Review Article

Multidrug Resistant Tuberculosis: Trends and Control

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Abstract

Multidrug resistant tuberculosis (MDR-TB) has been an area of growing concern and is posing a threat to the control of tuberculosis (TB). The exact magnitude of problem of resistance to anti-tuberculosis drugs worldwide was not known till the 1994-97 global project on anti-tuberculosis drug resistance surveillance initiated by the World Health Organization (WHO) and International Union Against Tuberculosis and Lung Diseases (IUATLD). The Global Tuberculosis Report 2014 estimated that an 3.5% of newly diagnosed and 20.5% of previously treated TB cases had MDR-TB. It has been estimated that 480,000 cases emerged and 210,000 deaths occurred due to MDR-TB globally in 2013. In India, estimates showed that the prevalence of MDR-TB among new and previously treated patients was 2.2% and 15%, respectively. It is estimated that 99,000 cases of MDR-TB emerge every year of which 62,000 were among notified cases of TB in 2013. The MDR-TB is a human-made problem and results largely from poorly managed cases of TB. Adequate, timely diagnosis and optimal treatment of MDR-TB will help curb the epidemic. Efforts must be focused on the effective use of anti-tuberculosis drugs in every new patient, so as to prevent the emergence of MDR-TB. **[Indian J Chest Dis Allied Sci 2014;56:237-246]**

Key words: Tuberculosis, MDR-TB, Trends.

Introduction

Drug resistant tuberculosis (TB) has been reported since the early days of introduction of anti-TB chemotherapy, but multi-drug resistant TB (MDR-TB) has been an area of growing concern in recent years, and is posing threat to global efforts for TB control. The exact magnitude of the problem of MDR-TB worldwide was not known till the 1994-97 global project on anti-TB drugs resistance surveillance initiated by the World Health Organization (WHO) and International Union Against Tuberculosis and Lung Diseases (IUATLD). The prevalence of MDR-TB mirrors the functional state and efficacy of TB control programmes and realistic attitude of the community towards implementation of such programmes.[1] This write-up aims to review the present status of MDR-TB globally.

Definition

Multidrug resistant tuberculosis (MDR-TB) is defined as disease due to *Mycobacterium tuberculosis* that is resistant to isoniazid and rifampicin with or without resistance to other drugs (the culture and drug susceptibility test results being from an accredited laboratory).

Types of Drug Resistance

Drug resistance is categorised into two types — Primary and Acquired. Primary drug resistance is defined as drug resistance in a patient who has not received any anti-tuberculosis treatment (ATT) in the past. The resistance that develops in a patient who has received prior chemotherapy is defined as acquired drug resistance. Recently the terms "resistance in new cases" and "resistance in previously treated cases" have been proposed for the use due to difficulty in confirming the validity of the patient's past history of treatment. When one is not sure whether the resistance is primary or acquired due to a concealed history of previous treatment or unawareness of treatment taken before, it is known as initial drug resistance. Thus, initial resistance is primary resistance plus some undisclosed acquired resistance. Combined resistance is defined as the sum of primary and acquired resistance.

Prevalence of MDR-TB: Global

A review of a series of 63 surveys of drug resistant TB carried out between 1985 to 1994 by the WHO led to the conclusion that the problem of drug resistance was global.[2] The overall prevalence of resistance to different anti-TB drugs obtained from different surveys carried out throughout the world are shown in tables 1 and 2. The rate of MDR-TB was very low in most of the surveys ranging from 0% to 10.8% for primary resistance and from 0% to 48% for acquired resistance. Multidrug resistance (MDR) was reported to range from 0.5% to 14.3% in surveys where there was no distinction between primary and acquired resistance. In most regions of the world, rates of MDR-TB were very low,[2] except in New York and Nepal where high

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rates of acquired type MDR-TB were reported. It is evident that the prevalence of drug resistant TB varies considerably throughout the world. The reasons for this variation in different surveys were the selection of patients studied, the degree of misuse of drugs, the quality of enquiry regarding previous treatment and the poor quality of culture and drug susceptibility facilities in many parts of the world.

prevalence of MDR was found in the former Soviet Union, Asia, Argentina and the Dominican Republic. The WHO for the first time introduced the term MDR 'hotspots' for areas where high prevalence of MDR-TB has been observed. The 'hotspots' referred to the countries or regions where the combined prevalence of MDR-TB exceeded 5%. The report concluded that resistance to anti-TB drugs was found in all the

Table 1. Global primary/initial drug resistance

Study	Any Drug	Any H %	Any S %	Any R %	Any E%	H+R%
Cohn *et al* review of 63 surveys (1985–1994)[2]	—	0.0–16.9	0.1–23.5	0.0–3.0	0.0–4.2	0.0–10.8
WHO-IUATLD surveillance (1994–1997)[3]	9.9 (2.0–40.6)	7.3 (1.5–1.7)	6.5 (0.3–8.0)	1.8 (0.0–16.8)	1.0 (0.0–9.9)	1.4 (0.0–14.4)
WHO-IUATLD surveillance (1996–1999)[6]	10.7 (1.7–36 .9)	6.2 (0.0–28.1)	5.2 (0.3–32.4)	1.2 (0.0–15.8)	0.6 (0.0–11.1)	1.0 (0.0–14.1)
WHO-IUATLD surveillance (1999–2002)[12]	10.2 (0.0–57.1)	5.7 (0.0–42.6)	6.3 (0.0–51.5)	1.4 (0.0–15.6)	0.8 (0.0–24.8)	1.1 (0.0–4.2)
WHO-IUATLD surveillance (2002–2007)[14]	17.0 (0–56.3)	10.3 (0.0–42.4)	10.9 (0.0–51.5)	3.7 (0.0–22.7)	2.5 (0.0–24.8)	2.9 (0.0–22.3)
M/XDR-TB Global report on surveillance and response (2010)[15]	—	—	—	—	—	0.0–28.3
Global TB Report (2013)[16]	—	—	—	—	—	3.7 (0.0–32.3)
Global TB Report (2013)[17]	—	—	—	—	—	3.6 (0.0–35.0)
Global TB Report (2014)[18]	—	—	—	—	—	3.5 (0.0–35.0)

H= Isoniazid; S= Streptomycin; R=Rifampicin; E= Ethambutol

Table 2. Global acquired drug resistance

Study	Any Drug	Any H %	Any S %	Any R %	Any E%	H+R%
Cohn *et al* review of 63 surveys (1985–1994)[2]	—	4.0–53.7	0.0–19.4	0.0–14.5	0.0–13.7	0.0–48.0
WHO-IUATLD Surveillance (1994–1997)[3]	36.0 (5.3–100.0)	—	—	—	—	13.0 (0.0–54.4)
WHO-IUATLD Surveillance (1996–1999)[6]	23.3 (0.0–93.8)	19.6 (0.0–50.0)	12.4 (0.0–53.4)	12.0 (0.0–50.0)	5.9 (0.0–32.1)	9.3 (0.0–48.2)
WHO-IUATLD Surveillance (1999–2002)[12]	18.4 (0.0–82.1)	14.4 (0.0–71.0)	11.4 (0.0–77.1)	8.7 (0.0–61.4)	3.5 (0.0–54.2)	7.0 (0.0–58.3)
WHO-IUATLD Surveillance (2002–2007)[14]	35.0 (0.0–85.9)	27.7 (0.0–81.2)	20.1 (0.0–83.5)	17.5 (0.0–62.5)	10.3 (0.0–54.3)	15.3 (0.0–62.5)
M/XDR-TB Global report on surveillance and response (2010)[15]	—	—	—	—	—	0.0–61.6
Global TB Report (2012)[16]	—	—	—	—	—	20.0 (0.0–65.1)
Global TB Report (2013)[17]	—	—	—	—	—	20.0 (0.0–69.0)
Global TB Report (2014)[18]	—	—	—	—	—	20.5 (0.0–62.3)

H= Isoniazid; S= Streptomycin; R=Rifampicin; E= Ethambutol

Considering the limitation of the previous studies, a WHO/IUATLD global project on drug resistance surveillance spread over 35 countries in 5 continents was carried out between 1994-1997.[3] The median prevalence of primary and acquired MDR was reported to be 1.4% (0-14.4%) and 13% (0-54.4%), respectively (Tables 1 and 2). Particularly high 35 countries and regions surveyed, suggesting that the problem was global.

A second WHO/IUATLD global project on drug resistance surveillance in 58 countries/geographical sites was carried out in 1996-1999.[4] Trends of drug resistance were also observed from 28 sites. The median prevalence of primary and acquired MDR was reported

as 1% (0-14%) and 9% (0-48%), respectively. Of the 58 sites surveyed, drug resistance among new and previously treated cases was reported from 54 and 48 sites, respectively. Most of the previous 'hotspots' of MDR-TB were confirmed again; however, new areas in Russia and China were added. This global survey tested a total of 61,415 patients with TB (median per site 661; range 41-12,675). These sites accounted for 610,000 (18%) of the 3.3 million cases of TB reported to WHO in 1997 and 1.5 billion (26%) of the world's 5.8 billion inhabitants. Several countries including 11 of the 22 high-burdened TB countries of the world had not yet been surveyed. A mathematical model had estimated the magnitude of MDR-TB worldwide and suggested that in the year 2000, 3% (273,000; 95% CI, 185,000-414,000) of all new and previously treated TB cases had MDR-TB.[5] The trend analysis confirmed that MDR-TB was not a major problem in countries that had been implementing TB control programmes according to international guidelines for several years. Botswana, Chile, Cuba, Czech Republic and Uruguay had all showed a very low prevalence of MDR-TB confirming that efficient TB control programmes prevents the occurrence and spread of MDR-TB. [4,6-11]

A third WHO/IUATLD global project on drug resistance surveillance in 77 countries/geographical sites was carried out in 1999-2002[12] representing 20% of the global total of new smear positive TB cases. It included 39 settings not previously included in the Global Project and reported trends for 46 sites. Median prevalence of primary and acquired MDR was reported as 1.1% (0-14.2%) and 7% (0-58.3%), respectively (Tables 1 and 2). This report analysed the distribution of MDR prevalence (among new cases) from 74 sites. After analysis, the cut-off value for hotspots was reset to MDR prevalence of more than 6.5% among new cases. There were 10 countries regarded as hotspots with MDR-TB prevalence, *viz* Ecuador (6.6%), Henan (7.8%), Latvia (9.3%), Lithuania (9.4%), Liaoning (10.4%), Estonia (12.2%), Uzbekistan (13.2%), Tomsk Oblast (13.7%), Israel (14.2%) and Kazakhastan (14.2%). Despite the expansion in coverage of drug-resistance surveillance for both new and previously treated cases in recent years, data on drug resistance was still not available from more than 100 countries. To estimate the levels of drug resistance in places where direct data was not available, Zignol *et al*[13], developed statistical models for sites where data were available and applied them to places where the data was not available. After their analysis, they revealed that the total number of MDR-TB cases estimated to have occurred worldwide in 2004 was 424,203 (95% CI, 376,019–620,061), or 4.3% (95% CI, 3.8–6.1) of all new and previously treated TB cases. Three countries—China, India, and the Russian Federation—accounted for 261,362 (95% CI, 180,779–414,749) MDR-TB cases (62% of the estimated global burden). In the same year, the total number of MDR–TB cases was 2.7% (95% CI, 2.4-3.8) of 8,987,743 new cases (242,794, 95% CI, 209,363-350,291) and 18.4% (95% CI, 14.2-31.7) of the previously treated cases (181,408, 95% CI, 135,276–319,017). This study provided a new comprehensive set of estimates of the incidence of MDR-TB in 184 countries globally. They have found lower rates of MDR-TB in countries of Central Europe, such as Hungary, Macedonia and Turkey in comparison to previous studies. Their study showed a positive correlation between the proportion of patients who had previously received treatment and proportion of MDR-TB cases among new cases.

A fourth WHO/IUATLD global project on drug resistance surveillance that included drug susceptibility test (DST) results from 91,577 patients from 93 sites in 81 countries and 2 special administrative regions (SARs) of China was collected between 2002 and 2007 and represented 35% of the global total of notified new smear-positive TB cases.[14] It included data from 33 countries that had never been previously reported. New data were included from the high TB burden countries including India, China, Russian Federation, Indonesia, Ethiopia, Philippines, Vietnam, Thailand and Myanmar. Between 1994 and 2007 a total of 138 sites in 114 countries and 2 SARs of China had reported data to the global project. The median prevalence of primary and acquired MDR-TB globally was 2.9% (95% CI, 2.2-3.6) and 15.3 % (95% CI, 9.6-21.1), respectively. The global population weighted proportion of MDR among all TB cases was 5.3% (95% CI, 3.9-6.6). It was estimated that 489,139 MDR-TB cases emerged in 2006 globally and the global proportion of MDR among all new and previously treated cases was 4.8%. According to the data, China and India carried approximately 50% of the global burden and Russia a further 7% in 2008. Multidrug and extensively drug-resistant TB (MDR-/XDR-TB) 2010 Global report on surveillance and response, estimated that 440,000 (95% CI, 390,000–510,000) cases of MDR-TB emerged globally in 2008. Among all incident TB cases globally, 3.6% (95% CI, 3.0–4.4) were estimated to have MDR-TB. These estimates, which lie in the same range as the previous ones, were based on more data and a revised methodology. Almost 50% of the MDR-TB cases worldwide were estimated to occur in China and India. In 2008, MDR-TB caused an estimated 150,000 deaths.[14] Surveillance of anti-TB drug resistance in the world during 2007–2010, published in 2012, updated the resistance to first-line anti-TB drugs.[15] The data was reported from 80 countries and 8 territories, 72 of which provided data from continuous surveillance and 16 from special surveys. The proportion of new TB cases reported as showing MDR in these years ranged from 0% to 28.3%. Proportions exceeding 12% (in countries reporting more than 10 MDR-TB cases from 2007-10) were documented in Belarus (25.7%), Estonia (18.3%), several oblasts of the Russian Federation (with

Murmansk having the highest level, 28.9%) and Tajikistan (Dushanbe city and Rudaki district, 16.5%). The proportion of previously treated cases having MDR-TB ranged from 0% to 65.1%. Countries or sub-national areas with proportions exceeding 50% included Belarus (60.2%), Lithuania (51.5%), the Republic of Moldova (65.1%), five oblasts of the Russian Federation, and Tajikistan (Dushanbe city and Rudaki district, 61.6%). The largest country that conducted a nation-wide survey in the reporting period was China, where 5.7% of new TB cases and 25.6% of previously treated cases were found to have MDR.

The Global Tuberculosis Report 2012[16] summarised the status of progress in global surveillance of anti-TB drug resistance, using the data on MDR-TB and XDR-TB. Data on drug resistance was collected and analysed from 135 countries worldwide (70% of WHO 194 Member States). This included 63 countries that have continuous surveillance systems based on routine diagnostic drug susceptibility test (DST) of all TB patients and 72 countries that relied on special surveys of representative samples of patients. During the past four years, most of the 27 high MDR-TB and 22 high-TB burden countries have expanded coverage of surveillance of drug resistance to obtain more accurate estimates of the burden of MDR-TB. Globally, 3.7% (95% CI, 2.1–5.2) of new cases and 20% (95% CI, 13–26) of previously treated cases were estimated to have MDR-TB. Proportions of MDR-TB in new TB cases ranged from 0% to 32.3% and were highest in Belarus (32.3%), Estonia (22.9%), Kazakhstan (30.3%), Kyrgyzstan (26.4%), the Republic of Moldova (19.4%) and Uzbekistan (23.2%). The proportion of MDR-TB in previously treated TB cases at country level ranged from 0% to 65.1%. Countries or sub-national areas with the highest reported proportions were Azerbaijan (Baku city, 55.8% in 2007), Belarus (75.6% in 2011), Estonia (57.7% in 2011), Kazakhstan (51.3% in 2011), Kyrgyzstan (51.6% in 2011) the Republic of Moldova (63.5% in 2011), Tajikistan (53.6% in 2011) and Uzbekistan (62% in 2011). There were an estimated number of 310,000 cases of MDR-TB among the notified cases of TB across the globe in 2011. India, China and Russian Federation contribute to almost 60% of the estimated global burden of MDR-TB.[16]

The Global Tuberculosis Report 2013[17] included data from drug resistant surveys and continued surveillance among notified TB cases. The data suggested that 3.6% of the newly diagnosed TB cases and 20% of those previously treated for TB had MDR-TB in 2012. The highest levels of MDR-TB were found in eastern Europe and central Asia, wherein some countries more than 20% of new TB cases and more than 50% of those cases previously treated for TB had MDR-TB. Among new cases, Azerbaijan (22.3% in 2007), Belarus (34.8% in 2012), Estonia (19.7% in 2012), Kazakhstan (22.9% in 2012), Kyrgyzstan (26.4% in 2011), Republic of Moldova (23.7% in 2012), Russian Federation (average: 23.1%, with Yamalo-Nenets autonomous area being the highest: 41.9% in 2011) and Uzbekistan (23.2% in 2011). Among previously treated cases, examples include Azerbaijan (Baku City: 55.8% in 2007), Belarus (68.6% in 2012), Estonia (50.0% in 2012), Kazakhstan (55% in 2012), Kyrgyzstan (68.4% in 2012), the Republic of Moldova (62.3% in 2012), Tajikistan (56.0% in 2012) and Uzbekistan (62.0% in 2011). Globally in 2012, an estimated 450,000 people developed MDR-TB and there were an estimated 170,000 deaths from MDR-TB.[17]

The Global Tuberculosis Report 2014[18] included data on anti-TB drug resistance and was available for 144 countries, accounting for 95% of the world's population. Globally, an estimated 3.5% (95% CI, 2.2–4.7) of new cases and 20.5% (95% CI, 13.6–27.5) of previously treated cases had MDR-TB. In 2013, there were an estimated 480,000 (range: 350,000–610,000) new cases of MDR-TB worldwide, and approximately 210,000 (range: 130,000–290,000) deaths from MDR-TB. Among patients with pulmonary TB who were notified in 2013, an estimated 300,000 (range: 230,000–380,000) had MDR-TB. Among new cases, the proportions with MDR-TB were highest in Belarus (35.2% in 2013), Kazakhstan (25.2% in 2013), Kyrgyzstan (26.4% in 2011), the Republic of Moldova (23.7% in 2012), the Russian Federation (average: 19.3% in 2012) and Uzbekistan (23.2% in 2011). Among the previously treated TB cases, the proportions with MDR-TB were highest in Belarus (54.5% in 2013), Kazakhstan (55% in 2012), Kyrgyzstan (55.1% in 2013), the Republic of Moldova (62.3% in 2012), Tajikistan (56% in 2012) and Uzbekistan (62.0% in 2011).[18]

Time Trends in MDR-TB: Global

The Global Project has collected data from 127 countries and trend analysis included data from all global reports between 1994 and 2010, as well as data provided between the publication of reports.[15] This included 64 countries that have continuous surveillance systems based on routine diagnostic DST of all the patients. The remaining 63 countries have relied on special surveys of representative samples of patients. Of the 127 countries with surveillance information, 56 have data for one year only, 20 for two years, and 51 for three or more years. Data on time trends in drug resistance were available from 71 countries. In a first group of countries, composed of Botswana, Peru and the Republic of Korea, the estimated notification rate of MDR-TB is increasing (+10.9%, +19.4% and +4.3% per year, respectively). In these countries, trends in notifications of new TB cases varied, with a clear increase in the Republic of Korea (+7.4% per year), a rather stable trend in Botswana (+0.3% per year) and a clear decline in Peru (–3.3% per year). A second group is composed of three Russian

oblasts where TB notification rates were stable or decreasing. Although in these oblasts, MDR-TB rates were on the rise until around 2005–2006, these have subsequently been falling in all three sites. In a third group of countries, composed of Estonia, Latvia and the United States, surveillance data suggested that both TB and MDR-TB rates have been falling for more than a decade. In the United States the rate of MDR-TB has decreased even more quickly than the TB case notification rate. A new analysis of trends published in the Global Tuberculosis Report 2014, focusing on the years 2008 to 2013 showed that, at the global level, the proportion of new cases with MDR-TB remains unchanged. However, serious MDR-TB epidemics in some countries jeopardise the progress achieved in control of MDR-TB.[18]

Prevalence of MDR-TB: India

Though the development of drug resistance in India was noted since the beginning of the chemotherapeutic era, it was based on clinical perception and several isolated reports, these failed to provide complete information of the national situation as a whole. The first definite step was taken in this direction in 1965–67, when the Indian Council of Medical Research (ICMR) conducted two surveys to estimate the prevalence of drug resistance.[19] Since then, several studies have been conducted in different parts of the country. Prevalence of MDR among new cases (Table 3) has varied between 0% to 5%.[6, 12-14, 16, 17, 20-34] The overall impression as seen in table 3 is that primary MDR has remained more or less constant over the years.

Table 3. Primary/Initial drug resistance in India

Study	Prevalence	Total	Any H %	Any S %	Any R %	H+R %
ICMR (1969)[19]	22	15.5	13.8	—	—	
Krishnanswamy and Rahim 1976[20]	—	10.6	9.5	—	—	
Trivedi and Desai (1988)[21]	20	13.9	7.4	0	0	
Chandrasekaran *et al* (1990)[22]	21.2	17.4	5.7	3	1.3	
Chandrasekaran *et al* (1992)[23]	Rural	34.9	32.8	5.1	4.4	3.4
	Urban	20.5	17.3	4.1	2.9	1.4
Parmasivan *et al* (1993)[24]	North Arcet of (1985-89)	25.0	13.0	4.0	2.0	1.6
	Pondicherry (1985-91)	13.9	6.0	4.0	0.9	0.7
Gupta *et al* (1993)[25]	19.5	10.1	7.6	3	0.7	
Jain *et al* (1993)[26]	—	18.5	—	0.6	0.4	
Jena *et al* (1996)[27]	7.9	2.9	4.9	1	0.4	
Parmasivan *et al* (2000)[28] (Tamil Nadu)		18.8	15.4	6.8	4.4	3.4
Prasad *et al* (2001)[29]	27.4	15.6	11.7	3.9	5.0	
WHO-IUATLD (1996–1999)[6]	18.8	15.4	6.8	4.4	3.4	
Paramasivan *et al* (2002)[30]	North Arcot (South) 1999	27.7	23.4	12.4	2.8	2.8
	Raichur (South) 1999-2000	21.9	18.7	7.2	2.5	2.5
WHO-IUATLD (1999–2002)[12]	Wardha	19.8	15.2	7.6	0.5	0.5
Sofia *et al* (2004)[31]		27.7	13.7	22.5	2.6	2.2
Mahadeo *et al* (2005)[32]	Mayurbhanj 2000-2002	5.3	2.5	3.9	0.7	0.7
	Hoogli 2000-2001	16.7	10.3	13.7	3.0	3.0
Zignol *et al* (2006)[13]	—	—	—	—	—	2.4
WHO/IUATLD (2002–2007)[14]		—	11.71	9.96	2.2	2.8
Jain *et al* 2008[33]	Lucknow	29.8	20.1	20.1	12.5	13.2
Ramachandran *et al* (2009)[34]	Gujarat 2005- 2006	21.0	11.0	15.0	2.5	2.4
M/XDR-TB Global report on surveillance and response (2010)[14]	—	—	—	—	—	2.3
Global TB Report (2012)[16]	—	—	—	—	—	2.1
Global TB Report (2013)[17]	—	—	—	—	—	2.2
Global TB Report (2014)[18]	—	—	—	—	—	2.2

H= Isoniazid; S= Streptomycin; R=Rifampicin; E= Ethambutol

The acquired MDR (Table 4) rates have varied from 6%–100%.[3,6,13,14,16,17,21,26,30,33-41] In a study conducted in Gujarat, it was found that 95% of the rifampicin resistant strains were also resistant to isoniazid or streptomycin or both. The WHO/IUATLD surveillance[3] in India reported the combined prevalence of MDR to be 13.3% (95% CI, 10.9–14.9) in 1998; however, this was done on a small sample of 2240 people around Delhi city, and therefore, was not representative of the country.[3]

44,653 cases (95% CI, 13,547–85,068) among 1,824,395 new cases or 2.4% (95% CI, 1–5) and 42,760 cases (95% CI, 6068–171,774) among 290,019 previously treated cases or 14.7% (95% CI, 2.1–56.9), respectively. The estimated incidence of MDR-TB among new and previously treated cases was 87,413 (4.1%) of all the TB cases in India.[13] The fourth global surveillance of WHO/IUATLD[14], carried out in 2002–2007 also reported new data from Gujarat giving the first reliable source of data with regard to MDR-TB among

Table 4. Acquired drug resistance in India

Study	Total Prevalence %	Any H %	Any S %	Any R %	H+R %
ICMR (1969)[19]	32 (22–74)	15–69	12–63	—	—
Trivedi and Desai (1988)[21]					
1980	50.1	34.5	26	2.8	95% of R resistant were resistant to H or S or both
1986	65.3	55.8	—	37.3	—
Datta *et al* 1993[35]	—	67.0	26.0	12.0	6.0
Jain *et al* (1993)[26]					
Delhi 50.7	50.7	—	33.3	33.3	
Outside Delhi	78.8	78.8	—	61.5	61.5
Chowgule and Deodhar (1998)[36]	25.6	15	53.6	66.8	10.7
WHO-IUATLD (1994–1997)[3]	32.4	28.8	18.1	14	13.3
WHO-IUATLD (1999–2002)[6]	50.0	50.0	12.5	25.0	25.0
Shah *et al* (2002)[37]	58.67	57.18	35.58	37.47	35.1
Deivanayagam (2002)[38]	71.0	66.3	35.6	55.5	54. 8
Paramasivan *et al* (2002)[30]					
North Arcot (South)	81.0	81.0	56.2	69.0	69.0
Raichur (South)	100.0	100.0	36.4	100.0	100.0
Prasad *et al* (2003)[39]	79.2	48.6	36.6	34.4	29.5
Zignol *et al* (2006)[13]	—	—	—	—	14.7
WHO-IUATLD (2002–2007) [14]	—	36.8	26.2	18.1	17.2
Jain *et al* 2008[33]	45.3	38.0	34.2	27.7	25.5
Ramachandran *et al* (2009)[34]	46.3	37.0	26.4	18.0	17.4
Paramasivan *et al* (2010)[40]	74.9	67.5	43.3	54.3	53.2
M/XDR-TB Global Report on surveillance and response 2010[14]	—	—	—	—	17.2
Prasad *et al* (2012)[41]	—	77.9	55.3	69.0	58.2
Global TB Report (2012)[16]	—	—	—	—	15.0
Global TB Report (2013)[17]	—	—	—	—	15.0
Global TB Report (2014)[18]	—	—	—	—	15.0

H= Isoniazid; S= Streptomycin; R=Rifampicin; E= Ethambutol

The WHO/IUATLD global drug resistance surveillance carried out between 1996–1999 reported the prevalence of acquired MDR-TB to be 25% (95% CI, 7.3–52.3).[6] A study conducted in two districts of South India showed that acquired drug resistance ranged from 69% to 100%.[30] Zignol *et al*[13], estimated the incidence of primary and acquired MDR-TB cases to be

previously treated cases in India. New data from Gujarat indicated that 17.2% MDR among re-treatment cases was higher than what was previously anticipated and it is estimated that 110,132 (95% CI, 79,975–142,386) MDR-TB cases emerged in India in 2006, representing over 20% of the global burden. The estimated prevalence among all TB cases was 4.9%

(95% CI, 3.9–6.2).[14] In India, estimates based on sub-national drug resistance data showed that MDR among new TB cases was 2.3% (95% CI, 1.8–2.8), and in previously treated patients was 17.2% (95% CI, 14.9–19.5). It is estimated that 99,000 (95% CI, 79,000–120,000) MDR-TB patients emerged in India in 2008.[14] The estimated prevalence of MDR-TB among notified pulmonary (PTB) patients in India is 5.3% (95% CI, 3.6–6.2). The estimated prevalence among notified new PTB patients in 2.2% (95% CI, 1.9–2.6) and in re-treatment PTB patients 15% (95% CI, 11–19). India accounted for an estimated 64,000 cases of MDR-TB among the notified TB cases in 2012.[16] In 2013, India accounted for an estimated 62,000 cases of MDR-TB among the notified cases of PTB.[18] These studies were conducted in different states mostly in institutions and tertiary care centers and these do not reflect the overall status of MDR problem in India. Therefore, it is necessary to conduct a country-wide multi-center drug resistance surveillance comprising both rural and urban areas in order to have a complete picture of the total situation in the country.

HIV Infection and Multidrug Resistant Tuberculosis

There is a well-documented association between TB and human immunodeficiency virus (HIV). Outbreaks of drug resistant forms of TB among HIV infected patients have been widely documented in nosocomial and other congregate settings[42,43] but little information is available about the as-sociation of HIV and drug resistant TB at a population level.[44,45] The primary reason for this lack of information is that HIV and anti-TB drug susceptibility testing have not been sufficiently accessible for joint surveys under routine conditions. The accelerating and amplifying influence of HIV infection and the delay in recognition and diagnosis of TB were found to contribute to outbreaks of MDR-TB among HIV infected patients in the USA.[42,46-48] Shafer *et al*[49] studied temporal trends and transmission patterns in New York City using restriction fragment length polymorphism (RFLP) and found clustering of MDR-TB cases, particularly among HIV infected persons who suffered disproportionately from drug-resistant disease, findings consistent with the above scenario. A subsequent survey of 167 consecutive cases of TB seen at five New York hospitals during 1992 and 1993 demonstrated that HIV-infected persons were significantly more likely to have been recently infected with MDR-TB; indeed, 79% of the drug-resistant cases were shown by RFLP to be clustered with the clear implication of recent transmission.[47] In the Fourth WHO/IUATLD global drug surveillance report,[14] eight settings in seven countries (Cuba, Honduras, Latvia, the Russian Federation [Tomsk Oblast], Spain [Barcelona and Galicia],Ukraine [Donetsk Oblast] and Uruguay) reported data on drug resistance stratified by HIV status. Four countries were not able to discriminate between negative and unknown HIV status. The data reported from the majority of countries were not strong enough to examine an association between HIV and drug resistance. However, data available from Donetsk Oblast, Ukraine, and Latvia indicated a significant association between HIV and MDR-TB. Additional information on the risk factors including history of hospitalisation or imprisonment was not available for this analysis, so the specific reasons for the association are not known. Both countries have a high underlying prevalence of MDR-TB, as well as an emerging HIV epidemic, that initially was concentrated among the risk groups, but has now become more generalised. However, several studies in India and other South-East Asian countries, having high prevalence of HIV seropositivity, have reported very low prevalence of MDR-TB in HIV seropositive patients in contrast to the western literature. The main reasons for an association between HIV/ acquired immunodeficiency syndrome (AIDS) and MDR-TB may be the acquired rifamycin resistance associated with HIV infection among TB patients under treatment and anti-TB drug malabsorption which has been documented in patient cohorts in settings of high HIV prevalence. In addition HIV-infected patients and drug resistant TB patients may have similar risk factors, such as history of hospitalisation. It is also possible that HIV-infected TB cases may be more susceptible to infection once exposed. The HIV-infected TB cases are more likely to be smear negative, and delayed diagnosis of drug resistance as well as unavailability of treatment have led to high death rates in people living with HIV. Both of these factors may suggest a lower rate of transmission. However, HIV-infected cases progress rapidly to disease, and in settings where MDR-TB is prevalent, this may lead to rapid development of a pool of drug resistant TB patients, or an outbreak. Despite some of the weaknesses in these data and subsequent analysis, the association between HIV and MDR-TB is of concern, particularly given the implications for the clinical management of these patients. Rapid progression to death in HIV-infected MDR-TB patients in both outbreaks and treatment cohorts has been widely documented.[42,50]Anti-retroviral treatment for HIV does appear to benefit co-infected MDR-TB patients; however, co-management of treatment for both diseases is very complicated.

Currently, most TB control programmes in high burden countries do not have the diagnostic infrastructure to either detect an outbreak or the programmatic capacity to manage an outbreak. Given the impact on mortality, outbreaks should be avoided at all costs. The development of infection control measures in congregate settings as well as diagnostic screening tools to rapidly identify drug resistant TB are a priority, for all countries, but particularly for those with high prevalence of HIV or MDR-TB. From a global

perspective, routine diagnosis of both HIV and drug resistant TB should be scaled up for patient benefit. Better surveillance data may help in developing an understanding of the relationship between HIV and MDR-TB.

Risk Factors of MDR-TB

Several risk factors have been identified in the causation of MDR-TB of which the three most important are—previous treatment with anti-tuberculosis drugs (which may be inappropriate, incomplete or erratic), high prevalence of drug resistant TB in the community and contact with a patient known to have MDR-TB. In patients with previous treatment or disease, the odds of MDR-TB were four to seven times higher than for persons with no history of past treatment. Other factors that may be responsible for an increased risk of MDR are co-infection with HIV, socio-economically deprived groups in slums, prisons, correctional facilities, day care centers, intravenous drug abusers and other immunocompromised states as in transplant recipients, patients with anti-cancer therapy, and patients with diabetes mellitus. Radiologically, far advanced PTB with cavitory lesions were four times as likely to harbor drug resistant organisms.[51-53]

Sources and Causes of MDR-TB

Multidrug resistant tuberculosis is a human made problem and results largely from poorly managed cases of TB.[54] The sources are many and the causes are multi-factorial. The blame must be shared by the government, the pharmaceutical industry, doctors, patients and their families, each of whom contribute in their own way to add up to the problem. The governments play their share by failing to improve the poor infrastructure in the National Tuberculosis Control Programme, unnecessary administrative control on purchase and distribution of drugs with a poor mechanism for quality control and bioavailability tests. The pharmaceutical industries contribute by manufacturing drugs of uncertain bio-availability in fixed dose or inappropriate drug combinations, poor storage condition of drugs and substitution by inferior quality drugs by pharmacies. The doctor, by his lack of knowledge regarding doses, duration of treatment, side effects and standard regimens, frequent change of brand names and poor patient motivation, contributes the lion's share to the problem. In one of the studies[55] where prescriptions of 449 doctors were analysed, 75% of the doctors were found to have made some prescription error. Added to this is the poor teaching and training facilities for them. Non-compliant patients due to poor economic condition, lack of information, side effects of drugs and social myths and misconceptions often do not adhere to treatment. Co-morbid conditions, such as diabetes, HIV, psychiatric conditions, habits of smoking and alcoholism make the patient more vulnerable.

Control of MDR-TB

The primary objective in the control of MDR-TB is to prevent its development in the first place. This can be done by Directly Observed Treatment, short-course (DOTS), which is the most cost effective method of treatment and prevention of MDR-TB. At the same time, since MDR-TB cases respond poorly to short-course chemotherapy, careful introduction of second-line drugs to treat MDR-TB to reduce further transmission of such strains will be required.[56,57] To control the emergence of drug resistant TB and MDR-TB, WHO, in 1998, had proposed the work plan known as 'DOTS-Plus', now known as programmatic management of drug resistant TB for which WHO had established the Green Light Committee.[58] The primary aims of the committee were to approve, conduct and oversee pilot projects based on guidelines for establishing 'DOTS-Plus' pilot projects. The 'DOTS-Plus' is a comprehensive management strategy to control TB and MDR-TB. Following the roll out and successful implementation of "DOTS-Plus" pilot projects for the management of drug resistant TB between 2000 and 2005, a new Stop TB Strategy was launched in 2006. The new Stop TB Strategy includes the diagnosis and the management of drug resistant TB.[59] The launch of the Stop TB Strategy was followed by the Global Plan to Stop TB, 2006-2015 that provided targets for scale-up and budgets required for the implementation of the strategy Stop TB partnership.[60] To combat the threat of XDR-TB, WHO convened a Global Task Force on XDR-TB in October 2006 and recommended to strengthen basic activities to control TB and HIV/AIDS, to avoid additional emergence of MDR- and XDR-TB as well as acceleration of treatment of MDR- and XDR-TB cases with universal access to sound management of MDR- and XDR-TB by 2015 in all countries.[61] The revised plan recommended the treatment of 1.6 million MDR- and XDR-TB cases by 2015 instead of 800,000 MDR-TB cases. It will require integration of MDR- and XDR-TB activities into general TB control activities. It will include the strengthening of laboratory services for adequate and timely diagnosis of MDR- and XDR-TB, surveillance of MDR- and XDR-TB, development and implementation of sound TB infection control policies, Advocacy communication and social mobilisation to sustain political commitment and resource mobilisation and the promotion of research and development into new diagnostics, drugs, vaccines and operational research on MDR-TB management. It is expected that full implementation of this response plan will save the lives of thousands of people infected by MDR- and XDR-TB and will be able to prevent and control MDR- and XDR-TB.

Conclusions

Multidrug resistant TB has been an area of growing concern and poses a threat to control of TB. It is estimated that more than 400,000 cases of MDR-TB emerge every year globally as a result of poor management of sensitive as well as drug-resistant TB cases. The MDR-TB is a human-made problem and its emergence can be prevented by prompt diagnosis and effective treatment of all TB cases. The DOTS-Plus programme now known as Programmatic management of drug resistant tuberculosis (PMDT) proposed by WHO highlights the comprehensive management strategy to control MDR-TB. Laboratory services for adequate and timely diagnosis of MDR-TB must be strengthened and programmatic management of MDR-TB must be scaled up as per the target set in the global plan. It must be emphasised that optimal treatment of MDR-TB alone will not curb the epidemic. Efforts must be focused on the effective use of first-line drugs in every new patient so as to prevent the ultimate emergence of MDR. The proper use of second-line drugs must be ensured to cure existing MDR-TB, to reduce transmission of MDR-TB and to prevent XDR-TB. Sound infection control measures to avoid further transmission of MDR-TB and research towards the development of new diagnostics, drugs and vaccines should be promoted to control MDR-TB.

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