDR pulmonary tuberculosis, 3 patients showed poly drug resistant tuberculosis whereas only 1 patient showed XDR extra-pulmonary tuberculosis and 1 patients showed extra-pulmonary MDR suspects as shown in fig. 2. An earlier work reported a high incidence of XDR-TB in Pakistan thereby expressing serious concerns inspite of the fact that a study in 2009, reported 4.5% rate of XDR among MDR-TB that is within the global average of 6.6%-23.7%. (Wright *et al*., 2009) (Hasan *et al*., 2010).

In 2008, ≈3-5 lac MDR-TB cases reported around the globe. Amongst all, 3.6% [95% CI (confidence interval): 3.0-4.4] were identified as multi-drug resistant

tuberculosis. However, nearly 50% of multi-drug resistant tuberculosis cases were recorded in India and China. WHO report in 2010 stated 150,000 deaths among MDR tuberculosis patients. Moreover, 27 countries including Pakistan were reported with a high burden of multi-drug resistance as well as annual incidence of MDR-TB was 4000 and at least 10% new cases were registered as MDR-TB (World Health Organization, 2010). The therapy of MDR-TB has involves expenses (50 to 200 times) than DS-TB. In all, the cost of therapy is 10 times greater than DS-TB.

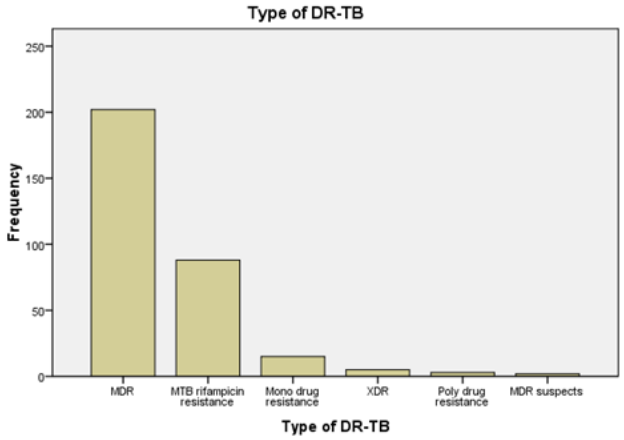

Fig. 3: Type of DR-TB patients

Approximately 5 lac cases of MDR-TB are reported each year globally, while 9% of MDR-TB was actually XDR (extensively drug-resistant) isolates of Mycobacterium. Unfortunately, prolonged treatment, toxicity, high expenses of therapy of DR-TB and low rate of success (i.e. <20%) were the major reasons for XDR Mycobacterium strains. (D'Ambrosio *et al*., 2015)

TB is one of the main health issues emerging around the globe, one third population are infected with tubercle bacilli and 1/sec is the rate of new infection. In India, new cases of MDR-TB were 2-3%, however, 12-17% were relapsed cases. The most important cause of MDR-TB might be non-adherence of patients towards anti-tuberculous therapy due to ADR. (Sood *et al*., 2016). The recent enhancement in DR-TB cases and the shortage of ATT agents is alarming for the future control of TB. The frequent emergence of DR-TB is mainly due to the utilization of one or more anti-tuberculous agents to sub-therapeutic levels. (Muttil *et al*., 2009).

Early identification is required to reduce the mortality percentage and to inhibit the disease transmission. (Boehme *et al*., 2010). In Pakistan, the cases of DR-TB have occurred more increasingly, however, very few cases are reported because of limited access to culture and sensitivity facilities around the country and many more pertinent factors.

The drug resistant TB cases have been periodically rising every year. On-going surveillance programs as well as efficient implementation of National TB Control Program (NTP) using direct observed therapy, short course procedure are essential in order to minimize the incidence of DR-TB. The preventive measure includes quick and accurate detection of TB cases and their effective management. An inappropriate control program may results to MDR-tuberculosis much faster when treated improperly. The direct observed therapy, short courses (DOTS) policy should be employed to prevent the emergence of resistant organisms and proper utilization of 2^{nd} line agents for the management of MDR-TB is the major step for the effective control and prevention of MDR-TB. (Javaid *et al*., 2008)

CONCLUSIONS

Early identification is warranted to reduce the mortality percentage and to inhibit the disease transmission. On-going surveillance program as well as efficient implementation of National TB Control Program (NTP) Pakistan using DOTs procedure is essential in order to minimize the incidence of DR-TB.

REFERENCES

Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, Allen J, Tahirli R, Blakemore R and Rustomjee R (2010). Rapid molecular detection of tuberculosis and rifampin resistance. *N. Engl. J. Med.*, **363**: 1005-1015.

D'ambrosio L, Centis R, Sotgiu G, Pontali E, Spanevello A and Migliori GB (2015). New anti-tuberculosis drugs and regimens: 2015 update. *ERJ Open Research*, **1**: 00010-2015.

Dye C (2006). Global epidemiology of tuberculosis. The Lancet, **367**: 938-940.

Goodhand JR, Greig FIS, Koodun Y, Mcdermott A, Wahed M, Langmead L and Rampton DS (2012). Do antidepressants influence the disease course in inflammatory bowel disease? A retrospective case-matched observational study. *Inflamm. Bowel Dis.*, **18**: 1232-1239.

Grover GS and Takkar J (2008). Recent advances in multi-drug-resistant tuberculosis and RNTCP. *Indian J. Community Med.*, **33**: 219.

Hasan R, Jabeen K, Ali A, Rafiq Y, Laiq R, Malik B, Tanveer M, Groenheit R, Ghebremichael S, Hoffner S and Hasan Z (2010). Extensively drug-resistant tuberculosis, Pakistan. *Emerging Infect. Dis.*, **16**: 1473-1475.

Irfan S, Hassan Q and Hasan R (2006). Assessment of resistance in multi drug resistant tuberculosis patients. *J. Pak. Med. Assoc.*, **56**: 397.

Javaid A and Ziaullah BA (2006). To study the outcome of patients with multi-drug resistant tuberculosis and

see the effectiveness of second line drugs available in Pakistan in the management of MDR-TB. *Pak. J. Chest. Med.*, 12.

Javaid A, Hasan R, Zafar A, Ghafoor A, Pathan A, Rab A, Sadiq A, Akram C, Burki I and Shah K (2008). Prevalence of primary multidrug resistance to anti-tuberculosis drugs in Pakistan. *The International Journal of Tuberculosis and Lung Disease,* **12**: 326-331.

Khurram M (2009). Factors affecting relapse of tuberculosis. *Journal of Rawalpindi Medical College,* **13**: 44-47.

Khurram M, Khaar HTB and Fahim M (2011). Multidrug-resistant tuberculosis in Rawalpindi, Pakistan. *J. Infect. Dev. Ctries.,* **6**: 29-32.

Kruk ME, Schwalbe NR and Aguiar CA 2008. Timing of default from tuberculosis treatment: A systematic review. *Tropical Medicine & International Health,* **13**: 703-712.

Muttil P, Wang C and Hickey AJ (2009). Inhaled drug delivery for tuberculosis therapy. *Pharm. Res.,* **26**: 2401-2416.

Pakistan Observer (2017). 119 TB treatment centres functioning across country [Online]. Available: http://pakobserver.net/119-tb-treatment-centres-functioning-across-.

Rao NA, Mahfooz Z and Irfan M (2009). Treatment outcome of multi-drug resistant tuberculosis in a tertiary care hospital in Karachi. J. Pak. Med. Assoc., **59**: 694.

Saeed W, Naseem A and Ahmed J (2009). Retrospective audit of patients treated for MDR-TB in re-treatment category. *J. Ayub. Med. Coll. Abbottabad,* **21**: 94-98.

Sampathkumar P (2008). Drug resistant tuberculosis: a global public health issue. *Int. J. Dermatol.,* **47**: 985-988.

Seung KJ, Omatayo DB, Keshavjee S, Furin JJ, Farmer, PE and Satti H (2009). Early outcomes of MDR-TB treatment in a high HIV-prevalence setting in Southern Africa. *PLoS ONE,* **4**: e7186.

Sood A, Bansal R, Sharma A, Himani H, Bhagra S and Kansal D (2016). Profile of adverse drug reactions in patients on anti-tubercular drugs in a sub Himalayan rural tertiary care teaching hospital. *International Journal of Research in Medical Sciences,* **4**: 4465-4471.

Toman K (1979). Tuberculosis Case-finding and Chemotherapy, Citeseer, Wold Health Organization, Geneva, Switzerland.

WHO (2000). Anti-tuberculosis drug resistance in the world: The WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance. *Report,* WHO/TB/2000, **2**: 278.

WHO (2010). Multidrug and extensively drug-resistant TB, Wold Health Organization, Geneva, Switzerland.

WHO (2017a). Drug Resistant Tuberculosis [Online]. Available: http://www.who.int/tb/areas-of-work/drug-resistant-tb/types/en/ [Accessed 2-October 2018].

WHO (2017b). Executive Summary [Online]. Available: http://www.who.int/tb/publications/global_report/Exec_Summary_13Nov2017.pdf?ua=1 [Accessed 5 july 2018].

Wright A, Zignol M, Van Deun A, Falzon D, Gerdes SR, Feldman K, Hoffner S, Drobniewski F, Barrera L and Van Soolingen D (2009). Epidemiology of antituberculosis drug resistance 2002-07: An updated analysis of the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. *The Lancet,* **373**: 1861-1873.

Zumla A and Grange JM (2001). Multidrug-resistant tuberculosis can the tide be turned? *Lancet Infect Dis.*, **1**: 199-202.