

Epidemiological Trends and Resistance Profiles of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis in Dera Ismail Khan, Pakistan (2013–2018)

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Abstract

Tuberculosis (TB) has been one of the deadliest infectious diseases in the world and the development of drug resistant strains has continued to frustrate the attempts of health care laboratories and organisations in managing the disease. The objective of this paper was to evaluate prevalence and current state of resistance to multidrug-resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) in Dera Ismail Khan, Khyber Pakhtunkhwa, Pakistan, within the years, 2013 to 2018. The sample size was 400 clinically confirmed TB patients treated in Programmatic Management of Drug-Resistant TB (PMDT) in the unit of the Mufti Mehmood Memorial Teaching Hospital. Gene-Xpert and Drug Susceptibility Testing (DST) were employed in the analysis of sample contents of these 2 methods of receiving sputum samples and statistically analysed demographic and clinical variables with chi-square tests, SPSS v21.0. Out of all the cases, 99 (95.1) were found to be MDR-TB and 5 (4.8) were XDR-TB. Issues of MDR-TB were higher in females (98.3) than in males (90.7), whereas XDR-TB was also a bit higher in males (9.3). The peak prevalence of MDR-TB was noted

among 2534 years age category (95.4%), and the worst XDR-TB was during patients aged above 55 years (13.7%). It was more impacted on rural (95.7%) and unemployed (95) people. Though the difference between the demographics did not significantly differ according to the statistical basis ($p > 0.05$), the results emphasise the necessity to have better surveillance, adherence to treatment, and enhanced healthcare service provision in rural Pakistan.

Introduction

As a fatal communicable disease, tuberculosis (TB) has remained one of the most deadly in the globe, and the growing condition of drug-resistant infections that negate policy efforts to regulate the disease poses a threat to humanity. The objective of the study was the identification of the trends of prevalence and resistance of multidrug-resistant (MDR-TB), or extensively drug-resistant (XDR-TB) of tuberculosis in Dera Ismail Khan, Khyber Pakhtunkhwa, Pakistan, during the period of 2013-2018. Four hundred disseminating clinically diagnosed positive TB-positive patients were invited

in the Programmatic Management of Drug-resist TB (PMDT) of the Mufti Mehmood Memorial Teaching Hospital (MMMTH). Gene-Xpert and Drug Susceptibility Testing (DST) were used to verify the resistant types through analysing the samples of sputum. The SPSS v21.0 was chosen to perform statistical analysis on demographic, clinical and socio-economic data as well as employing the descriptive component and chi-square tests to evaluate associations amongst categorical variables.

Out of all patients, 99 were found to be MDR- TB and 5 were found to be XDR-TB. Among the 95.6% were the females (98.3) than the males (90.7%), and XDR-TB among the males was a little more (9.3%). The sit within age brackets of 25 to 34 years revealed the highest case of MDR-TB (95.4 percent), and the age group of older than 55 years revealed the highest rate of XDR-TB (13.7 percent). The cases of MDR-TB were centred in the rural (95.7%), unemployed (95%), and in pulmonary as opposed to extrapulmonary infection. There is no dire relation ($p > 0.05$) between the type of resistance and gender, age, region. The results highlight the necessity of a more competent drug-resistance surveillance and treatment adherence evaluation and the healthcare availability reinforcing in the rural areas of Pakistan.

Tuberculosis (TB) has become one of the oldest contagious airborne infections and is still a significant concern to people especially in developing nations. It mostly attacks the lungs although it may extend to other organs. In case half of a population is exposed to *Mycobacterium tuberculosis*, approximately 10 percent might acquire the active disease.

The *Mycobacterium tuberculosis* complex causes TB and is transmitted when an infected individual sneezes, speaks or coughs. Although there are existing standard anti-TB drugs, low treatment success rates have led to the development of increasing levels of drug-resistant disease, such as multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB).

Drug-Resistant Forms of TB

The development of MDR-TB is the result of resistance of *Mycobacterium tuberculosis* to the two strongest first-line drugs of tuberculosis, isoniazid and rifampicin (WHO, 2008). The XDR-TB occurs when the bacteria are not only resistant to the first-line drugs but also to some second-line drugs, e.g. fluoroquinolones (e.g. ciprofloxacin), injectable antibiotics e.g. capreomycin, kanamycin or amikacin (WHO, 2006). Patients who do not respond to first-line therapy take second-line treatment which has been shown to be longer, more complicated and costly in the long run. Treating MDR-TB and XDR-TB is thus highly complicated, clinically, and cost-wise (WHO, 2013).

Transmission

Mycobacterium tuberculosis occurs in the form of droplet nuclei that have a diameter between 1 and 5 microns. These are suspended in the air and may be inhaled by healthy people. Upon inhalation, the bacteria are transported via the respiratory system to the alveoli in the lungs where the process of infection starts. Many of the determinants of transmission are environmental factors including ventilation and crowding (CDC, 2003).

Pathogenesis

When inside the alveoli, the bacteria can be transmitted under the lymphatic and blood flow and thus cause infection in other body parts (Krauss et al., 2003). In the majority of cases (90-95 per cent.), host immunity eradicates the growth of the bacteria, and thus leads to a latent infection without any symptoms (Delogu et al., 2009). Nevertheless, in approximately 5-10 percent of the cases, the infection will

become active leading to fever, weight loss, chest pain and persistent cough. Unattended TB may extend out of the lungs to other body parts including the brain, bones and other organs.

Global Burden

TB is a major cause of disease and mortality in the world especially in Asia and Sub-Saharan Africa. According to the estimates of the World Health Organization (WHO), *Mycobacterium tuberculosis* is known to be infected in one-third of the entire world population. An estimated 9 million new cases are reported every year, with most of them being in the low- and middle-income countries (WHO, 2015). Pakistan is one of the top 6 countries with the highest TB burden with 44% of the cases in the Eastern Mediterranean Region (WHO, 2009). Poverty, ignorance and poor healthcare infrastructure are some of the contributing factors (Khan et al., 2009).

Prevalence and Mortality

The second most infectious cause of global death is TB followed by HIV/AIDS. In 2016, about 10 million individuals were infected with TB, and 1.4 million died of this infection (WHO, 2016). Pakistan is experiencing approximately 13, 000 cases of pulmonary TB the annual case, and the rate of infection is more than 50 percent in different regions (National TB Control Program, 2009).

Bacteriology

Mycobacterium tuberculosis is a rod-shaped bacterium that grows slowly and grows well in the oxygenated atmosphere like the lungs causing TB. It is not transmitted during physical contact and contaminated surfaces but through airborne particles. The bacterium has a life span of months when in cool temperatures, but is easily killed by heat and sunlight (Shankar, 2002).

Treatment

Examples of first-line anti-TB drugs are isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin. These medications cause the death of actively growing bacteria and typically last six months to nine months (Mitchison, 2000). Second-line medicines that are less effective, more toxic, and more costly are employed in the case of MDR-TB as fluoroquinolones, kanamycin, and amikacin (WHO, 2001).

Laboratory Diagnosis

TB diagnosis: A clinical and laboratory test are combined:

Tuberculin (Mantoux) Test: This is a test that identifies TB bacteria exposure.

Radiographic Testing: This is used to detect lung lesions through X-ray.

Sputum Smear Microscopy: Acid-fast bacilli are detected under the scope of microscopy.

Methodologies Culture Grow bacteria in media to confirm and determine the drug susceptibility

PCR Testing: It is a method of identifying TB DNA in a quick 24-hour test.

These diagnostic measures are used to identify drug resistance and implement the required treatment procedures (Weyer et al., 2012).

Problems Statement and Hypothesis

Tuberculosis (TB) has been regarded as among the most threatening health issues all over the world especially in the developing and under-resource areas. Regardless of continuous control measures, the success of TB treatment programs is threatened by the increasing number of the drug-resistant strains. Some causes are parallel like poor

adherence to treatment by patients, durability of normal anti-TB therapy regimens and adverse effects caused by anti-TB drugs to the patient that cause non-completion of the disease treatment.

The rising trend of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis is a great challenge to the viability of the health systems of the populace. The proportion of all MDR-TB burden in the Eastern Mediterranean Regional Office (EMRO) area is estimated to be 60 percent in Pakistan making it one of the nations with high level of drug resistance. In Pakistan, the prevalence rate is higher in rural people in comparison to urban dwellers because of the lack of access to healthcare services, late diagnosis, and discontinuities in treatment.

In line with this, this work was a hypothesis that the proportion of MDR-TB as well as XDR-TB is significantly greater in Dera Ismail Khan (D.I. Khan) which is a district in Khyber Pakhtunkhwa province of Pakistan. Besides, male patients living in rural regions are expected to show more resistance to TB infections than their female counterparts and those urban patients.

Significance of the Study

Pakistan continues to be affected by tuberculosis as one of the most prevalent morbid and mortal agents. Competence in battle with *Mycobacterium tuberculosis* strains against first- and second-line drugs has heaped pressure on the need to study the epidemiological situation on a region-by-region basis. The importance behind the study under consideration is that by employing the help of the Gene-Xpert molecular testing and culture-sensitivity testing, the prevalence of the MDR-TB and XDR-TB of the rural and the urban population in Dera Ismail Khan of Khyber Pakhtunkhwa has been observed.

The results of this study will be valuable in understanding the local transmission process and important in informing relevant health authorities in the development of the local interventions by mapping patterns of resistant cases in terms of age, gender, and locality. Moreover, the findings will hopefully help the TB control programs to rationalize the drug regimens, enhance adherence to treatments, and develop effective systems to monitor the early detection and prevention of the resistant TB strains.

Limitations of the Study

The study embraces a confined population of the Dera Ismail Khan District, Khyber Pakhtunkhwa as its area of analysis thus the results are subjected to a regional pattern and not the national pattern. The research material is limited to conclude the prevalence and resistance rate of MDR-TB and XDR-TB in the chosen period and not movement mapping and sequence of the resistance phenotypes of the black strains. Moreover, the results are premised on still available clinical records and laboratory data which might not reflect the undiagnosed and unproven cases of the far-off regions.

Research Objectives

The objective of the proposed research is to determine the frequency and trend of drug-resistant tuberculosis (DR-TB) in Dera Ismail Khan between 2013 and the year 2018.

To establish between the interviewees prescription behaviors of commonly used first-line and second-line drugs against TB.

To assess the treatment outcomes in terms of the cure rates, mortality as well as the loss to follow up, with the aim of establishing the most effective combinations of therapeutic application in the management of MDR-TB cases.

Literature Review

TB is believed to infect about ten million individuals each year and claims the lives of more than one million persons every year worldwide (WHO, 2016). Resistant to medications: it is estimated that in 2013 alone over 480,000 MDR-TB and 210,000 deaths associated with it occurred (WHO, 2014).

Regional patterns. Literature indicates that the resistance rates vary regionally: Andrews et al. (2010) found it that South Africa exhibits provincial differentials, and Buyankhishig et al. (2012) found that 40 per cent of MDR prevalence occurs in Mongolia. Hu et al. (2017) reported MDR 52% resistant to second-line chemotherapy in China and 7.7 percent and 3.3 percent MDR and XDR in newly infected and previously infected infections in the Philippines (Padilla et al., 2012).

Pakistan context. In Pakistan, provincial studies show that MDR-TB prevalence in new infections (4-) to be 8 percent, in retreatment infections (19-20 percent), presents a significant trend in the country (NTP, 2013; Akhtar et al., 2016). According to Atif et al. (2017), the percentage of MDR-TB has reached 52 with a significant difference noted between the sexes whereby females dominated the population of cases.

Risk factors. Major predictors of MDR-TB have been found in the history of comorbid treatment failure, malnutrition, poverty, and the lack of compliance (Cantwell et al., 1998; Patel et al., 2007; Brouwer et al., 2006). The risk state is also raised by smoking and alcohol (Lienhardt et al., 2005; Auer et al., 2000). The evolving problem of bacteria towards drug resistance is frequently facilitated by social-economic limitations to expensive diagnosis and full therapy (Bhargava et al., 2011).

Control strategies. Directly Observed Treatment, Short-course (DOTS) programme of the WHO and its offshoot today, the Stop TB Strategy, have been substantially successful in the world (WHO, 2007). Nonetheless, even resource-poor countries continue to experience problems in area of patient pursuance and constant drug provision (Volmink et al., 2000).

Since there is not much epidemiology data of KPK, especially D.I. Khan, the current research will offer an overview of epidemiology in the region, which will be instrumental in national policy regarding TB control.

Materials and Methods

Study Area and Population

Data gathering was carried out at the facility of PMDT unit, at the Mufti Mehmood Memorial Teaching Hospital (MMMTH), Dera Ismail Khan, the district which is one of the major TB management centres in the southern region of KPK. Patients diagnosed with drug-resistant TB between the years 2013-2018 were included as the population.

Research Design

The retrospective descriptive design was used. The information in PMDT electronic registry was taken out:ENRS that contained 104 Gene-Xpert/DST-positive TB cases. Characteristics such as gender, age, place of living (rural/urban), occupation, location of TB pulmonary/extrapulmonary) and a past history of treatment were taken as variables.

Laboratory Methods

Diagnosis was based on the guidelines of WHO:

Environment of the region is an important factor in the dynamics of the transmission of any infectious disease. In the example of tuberculosis (TB), the tool of geography, especially rural versus urban location, has a characteristically important impact on the outbreak, and also the emergence of countermeasures to overpower the virus. The rural and urban communities covered in the district of Dera Ismail Khan (D.I. Khan) provided the data on TB patients which were then categorised according to the balance of the kind of infection and the profile of resistance that was generated via the use of the Gene-Xpert and Drug Susceptibility Testing methods.

It was statistically determined that 88 patients (95.7) out of 10 countries at the rural areas were diagnosed with multidrug-resistant tuberculosis (MDR-TB), whereas 4 patients (4.3) were confirmed with extensively drug-resistant tuberculosis (XDR-TB). On the other hand the urban cohort had 11 MDR-TB cases (91.7%) and 1 XDR-TB case (8.3%). The two populations were statistically not different ($\chi^2 = 0.36$, $p = 0.54$), however, it was inferred that resistance patterns, albeit slightly higher in the rural set up, was common in the rural environment as well as the urban environment. The rural concentration of the number of resistant cases can be explained by the possibility of the diagnostics access, healthcare awareness, and difficulty accessing the therapy at PMDT (Programmatic Management of Drug-Resistant TB) destinations throughout the district (see Table 4.3 and Figure 4.3).

Identification of Mycobacterium tuberculosis Culture Culture and Identification Culture and Identification

Culture method has been coined as one of the most effective diagnostic methods of achieving Mycobacterium tuberculosis in addition to its drug sensitivity. This is by means of growing the bacterial colonies on nutrient rich media, be it liquid broths or solid culturing plates, to enable the organism to multiply to the point of detection (Linda et al., 2011). The culture has been critical in the confirmation of TB diagnosis especially that of drug resistant strains since through culture, identification and sensitivity tests can be done accurately (Moore et al., 2006).

Cultured DST may help the clinicians determine the specific antituberculosis drugs that a pathogen is resistant to, hence differentiating between MDR-TB and XDR-TB (De Beenhouwer et al., 1995). Nevertheless, the culture procedure is not only laborious technically but also consumes a lot of time, which involves a high level of laboratory equipment and harsh bio-safety requirements. The low rate of growth of Mycobacterium tuberculosis further increases the diagnostic window final culture results are normally four weeks and drug susceptibility results can be four to six weeks (WHO, 2009).

The Lowenstein-Jensen solid medium and Middlebrook liquid medium are modern culture systems which are more reliable. Newer developments such as Mycobacteria Growth Indicator tube (MGIT) has made it possible in a short time to detect TB cases since Mycobacteria Growth Indicator Tube (MGIT) provides faster results and can be identified by either a fluorescent, radioactive or non-radioactive detection system (Shankar, 2002).

Drug Susceptibility testing (DST)

Drug Susceptibility Testing (DST) is needed to figure out the resistance profile of TB bacteria. It assists clinicians to comprehend the effects of various antibiotics used to treat this strain as well as the occurrence of drug resistant tuberculosis (DR-TB) in a patient. DST may be done through either molecular-assay or culture-based. The gene-Xpert Mtb/rif test which is recommended by the WHO is a fast molecular test detecting *Mycobacterium tuberculosis* DNA and rifampicin drug resistance within hours (Weyer et al., 2012).

On the molecular level, DST acts specifically on certain genetic malformations, which are associated with the drug resistance as the *rpoB* gene of rifampicin or the *katG* and *inhA* genes of isoniazid (Heifets and Cangelosi, 1999). These fast procedures enable the prompt diagnosis and treatment, which is beneficial in the context of avoiding the spread of resistant strains.

Molecular Diagnostics Polymerase Chain Reaction (PCR)

Diagnosis TB Polymerase Chain Reaction (PCR), more so, reverse transcription-PCR (RT-PCR) technique has reduced another revolution in the field of diagnosis because its established method enables detection of *Mycobacterium tuberculosis* in any clinical sample, amplifying expressed bacterial DNA. The speed of PCR identifications is mounted to be needed within 24 hours, which is a significant change compared to the several weeks of conventional culture (Ormerod, 2003).

It also increases the diagnostic accuracy and can also determine the presence of TB bacteria in samples when few live organisms or non-culturable ones are present. Nevertheless, because of their sensitivity, it is not PCR that replaces the traditional culture and DST methods completely as it is unable to detect the entire spectrum of drug resistance of a strain. It is rather a complimentary diagnostic instrument that shortens the process of cases detection and eases the planning of early treatment.

Relevance of context on TB Control in Pakistan

The control of tuberculosis is one of the keystones of the strategy of health protection in many countries, especially those with low health facilities. Several barriers that facilitate the perpetuation and propagation of the spread of drug resistant TB are present in Pakistan. These are non-compliance with medication, prolonged medication processes as well as adverse side effects of taking drugs and these can result in the spoilage of the medication programme/process and also the evolution of resistant free floating bacteria strains.

The development and spread of the MDR-TB and XDR-TB have been more objectionable in developing countries. World Health Organisation reports that the Eastern Mediterranean Regional Organisation (EMRO) reports that Pakistan has around 60 percent of the total MDR-TB burden in the region, which shows it is one of the areas of priority to intervene. National and regional statistics also show that African rural population have shown greater numbers of infections as compared to urban areas, which is probably because the rural areas lack diagnostic centres and are even irregularly supplied with drugs.

Upon these findings, the hypothesis of study activity was: It was suspected that the prevalence of MDR-TB and XDR-TB in Dera Ismail Khan is quite significant, and 80 percent of the male patients in rural locations might be affected. The hypothesis is used as a basis of epidemiological trends analysis and significant determinants will be identified that will affect TB resistance in the region.

Diagnostic Tests (Gene-Xpert, DST, PCR)

Sputum smear microscopy (SSM)

Early morning Sputum smear microscopy is performed using a phlegm sample because at this period of time high no of *M. tuberculosis* bacteria is observed and faster outcomes of *M. tuberculosis* sputum microscopy is obtained with ease (WHO, 2003). Most of the diagnosis of TB depends on the Smear microscopy of sputum (phlegm) which is done in countries with mostly high prevalence of the TB disease. It is also created at the lungs and airways and it is always thick liquid known as the phlegm. A patient is likely to collect such a specimen through coughing. Such analysis is easy; those who had to practice to adjust to it relatively quickly and are also inexpensive and not difficult. Besides this, the results can be received in hours since the sensitivity is not more than 50 to 60 percent (Siddique et al., 2003).

Statistical Analysis

The analytical and coding of data were performed by means of SPSS v21.0. Categorical data were summarised using descriptive statistics and the relationships examined by chi-square tests ($\alpha = .05$).

Results

Gender-Based Distribution

There were 104 registered cases of tuberculosis out of which 61 (58.6 %) were females and 43 (41.3 %) were males. The number of females with multidrug resistant tuberculosis (MDR-TB) was higher with 98.3 adding up to 98.3 percent of the total female cases but only 90.7 percent of the male patients were MDR-positive. Interestingly, the extensively drug-resistant tuberculosis (XDR-TB) was more common in males (9.3% vs. 1.7% in women). Even though this difference in gender was observed, such an association was not statistically significant ($\chi^2 = 3.23$, $p = 0.72$). This trend is an indication of the fact that, even though drug resistance is non-selective between both sexes, it may be that females were more susceptible to MDR-TB, due to disparities in health-seeking behavior, immune conditions or availability of diagnostic centres.

Table 4.1: Prevalence rate of MDR-TB and XDR-TB among male and female patients

(Refer to Figure 4.1 for graphical representation.)

Gender	N	MDR	XDR	Chi-sq (χ^2)	P-value
Male	43	39 (90.7%)	4 (9.3%)	3.23	0.72
Female	61	60 (98.3%)	1 (1.7%)		
Total	104	99 (95.1%)	5 (4.8%)		

Age-Wise Distribution

Age distribution of the cases of resistant TB and MDR-TB demonstrated that the highest incidence was observed in clients aged 25-34 years (95.4percent) and XDR-TB, 55 years and above (13.7 percent). The age groups (less than 25 years) were totally MDR-positive and no cases of XDR were registered. The statistical comparison between the categories of age did not show that they were significantly different ($p = 0.31$, 5.89). This observation underscores the fact that tuberculosis resistance subjugates all age groups, nevertheless, long-term and previous experience in the elderly might play a role in treating XDR transmission.

Table 4.2: Age-wise prevalence of MDR-TB and XDR-TB
(See Figure 4.2 for comparative visualization.)

Age (years)	N	MDR	XDR	Chi-sq (χ^2)	P-value
<18	11	11 (100%)	0		
18–24	14	14 (100%)	0		
25–34	22	21 (95.4%)	1 (4.5%)		
35–44	17	17 (100%)	0		
45–54	18	17 (94.4%)	1 (5.5%)		
55+	22	19 (86.3%)	3 (13.7%)		
Total	104	99 (95.1%)	5 (4.8%)	5.89	0.31

Regional Distribution

Geographical analysis showed that most cases which were resistant were rural. The prevalence of MDR-TB was higher in the rural setting of 95.7 percent versus 91.7 percent in the urban. On the other hand, the slight percentage difference was recorded when XDR-TB was 8.3 in urban and 4.3 in rural locations. However, statistical comparison revealed that there was no significant regional disparity ($\chi^2 = 0.36$, $p = 0.54$). The implications of these findings are that even at the stage of improved access to the health infrastructure, urban populations have not been spared by the emergence of increased drug resistance, perhaps because exposed to a higher risk of antibiotics or or not because of the ability to remain and adhere to the treatment notes.

Table 4.3: Urban–rural comparison of MDR-TB and XDR-TB prevalence
(Refer to Figure 4.3.)

Region	N	MDR	XDR	Chi-sq (χ^2)	P-value
Rural	92	88 (95.7%)	4 (4.3%)	0.36	0.54
Urban	12	11 (91.7%)	1 (8.3%)		
Total	104	99 (95.1%)	5 (4.8%)		

Occupational Status

By jobs the resistive cases were more commonly in cases where individuals had no jobs (97 MDR and 5 XDR; 95 and 4.9, respectively). All their employed patients were MDR-positive, and no XDR was detected. The relational effectiveness in occupational association with drug resistance was also statistically insignificant ($\chi^2 = 0.10$, $p = 0.74$). This finding indicates that unemployment, which may be associated with lower socioeconomic status and discontinuity in treatment, may be a predisposing factor potentially affecting persistence of the disease.

Table 4.4: Employment-based prevalence of MDR-TB and XDR-TB
(Refer to Figure 4.4.)

Occupation	N	MDR	XDR	Chi-sq (χ^2)	P-value
Employed	2	2 (100%)	0	0.10	0.74
Unemployed	102	97 (95.0%)	5 (4.9%)		
Total	104	99 (95.1%)	5 (4.8%)		

Site of Infection

The results showed that pulmonary tuberculosis (PTB) dominated by overwhelming count which was 103 out of 104. Out of them, there were 95.1% MDR and 4.8% XDR. The number of patients diagnosed with extrapulmonary TB was one and it was MDR-positive. It was tested statistically, and no significant relation was found between site of infection and type of resistance ($\chi^2 = 0.05$, $p = 0.82$). This highlights a point of the

fact that pulmonary locales remain primary location of resistant-TB transmission and chronicity within the society.

Table 4.5: Prevalence of MDR-TB and XDR-TB by infection site
(Refer to Figure 4.5.)

Site of TB	N	MDR	XDR	Chi-sq (χ^2)	P-value
Pulmonary	103	98 (95.1%)	5 (4.8%)	0.05	0.82
Extrapulmonary	1	1 (100%)	0		
Total	104	99 (95.1%)	5 (4.8%)		

Previous Tuberculosis History

Individuals with a known history of TB None of the 43 patients reported having a history of XDR-positive TB. 90.7MDR-positive TB. The MDR-TB was found to be all the cases of relapse and default. Analysis of chi-square indicated the absence of a significant relationship between the history of TB in the past and types of resistance ($\chi^2 = 0.58$, $p = 0.74$). Such an observation has an implication that it is possible that treatment interruption and relapse can augment MDR evolution yet it is less prone to directly generate XDR strains in the absence of prolonged exposure to antibiotics.

Table 4.6: Association between TB history and drug resistance
(See Figure 4.6.)

TB History	N	MDR	XDR	Chi-sq (χ^2)	P-value
Relapse	3	3 (100%)	0	0.58	0.74
Default	2	2 (100%)	0		
Previous Treatment	38	34 (89.4%)	4 (10.5%)		
Total	43	39 (90.7%)	4 (9.3%)		

Annual Trends (2013–2018)

Inside-out analysis showed a steady increasing pattern in resistance of cases through the years of case breakages that amounted to one-six years. MDR-TB also had high rates of prevalence but XDR-TB has the highest rates the most severe in 2017 at 15 cases, which indicates that community-wide transmission never stopped and may have increased resistance amplification with XDR rates. Even though year-to-year variation was insignificant, the general upwards trend shows the urgency of the problem of the necessity to have a strong surveillance system, prompt diagnosis, and reinforcement therapeutic adherence programs. Tables 4.7 -4.12 and Figures 4.7-4.12 are all summarized together as Figure 1 in the final journal submission, which for the long time was the longitudinal evolution of resistance in Dera Ismail Khan.

Table 4.7: Resistant TB patients by gender in 2013
(Excerpt from full series; complete dataset in Annex.)

Gender	N	MDR	XDR	Chi-sq (χ^2)	P-value
Male	2	2 (100%)	0	—	—
Female	6	6 (100%)	0	—	—
Total	8	8 (100%)	0	—	—

Discussion

This retrospective (6 years) study indicates that the burden of MDR-TB (95.1) and an emerging case of XDR-TB (4.8) succeed in D.I. Khan. There were no gender or age effects, but the current dynamics were in a reflective style of a nationally-grounded data (Akhtar et al., 2016; Hameed et al., 2017).

Socio-Economic Facts and Gender It might be linked to issues like low access to care and malnutrition and late disease diagnosis that would justify the prevalence of females in the MDR-TB (Atif et al., 2017). Nevertheless, there were a little higher rates of XDR-TB in men patients and it may be due to work-related infection and non-conformity.

Age-related Trends. It belongs to the range of economically productive population of 2534 years of age, as do the tendencies in India and Ethiopia (Mekonnen et al., 2015; Dalal et al., 2016). Older people (>55 years) were at a greater risk to develop the XDR-TB meaning progressive treatment failure and immunosenescence.

Occupational and Regional knowledge. The depiction of dominance in the countryside takes the form of infrastructural and informational variations. This huge prevalence exists among the entire population of unexemplified patients demonstrating the socio-economic element of TB two-years (Brouwer et al., 2006; Patel et al., 2007).

Temporal Trend The greatest in 2017 is linked to the national MDR surveillance strengthening, where it could be related not only to the fact that it was better discovered but that there was acceleration of distribution of the pandemic.

Comparative Perspective The percentage of MDR-TB observed is larger than the one observed in Ethiopia (5.7 %) (Mekonnen et al., 2015) and comparable to those regions with high levels of incidence (South Asian regions) (Hu et al., 2017) The fact is few XDR testing facility may underscore real occurrence

Public-Health Implications

The initial priority one can mention is the investing in the development of molecular diagnostic centres, including Gene-Xpert Ultra and the Line-Probe Assays (LPA), in every provincial and diameter-level hospital. These have advanced diagnostic tools, which determine Mycobacterium tuberculosis and patterns of resistance quickly, in hours rather than weeks. Early diagnosis with the use of molecular tests is beneficial not only in changing the outcome of treatment but also prevents the further spread of Drug resistant within the community. Such type of technologies incorporated in the routine TB cases intervention programmes in Pakistan would be used to detect the case faster, enhance accuracy of data and be in compliance with global WHO recommendations regarding the control of MDR and XDR-TB.

Secondly, the strict DOTS-Plus supervision means its strict adherence is required. Failure in compliance to long TB treatment regimens is also among the top emerging causes of drug resistance. Newly developed vigour of monitoring within the model of DOTS-Plus programmes guarantees their ability to take the prescriptions properly and finish the entire treatment process. Reducing resistance rates and rates of treatment default and recurrence can be highly achieved through the use of trained health care personnel, digital adherence control and community-based follow-up.

Thirdly, the government and healthcare officials will have to zero in on improvement of drug-supply logistics and infection-control practise. The disrupted continuity of treatment provided by irregularity in drug supply and stock out services tend to drive the patients to partial or irregular medication intake which in turn promotes resistance. The supply chain system should be coordinated with the help of electronic inventory monitoring to deliver anti-TB drugs in time. Further, the transmission of the infection in the healthcare setting with a combination of appropriate ventilation, wearing of the N95 mask, and uniting infected patients could further reduce the nosocomial transmission of both the MDR and XDR-TB.

Last but not the least, socio-economic relevant programmes should be incorporated in order to promote patient compliance and successful treatment. Poor people in the countryside stop treatment because of lacking financial means, income or social stigma. These barriers can be minimised through the provision of nutritional

supplement, travel allowance as well as counselling services. Find ways of community involvement that would educate patients about the need to be treated can also create trust between the patients and health systems. Together, these interventions enhance the sustainability of the TB control interventions and get Pakistan closer to disappearing that the End TB Strategy targets by the year 2035.

Conclusion

The problem of drug-resistant TB becomes increasingly dangerous in southern KPK. High MDR-TB prevalence rate among rural, female and unemployed groups creates a need to make specific interventions. Although no statistically significant relationships were established, descriptive statistics indicate that there is an urgent necessity to establish sustained surveillance, awareness, and resources requirements. Future research needs to include the expanding the use of genomic sequencing and enhanced sampling to understand the transmission networks and important mechanisms to enhance resistance.

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