Enhancing Detection Or Focusing Cure? What Is The Best Strategy To Prevent Tb Drug Resistance In Pakistan?

I Khan, R Chotani, S Khan, U Laaser

Citation

Abstract
The World Health Organization (WHO) has declared tuberculosis (TB) a global emergency of the millennium. Substandard control practices, synergism of TB with HIV/AIDS as well as rapidly emerging multi-drug resistance (MDR) have complicated control measures in TB endemic countries. Coupled with the emerging challenges, high burden country like Pakistan has extremely limited resources to spend on interventions. WHO recommended that Directly Observed Treatment Strategy; short course (DOTS) plays a crucial role in eradicating the infection and in the prevention of MDR. Pakistan is at particular risk as DOTS has been available only to 15% of the infected population. With respect to MDR detection and management, the article aims at assessing the TB control situation in Pakistan. Like other 21 high burden countries, very little has been focused on patients who frequently interrupt treatment and actively trace those who develop resistance to commonly prescribed TB drugs. According to the WHO, poor TB control program is more threatening than no program. The existing program has paid very little attention to the increasing number of chronic defaulters i.e., those who interrupt treatment for more than two months (sputum smear positive). Less effort has been provided to measure the magnitude of resistant TB in the community. This study was conducted to explore the trends of resistant TB and the capacity to detect chronic interrupters in order to fine tune the TB program in accordance with the epidemiological pattern. The results depict an increasing trend of MDR-TB in the Northern Province of Pakistan. Moreover the results show that the current TB control program focuses merely on case detection rather than treatment completion or cure. It usually delays the sputum conversion in many non-adherent cases and ultimately leads to resistance.

INTRODUCTION
Globally multi-drug resistance tuberculosis (MDR-TB) has become more frequent in the past few years (1). MDR-TB is defined as resistance to at least two drugs such as Isoniazid (INH) and Rifampicin (R). The World Health Organization (WHO) estimates that 50 million people worldwide are already infected with drug-resistant tuberculosis (1). Countries and regions are named “hot spots” where MDR-TB makes up more than 3 percent of the new TB cases. For example, in Estonia nearly 37 percent of the new TB cases were resistant to at least one drug. Resistance to all four drugs tested was 8.5 percent among new tuberculosis patients and the country had the highest level of MDR-TB (14.1 percent) of any area of the world among TB patients who had never been treated before (3). WHO survey in 1997, found 1.4 million drug-resistant tuberculosis cases in China (4). Of the four Chinese provinces surveyed, the highest rates of drug-resistant TB and MDR-TB were in Henan province, the most populous province in China. The prevalence of any drug resistance among new TB cases was 35 percent, and ranged around the already high rate of 15 percent in the other provinces surveyed. Moreover, resistance in previously treated cases was the highest in Henan province. India, with the largest burden of TB in the world, is estimated to spend $3 billion on TB prevention, diagnosis and control annually. Even so, over 400,000 people die from TB in India each year (1). WHO surveyed the state of Tamil Nadu and found another MDR-TB hot spot with 3.4 percent of new cases found to be multidrug resistant. According to the WHO, levels of MDR-TB will reach an alarming state in south East Asia if prompt steps are not taken (5). The incidence of TB increases rapidly in settings where TB control is poor, patients are immuno-compromised and also among those with HIV/AIDS or malnutrition (6). Globally, an estimated 20% of patients with TB default or fail to respond to therapy and develop MDR-TB (7). Furthermore, a poorly functioning programme can create MDR-TB much faster than it can be treated, even if unlimited resources are available. MDR-TB results from poor TB management, i.e. inadequate drug treatment followed by lapses in infection
control, and its prevalence is up to ten times higher in previously treated patients than in new patients (\(n\)).

**Figure 1**

Table 1: Treatment Outcomes of New smear (%) positive cases in Pakistan (cohort 1999*)

<table>
<thead>
<tr>
<th>Year</th>
<th>Died</th>
<th>Faled</th>
<th>Defaulted</th>
<th>Transferred</th>
<th>Retreated</th>
<th>Transmised</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>20</td>
<td>55</td>
<td>79</td>
<td>21</td>
<td>21</td>
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</tr>
<tr>
<td>1999</td>
<td>45</td>
<td>12</td>
<td>67</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>1998</td>
<td>66</td>
<td>16</td>
<td>57</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>1997</td>
<td>80</td>
<td>20</td>
<td>67</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>1996</td>
<td>90</td>
<td>10</td>
<td>57</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>1995</td>
<td>100</td>
<td>0</td>
<td>57</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
</tbody>
</table>

*Cases diagnosed during 1999 and received follow-up through 2000, NA: Not available (source: WHO, 2001)

**Figure 2**

Figure 1: Case Detection Rate of New Smear Positive Cases (%): Pakistan, 1995-2000

With the population of 152 million, Pakistan ranks eighth among the list of 22 TB high burden countries (177 per 100,000) and death toll due to TB mounts to around 50,000 annually (\(\)\). Resistance to TB drugs has been widely reported from various parts of the country, however, pertinent data that depicts a national profile is lacking. Merely 15% [2001] of the smear positive population received DOTS coverage in the country and fairly large number of TB patients gets their treatment under non-DOTS control units or from private sector (\(\)\). Program performance especially from non-DOTS areas has been of great concern. Review of TB cohort (1999) in Pakistan brought about some striking results that progress in TB control has been very sluggish (\(\)\). In spite of recent donations, no practical steps have been taken so far to look into the issue of MDR-TB in the country. In Pakistan, the orientation of NTP to the community oriented problems has been vague. High priority has been given to increase case detection at TB facilities than improving the cure rate of already detected cases. According to the TB control dynamics, both aspects are vital for NTP to achieve the national targets of 75% for case detection and 85% of cure rates. With respect to the peculiar demographic situation of Northern West Frontier Province (NWFP), the reservoirs of infection significantly increased in the last decade (\(\)\). This article specifically aims at assessing the epidemiology of drug resistance and analyses trends in case detection, and the capacity of TB facilities to detect patients who frequently interrupt and do not report to the centre about their sputum status.

**DESIGN & METHODS**

The survey was carried out using a hybrid methodology, coupling both quantitative (inventory forms) for Health Facility Survey (HFS), qualitative research methods (Key informant interviews) and encompassed a cross-design synthesis. Through District TB register, all patients registered in the last six months were traced, contacted and invited to the TB facility for periodic physical and microbiological examination. Special attention was given to those with a chronic history of interruption/defaulter or patient with repeated positive sputum smear (SS) profile. HFS of TB unit/centres was carried out in (October-December 2000) in the three districts (Mardan, Sawabi & Peshawar) of NWFP. It was intended to collect information about the treatment outcomes, resources and the availability of facilities for detection, management and follow-up of resistant TB cases. Chronic defaulters, repeated SS positive and resistant cases were subjected to sputum microscopy, drug susceptibility testing (DST) and adherence based interview. Descriptive statistics in this survey present many facets of the strengths and weaknesses of TB control and services provision in the NWFP, Pakistan. NWFP is divided into 24 districts; every district has at least one independent TB facility or TB unit located in a district hospital, which is mutually run, by local government and an NGO. Italian Cooperation for Development (ICD), and the Saudi Red Crescent (SRCs) Society and Geneva Anti-TB Association (GATA) units have longstanding contributions and provide technical and financial support to the TB control activities in this area. The survey team consisted of four physicians with public health background and experience in TB case management, eight local national health workers, a sociologist and a District TB control officer.

**BACKGROUND INFORMATION ON RESISTANT TUBERCULOSIS**

Resistance to anti-microbial agents in previously susceptible organisms occurs wherever antibiotics are used for the treatment of infectious diseases in humans. With the overwhelming use as well as misuse of antibiotics, over the past decades, microorganisms including Mycobacterium tuberculosis have developed significant resistance, posing new threats to both clinical management and control...
programs. Resistance of M. tuberculosis to antibiotics is a man-made amplification of spontaneous mutations in the genes of the tubercle bacilli. Treatment with a single drug - due to irregular drug supply, inappropriate prescription, or poor adherence to treatment - suppresses the growth of susceptible strains to that drug but permits the multiplication of drug-resistant strains. This phenomenon is called acquired resistance. Subsequent transmission of such resistant strains from an infectious case to other persons leads to disease, which is drug-resistant from the outset, a phenomenon known as primary resistance \(^1,14\).

Dramatic outbreaks of multi-drug-resistant tuberculosis (MDR-TB) in 22 high burden countries from TB have recently focussed international attention on the emergence of strains of M. tuberculosis resistant to anti-TB drugs. MDR-TB defined as resistance to the two most important drugs, isoniazid (INH) and rifampicin (RMP) - is a potential threat to tuberculosis control \(^8,9\). Patients infected with strains resistant to multiple drugs are extremely difficult to cure, and the necessary treatment is much more toxic and expensive. Drug resistance is therefore a potential threat to the standard international method of TB control: the DOTS strategy (“Directly Observed Treatment, Short-course Strategy”). The reports of recent resistant cases from Northern Pakistan have increased more suspicion about the control situation \(^9,13\). Sporadic studies have already reported the increasing incident of multi-drug resistance from various corners of the country including NWFP \(^9,12,13\). The issue of MDR-TB is complex to understand however; there is growing consensus on the fact that the covert epidemiology of MDR and geography of NWFP have a potent link with one another. The figures in table 2 reveal the synopsis of reported resistant cases and illustrate the increasing acquired resistance to multiple TB drugs at various times. Several aspects of resistance pattern in the area have yet to be unveiled and thoroughly investigated. Compared to other parts of the country, NWFP has predominantly more frequent episodes of MDR-TB \(^9,10\).

Each area in Pakistan differs in the level and pattern of resistance. The magnitude of acquired resistance to multiple drugs and above all to most commonly prescribed drugs like, Isoniazid (INH), Refampicine (R), Ethambutol (E), Pyrazinamide (P), and Streptomycine (S) have been commonly observed.

**TRENDS OF TREATMENT OUTCOME IN THE**

**NWFP**

With a population of more than 20 million, NWFP is one of the four Provinces in Pakistan that has passed through an unprecedented socio-economic, demographic and epidemiologic turmoil. Having a 2500 kilometres long border with Afghanistan, NWFP hosts more than two million Afghans refugees, and contributes heavily to the increasing national burden of TB \(^2\). Alarming, TB cases reached up to 554/100,000 annually till the end of 1998 \(^9,10\). Errors in prescription, physicians practices and knowledge in TB case management has been widely debated \(^12,13\). With the largest rural-urban disparities, NWFP has the worst urban-rural morbidity rates 196-206 per 1,000 of population in the country \(^1\). A study conducted by WHO in 1998 revealed that only one in four TB cases were properly managed and treated and only a fraction of cases are reported to the Pakistan's National TB Control Programme (NTP). Tuberculin survey in 1985 showed that the annual risk of TB infection (ARI) among Afghan children was 13.8%, while it was 13% in the native children. Moreover higher incidence of adults TB cases has also been widely reported among Afghan refugees residing inside Pakistan \(^13,22\). The coverage of the existing TB control program does not reach to all smear positive and infected cases. From 1985 to 1998 more than 19,000 sputum smear positive pulmonary cases were detected among Afghans in the NWFP. An abrupt upward trend has been observed in the number of total registered TB cases (SS positive pulmonary TB cases) from 1993 (n=1,282) to the 1999 (n=39,991) in both native and immigrant population of NWFP. TB control activities in the NWFP gained its momentum by the mutual support of NGOs, still significant proportion of already detected smear positive cases are not thoroughly supervised and followed up that turned into chronic or moderate interrupters. This also explicates the level of dissatisfaction with the quality of TB care available. Constantly, static pattern of the number defaulters shown in figure 2 signifies poor follow up and treatment completion, a challenge lying ahead of TB control. Overall, statistics have shown little evidence of any kind of resistance reported to the district authorities. Similar pattern of treatment outcomes in Sialkot-Punjab and Balochistan study \(^9,10,13\) was strongly attributed to the increase in the number of potential resistant cases.

**RESULTS**
NATIONAL TB CONTROL PARAMETERS

Analysing the progress achieved in treatment outcomes chronologically, the TB control scenario (see Table 1 and Figure 1) in Pakistan reveals that the program is not vigilant enough to follow up TB cases till they complete the treatment and get cured once they are detected. Our research substantiates the fact that chronic interrupters/defaulters and relapse cases have a higher tendency to develop resistance than the normal or newly smear positive case. Periodic surveillance to monitor the severity of the situation is rare and tracing resistant cases or follow up of defaulters/relapse cases has remained largely out of focus. Comparison between the treatment outcomes of DOTS and Non-DOTS program verify the fact that larger number of defaulters, interrupters and resistant cases are expected from the Non-DOTS areas in the country (8). Monitoring information on treatment outcomes from the non-DOTS program or from the private sector does not exist so far, making it very difficult to have a real sense of the situation. Universally known DOTS provides 100% cure from TB and effectively prevent the development of resistance among those infected (8). Limited coverage of DOTS in Pakistan has bedevilled the prospects of TB control so far and the magnitude of MDR-TB is rapidly increasing. Looking at figure 1, the trend of case detection passed through a turbulent phase as the NTP could not expand beyond the initial 25 DOTS demonstration sites (districts) across the country. Reports disclosed some vital facts that DOTS implementation and scaling up process was fairly slow even in the specified sites. Financial insufficiencies, lack of motivated trained therapy implementers and shortages of drugs at the primary level have greatly arrested further nation-wide plans for DOTS extension activities (9, 12, 29).

Table 2: Chronicle of Multiple Drug Resistance In Pakistan

<table>
<thead>
<tr>
<th>Source &amp; Year</th>
<th>Type &amp; Degree of Resistance</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilani, S, et al. 1995</td>
<td>27% Primary resistance to INH</td>
<td>Lahore-Punjab</td>
</tr>
<tr>
<td>Arab M, et al. 1990</td>
<td>44% Primary resistance to INH</td>
<td>Peshawar-NWFP</td>
</tr>
<tr>
<td>Siddiqi, et al. 1997</td>
<td>48% Primary resistance to INH &amp; PAS</td>
<td>Lahore-Punjab</td>
</tr>
<tr>
<td>Raja, A, et al. 1993</td>
<td>41% Primary resistance to INH</td>
<td>Lahore-Punjab</td>
</tr>
<tr>
<td>Ansari, A, et al. 1989</td>
<td>33% Primary resistance to INH</td>
<td>Lahore-Punjab</td>
</tr>
<tr>
<td>ECO study, 1992-93</td>
<td>16% Primary resistance to INH &amp; E</td>
<td>Peshawar-NWFP</td>
</tr>
<tr>
<td>Khan, A, et al. 1999</td>
<td>17% Primary resistance to INH &amp; E</td>
<td>Karachi-Smith</td>
</tr>
<tr>
<td>Khan, A, et al. 1999</td>
<td>16% Primary resistance to INH</td>
<td>Karachi-Smith</td>
</tr>
<tr>
<td>Hussain, M, et al. 1996</td>
<td>15% Primary resistance to INH</td>
<td>Karachi-Smith</td>
</tr>
<tr>
<td>ECO study, 1994</td>
<td>13% Primary resistance to INH</td>
<td>Peshawar-NWFP</td>
</tr>
<tr>
<td>Kamarat, K, et al. 1999</td>
<td>8% Primary resistance to INH</td>
<td>Rawalpindi-Federa</td>
</tr>
<tr>
<td>Sardar, A, et al. 1999</td>
<td>7% Acquired resistance to INH, E</td>
<td>Gujranwala-Punja</td>
</tr>
<tr>
<td>Khan, M, et al. 2002</td>
<td>11 cases, Acquired resistance to INH, E, S</td>
<td>Mardan-NWFP</td>
</tr>
</tbody>
</table>

Figure 3

Figure 4: The Trend of TB Case Registration & Outcome in NWFP

DRUG RESISTANCE PROFILE IN THE NWFP

The number of chronic defaulters (with and with out sputum smear positive), relapse, and pattern of resistance to the TB drugs were different in the Districts of Mardan, Sawabi and Peshawar. Surprisingly, the number of deaths (being infected or smear positive at the time of death) was more in the district of Mardan, where TB control was poor and resistant TB more frequently reported. Figure 3 and 4 present details of data collected by the health facility survey. The number of defaulters and resistant TB cases was higher in the District Mardan followed by Sawabi and Peshawar where resistance has been already reported in other research (9, 12, 29). Relative to other areas in the country, higher incidence of resistant TB has already been reported from the same locality where large number of migrants and unstable population reside (7). The number of transferred and lost cases was 78 and 147 respectively in the District of Mardan. Similarly the number
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of transferred and lost cases was 21 and 30 in Peshawar, and 12 and 37 in Sawabi respectively.

Figure 5

Table 3: MDR Profile of selected TB Units in NWFP-Pakistan, 2000

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Primary resistance</th>
<th>Acquired resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>% of all cases</td>
</tr>
<tr>
<td>INH-R-S</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>INH-R-E-S</td>
<td>1</td>
<td>0.07</td>
</tr>
<tr>
<td>HRE</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>HR</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 6

Figure 3: Distribution of cases by treatment outcome, 2000

Generally, majority of patients were chronic interrupters and defaulters with predominantly acquired resistance to multiple TB drugs. Admittedly, all resistant patients had the previous history of chronic disruption to therapy. In the pursuit of more effective therapy, 2% of patients in Sawabi, 9% in Mardan and 3% in Peshawar used remedies other than medical, such as, homeopathic, herbal and traditional medicine. Inadvertently, ignorance of the program to the non-adherent status of the chronic defaulters, interrupters (with sputum smear positive) was common. This has allegedly delayed the sputum conversion in patients and also the restarting of the appropriate and timely chemotherapeutic regimen. The facilities overall made no efforts to trace and improve the adherence of this particular group of patients.

Coupled with the scrutiny of the culture sensitivity reports and sputum microscopy, physical examination of patients provided insight into the pattern of drug resistance. Acquired resistance to four major drugs was more prevalent than the primary resistance. Overall in the category of primary resistance, mono-resistance was noticed mainly to 11 cases of INH, 9 of R, 0 of E, and 19 of S, while it was 52 of INH, 23 of R, 14 of E, and 23 to S in the category of acquired resistance respectively. More surprising was the resistance observed to the major and multiple anti-TB drugs. Table 3 shows brief overview of MDR (n=266) cases traced in all three facilities. Pulmonary TB was predominantly (82%) more than the extra-pulmonary cases among all the resistant cases. Overwhelming resistance was observed for multiple TB drugs commonly prescribed in the regimens.

More in-depths research is required to investigate the reasons for patient's non-adherence in the community. Patient's willingness to visit the facility at daily basis was poor and greatly jeopardized the supervision and follow up of cases. As shown in the figure 3, non-adherence was commonly observed with the prescribed therapy and was attributed to the shortage of drugs and lack of proper diagnostics. In the District of Mardan, DOTS has been initiated since 1995 on a limited scale. The responsibility of direct supervision was assigned to the national health workers (NHWs), already appointed for primary health care activities. All facilities on the contrary, were lacking in the trained staff to implement supervised therapy or to conduct door-to-door campaign in the community. Misconception exits on the term DOTS among the health care providers. Patients were advised to visit the facility on monthly or weekly basis, which transformed DOTS to monthly (MOTS) or weekly directly observed treatment (WOTS) short-course respectively. Non-compliance with the NTP's guidelines was observed during case management. Chronic patients (SS positive) were given less education about therapy and not subjected to DOT but were rather put on longer therapies which was supplemented with antibiotic (10, 13, 23, 26).

CAPACITIES AND FACILITIES IN THE TB UNITS

Capacities in terms of diagnostics, manpower and drugs in the surveyed facilities were extremely insufficient. On average, each TB unit deals with 80 patients per day and spends less than ten minutes while examining the patient. With respect to the increasing caseload, facilities are extremely limited. This has greatly undermined the performance and the quality of care in District Mardan and Peshawar. Shortages of commonly recommended drugs like INH, R and E has become very often. Drugs supply is done annually or after six month each and some facilities have to wait even longer to receive their stocks. Facilities usually do not provide Drug Susceptibility Testing (DST) for MDR-TB and screening of HIV-TB synergism is entirely non-existent. Except those supervised by the international NGOs, that provide such diagnostics facilities on limited scale, patients are otherwise sent to the private laboratories. Patients in most resistant states are advised second line drugs (e.g.,
amikacin, kanamycin, capreomycin, cycloserine, paraaminosalicylic acid (PAS), ethionamide, and the fluoroquinolones) from the private markets which are highly expensive and mostly out of their financial reach. This has put the health care providers as well as the patients into a financial dilemma. This has been the most commonly reported reason for frequent disruption of the therapy (10, 15, 17, 19, 20, 21). In the diagnosis and follow up cases, x-ray examination and blood profiling is more emphasized than sputum microscopy. Sputum Microscopy is available but performed in un-standardized manner with unhygienic and locally modified methods, which do not comply with IUATLD/WHO guidelines (17, 23, 27). The chances of exogenous re-infection and cross-contamination are more than high which might also pertain to the confusion in mixed infections, exogenous re-infection and cross-contamination. Unavailability of appropriate media for the growth of bacilli, necessary apparatuses and chemicals greatly limit laboratory capacities in the TB units. Disposable syringes and gloves are not available.

The questions on laboratory hygiene were phrased in a similar manner in all TB units. Facilities that normally do or do not use the disposable items were asked about the disposal practices. The staff in the facilities of district Mardan argued that the heavy number of patients and shortage of essential laboratory items greatly compromises the personal protection measures and also the patient’s protection against contracting infection.

**Figure 7**
Table 4: Major components for the implementation of a DOTS-Plus strategy

<table>
<thead>
<tr>
<th>Component</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) efficient, effective and integrated TB control programme;</td>
<td></td>
</tr>
<tr>
<td>(ii) frontline and second-line anti-TB drugs provided free of charge to</td>
<td>each patient with MDR-TB;</td>
</tr>
<tr>
<td>the patients;</td>
<td></td>
</tr>
<tr>
<td>(iii) drug susceptibility tests for frontline and second-line anti-TB</td>
<td>drugs, not charged to the patients;</td>
</tr>
<tr>
<td>drugs;</td>
<td></td>
</tr>
<tr>
<td>(iv) appropriately designed regimens for MDR-TB, standardised or</td>
<td>individualised;</td>
</tr>
<tr>
<td>individualised;</td>
<td></td>
</tr>
<tr>
<td>(v) a reporting system for data management, monitoring and evaluation</td>
<td>of individual and aggregated data on MDR-TB cases;</td>
</tr>
<tr>
<td>of individual and aggregated data on MDR-TB cases;</td>
<td></td>
</tr>
<tr>
<td>(vi) community-based strategies, with the participation of local</td>
<td>governments in order to enhance adherence to the regimens;</td>
</tr>
<tr>
<td>governments in order to enhance adherence to the regimens; and</td>
<td></td>
</tr>
<tr>
<td>(vii) the adequate training and organisation of health professionals</td>
<td>responsible for the cure of MDR-TB patients.</td>
</tr>
<tr>
<td>responsible for the cure of MDR-TB patients.</td>
<td></td>
</tr>
</tbody>
</table>

Source: WHO, 2001

**DISCUSSION**

TB control in Pakistan has some serious shortfalls. The program has been widely criticized for its low impact and for not responding to the changing TB pattern. Diversified approach adopted in both public and private TB units have created challenges like drug resistance in the country. Starting from the planning and management, limited coverage, poor quality of TB care and active surveillance has been widely blamed for the current situation. Coupled with the increasing burden of MDR-TB among the indigenous population, the influx of TB cases across the borders has added to the ongoing epidemiological transition in the country (9, 10, 11, 12, 13). TB control in Pakistan has received little attention so far. However this has started changing in the last few years. Realizing the seriousness of the control situation, several international NGOs like ICD, ATAG, SRCS and GL&TBC have started TB control programs for more than three millions of Afghan refugees inside Pakistan. However, majority of smear positive population have either no or poor access to TB control services. Research on TB control dynamics has already shown that no control is better than poor control (14). It provides favourable conditions to delay sputum conversion, weakens the physical conditions of the patients and gives Mycobacterium a chance to develop resistance.

Our study provided significant clues about the epidemiological transition taking place particularly in the Northern Pakistan. In spite of the increasing number of defaulters, chronic treatment interrupters and resistance to TB drugs, NTP still emphasizes on detection of cases rather than cure, follow up or treatment completion. Resistance pattern provides ample proof for local health care providers to reconsider their treatment regimens, i.e., pay more attention to the cure of already registered patients and
strictly follow chronic interrupters (SS positive) and resistant cases. Acquired resistance is higher than the primary and more frequent to the two widely prescribed TB drugs, isoniazid and rifampicin in Pakistan. Acquired resistance shows more recent program mismanagement and is more lethal to control program where the treatment success rate is less than 70%. In such situation DOTS needs to be a top priority in order to improve program performance (2). Tuberculosis in Pakistan has a “knock on” effect especially through migration and overcrowding that has brought significant increase in the number of cases. Though the reasons for this increase are multi-factorial, however, it is still within the capability of health authorities to exert efforts and to conduct extensive research to regain the upper hand in the war against tuberculosis. The programme benefits of treatment against MDR-TB are being evaluated elsewhere (2). The costs are substantial and treating new drug-resistant strains costs approximately $5,000 per patient and multidrug-resistant strains are often incurable even with potent antibiotics. Such treatment requires the administration of drugs that are more toxic and less effective and are given for at least three times longer period and exponentially more than the cost of basic short-course chemotherapy regimens (3). The highest priority in stopping MDR-TB must therefore be in its prevention. The establishment of DOTS programmes has long been shown to reduce the development of MDR-TB in addition to cutting TB mortality by 70% (2, 28).

A good laboratory and directly observed therapy are integral part of any successful TB control Program. To screen MDR among patients, detection facilities and the needs of laboratories are not met in any of the facilities selected for survey. Pakistan is a resource-poor country, where national programmes can barely afford universal access to DOTS. Settings with multi-drug resistance levels above 5% represent public health emergencies, which require a complete overhaul of control activities and outbreak control operations, and co-2). Episodes of MDR in crowded settings such as shelters or prisons, refugee camps particularly among debilitated individuals, are a common denominator in MDR-TB in high burden countries. No single intervention can control MDR-TB but the various tools available should be applied wisely. This is imperative that the DOTS intervention be first modified locally with the subsequent emphasis on the availability of second-line drug treatment. In the absence of an effective TB control programme, a narrow focus on MDR-TB therapy could, paradoxically, make a bad situation worse. Pakistan can't afford to spend resources on curing a single case of MDR-TB that could be used to treat 100 new TB patients. Acquired MDR-TB is ubiquitous in NWFP and the area is near to emerge as a hot spot in the country. This certainly requires urgent attention and prompt actions of the local as well central Government. Worldwide, less than one-third of patients with TB are treated in DOTS programmes. At the most, half the estimated number of the patients with TB is officially detected and hardly 60% complete the treatment (2, 3). Thus, from a public health perspective, the top priority should be given to the expansion of DOTS and then to implement DOTS-Plus strategy. The major components for the implementation of a DOTS-Plus strategy are in table 4.

As Pablos-Méndez et al. suggested (2), a DOTS-Plus strategy is essential to control MDR-TB once DOTS programme has been successfully established and is being adequately implemented. Countrywide public health and political commitment is vital to sustain the DOTS strategy that remains the most important element for implementing DOTS-Plus strategies. The DOTS-Plus initiative has led already to the dramatic decline in the prices of second-line drugs (3-30). Globally pilot projects have started implementing DOTS-Plus and will provide important guidance on the evidence-based expansion of treatment against MDR-TB. Additional funds need to be allocated for NTP, as it is essential to increase human and financial resources for the expansion of DOTS. The top priority should be to improve basic treatment strategies in order to prevent the emergence of MDR-TB. Only a comprehensive approach, tailored to local conditions, can be expected to prevent the epidemic regarding MDR-TB. For treatment to be undertaken on a large scale it is important to reduce the cost of second-line drugs further, implement outbreak control, maintain surveillance, improve diagnostic testing, and develop new anti-TB drugs.

In the light of facts stated above it is recommended that: a) Immediate policy steps be initiated to standardize treatment regimen, universally implement DOTS and DOTS Plus in areas where MDR is highly prevalent; b) National commitment be made to accelerate detection, enhance cure rates and improve adherence and awareness among TB patients; c) effective partnerships be built for sustainable actions; d) Emphasis be focused upon capacity building, resources provisions and active case finding; e) Laboratories be equipped with all essential procurement required for
MDR detection at all fronts and; f) More clinical and community based research be conducted and periodic surveillance regarding MDR-TB be instituted.

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GLOSSARY
Mycobacterium tuberculosis: bacteria that cause latent TB infection and TB disease.

Pulmonary TB - TB disease that occurs in the lungs, usually producing a cough that lasts longer than 2 weeks. Most TB disease is pulmonary.

Extra-Pulmonary TB: TB involving other areas than lungs.

Sputum Smear: a test to see whether there are TB bacteria in your phlegm. To do this test, lab workers smear the phlegm on a glass slide, stain the slide with a special stain, and look for any TB bacteria on the slide. This test usually takes 1 day.

Sputum- phlegm coughed up from deep inside the lungs. Sputum is examined for TB bacteria using a smear; part of the sputum can also be used to do a culture.

TB disease - an illness in which TB bacteria are multiplying and attacking different parts of the body. The symptoms of TB disease include weakness, weight loss, fever, no appetite, chills, and sweating at night. Other symptoms of TB disease depend on where in the body the bacteria are growing. If TB disease is in the lungs (pulmonary TB), the symptoms may include a bad cough, pain in the chest, and coughing up blood.

Treatment success rate: the proportion of new patients who complete the scheduled treatment whether bacteriological cure is documented or not

Primary drug resistance: Resistance developed in patients who have not had prior treatment with anti-TB.(if it is certain that patient has not had previous treatment)

Acquired drug resistance: Resistance developed in patients with a record of previous treatment of more than one month.

Multiple drug resistance: Resistance developed to two or more vital anti-TB drugs in one time.

Relapse Case: when a sputum smear negative patient turns to be positive again

Failure Case: It is a TB patient who excretes bacilli either after 5 months of chemotherapy given after direct observation by a health worker or after completion of fully supervised retreatment regimen of 8 month.

Defaulter case: failure of a patient after registration (sputum smear positive)have not collected drugs for more than two months.

Isoniazid (INH): a drug used to prevent TB disease in people who have latent TB infection. INH is also one of the five drugs often used to treat TB disease.

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