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Emerging Public Health Issues in Drug-Resistant Tuberculosis

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Abstract

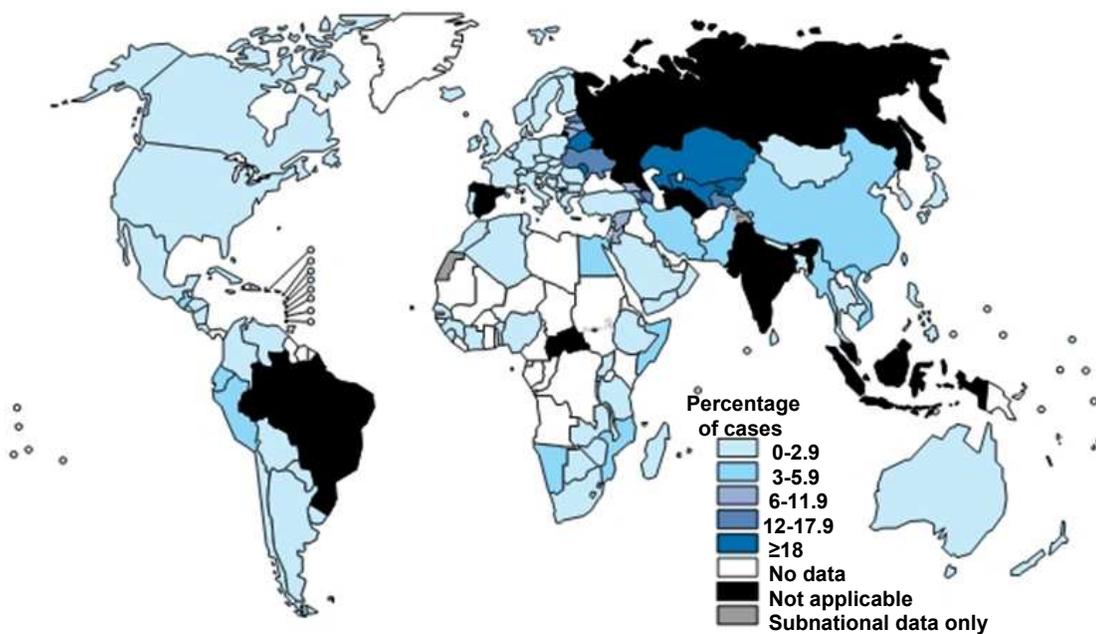
Drug Resistance is a major challenge in the control of Tuberculosis which itself remains a global public health problem. Resistance is commonly encountered as MDR TB but a subset, XDR TB which has about a comparatively fivefold increase in mortality is now identified in 84 countries worldwide and increasing rates are currently reported from 65 countries. The actual burden of MDR TB is unknown though estimates have been made based on notification of cases which are usually underreported. More so there is under diagnosis in non HIV immune suppressed adults and pediatric populations largely due to lack of readily accessible diagnostic tools. In some case series, MDR TB has been found occurring mostly in newly diagnosed patients or relapse cases after previous cure and completion of treatment rather than in patients with improperly treated disease. Clinical and laboratory monitoring once therapy has been instituted have also been a daunting task both from institutional and patient points of view. The impact of these factors are highlighted and discussed as the world moves towards attainment of the 2015 global target to halve TB prevalence and death rates within the context of Millennium Development Goals (MDGs).

Keywords: Tuberculosis, Drug Resistant, Public Health

1. Introduction

The man who moves a mountain begins by carrying away small stones – Confucius.

Drug resistance is a major challenge in the control of Tuberculosis (TB), which itself remains a global public health problem. Resistance is commonly encountered as Multidrug-Resistant Tuberculosis (MDR TB), but a subset, Extensively Drug-Resistant Tuberculosis (XDR TB), which has about a comparatively fivefold increase in mortality, is now identified in 84 countries worldwide and increasing rates are currently reported from 65 countries. The World



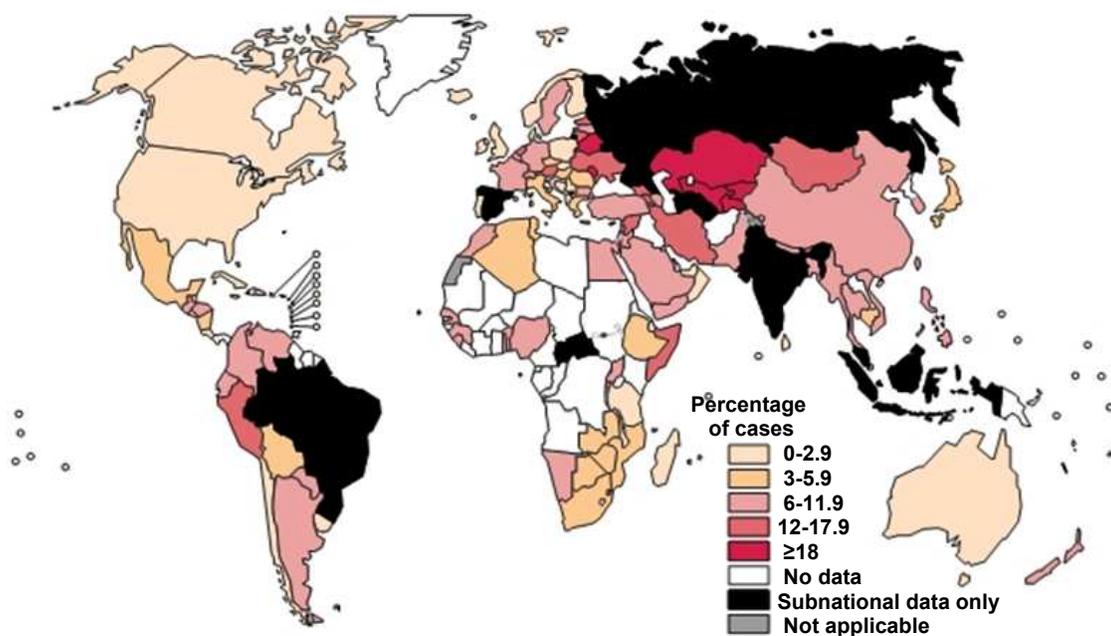
Figures are based on the most recent year for which data have been reported, which varies among countries.

Figure 1. Percentage of new TB cases with MDR-TB (Adapted from WHO Global TB Report, 2014)

Health Organization (WHO) has designated 22 countries of the world as high-burden countries for Tuberculosis (HBCTB) and 27 as high-burden countries for multidrug-resistant Tuberculosis (HBC MDR TB), making a total of 36 countries in either of these categories [1]. The latter are countries where at least 4,000 cases of MDR TB are identified per year and/or at least 10% of newly registered TB cases are MDR TB.

MDR TB and XDR TB epidemics are largely driven by transmission and are mainly found in new cases and patients with TB relapse [2]. Since 1994, WHO has been receiving and analyzing data on anti-TB drug resistance from countries via its Drug Resistance Surveillance Project, which depends on continuous data based on rapid molecular diagnostics and drug sensitivity testing (DST). However, neither is widely or routinely available due to prohibitive costs involved, especially in low- and middle-income economies that are also high-burden countries. In these low- and middle-income high TB burden countries, cases of MDR TB are identified mainly through special surveys rather than continuous surveillance reporting. In 2013, only 11 of the 36 HBCTB/HBC MDRTB had up-to-date data through these drug-resistance surveys. From these surveys it is clearly understood that the MDR TB burdens attributed to these countries are only estimates based on notification of cases which in most countries is incomplete and as such may only be the tip of the iceberg (Figures 1 & 2).

Despite these shortfalls in the determination of exact incidences, especially where TB burden is highest, there have been recent global efforts to bridge the gap between diagnosis and appropriate therapy with second- and third-line drugs. Treatment after diagnosis of MDR TB and follow-up of confirmed cases is however bedeviled with unavailability of human resources, accessibility to second-line drugs in high MDR TB areas, and logistics. Global treatment



Percentages of previously treated TB cases with MDR-TB in Bahrain, Bonaire, Israel, Saint Eustatius and Saba, and Sao Tomé and Príncipe refer to only a small number of notified cases (range: 1-8 notified previously treated TB cases).

Figure 2. Percentage of previously treated TB cases with MDR-TB (Adapted from WHO Global TB Report, 2014)

targets have not been met. but there are concerted efforts to achieve them through restructuring of programs and Programmatic Management of Drug-Resistant TB (PMDT).

The key to overcoming MDR TB and XDR TB will eventually lie in the balance between prompt diagnosis and treatment of cases on one hand and prevention of transmission of drug-resistant bacilli to vulnerable populations with whom they are in contact on the other. Particular attention needs to be given to unrecognized groups: the pediatric patients in whom a high degree of clinical skill must be displayed to ensure prompt laboratory diagnosis and the health care workers whose infection can be prevented through deliberate control methods.

2. Epidemiology of MDR TB

It is estimated that more than 90% of new TB cases and death occur in the high TB burden developing countries [3]. Multidrug anti-tuberculous therapy had been found effective when using the Directly Observed Therapy Short Course (DOTS) strategy to improve compliance to treatment of TB. With the emergence of MDR TB, the DOTS strategy was expanded to accommodate second-line drugs in the Directly Observed Therapy short course with MDR diagnosis, management, and treatment (DOTS PLUS) strategy. Treatment failure, however, can still occur leading to relapse and development of drug-resistant TB strains to second-line drugs which is the XDR TB [4].

Multidrug-resistant Tuberculosis (MDR TB) is defined as resistance to at least both Isoniazid and Rifampicin with or without resistance to other first-line drugs. [5]. A subset of this is

Extensively Drug-Resistant Tuberculosis (XDR TB) where there is also resistance to fluoroquinolones and at least one injectable second-line drug (such as Amikacin, Kanamycin, or Capreomycin) in addition [6]. XDR TB was first noted in the late 1980s and 1990s and reported by WHO and Center for Disease Control (CDC), USA, in 2004.

In a survey of some of their National Reference laboratories, it was observed that 20% of resistant strains tested were MDR TB, while 10% were XDR TB. Asia and Eastern Europe had the highest rates [7]. From recent reports, about 60% of the global burden of Multidrug-resistant TB is in China, India and Russia occurring in 3.7% of new TB cases (CI: 2.1-5.2%) and 20% of previously treated TB cases (CI:13-26%). In countries where there are data available, 9% of MDR-TB cases have XDR (CI: 6.7-11.2%) and 14.5% have fluoroquinolone resistance (CI: 11.6-17.4%) [8].

According to the WHO, Eastern Europe's rates of MDR TB are the highest and MDR TB makes up to 20% of all new TB cases, while in The Union State, it accounts for 28% of new TB cases. In Africa, reports of MDR TB based on continuous surveillance as in South Africa [9] show progressively increasing MDR rates despite overall decreasing numbers of TB cases. This is attributed to improved notification through laboratory surveillance. In developing countries with limited access to TB drug sensitivity tests, prevalence of MDR TB is dependent on special national surveys [1] and hospital-based clinical researches as in Nigeria [10-18]. Most of the hospital-based reports in Nigeria indicate that there is some level of MDR TB, which though not documented on a regular basis show progressive increase over time. This case scenario plays out in other developing countries where continuous surveillance or monitoring of MDR TB is not available. In Nigeria, as well as in other high-burden countries such as South Africa and India, it has been noted that the increasing TB prevalence may be driven by HIV coinfection [19]. Most of these reports are, however, based on testing of adult populations.

Pediatric MDR TB has been majorly underreported in continuous surveillance and special surveys. However, in some countries like South Africa, some modest efforts have been made to document and monitor progress of disease in these populations. A recent meta-analysis [20] of WHO data between 1994 and 2011, testing associations between MDR TB and age groups <15 years, and those >15 years, revealed that MDR TB was positively associated with age <15 years in Germany, Namibia, South Africa, UK, and USA. The data also revealed that similar proportions of children and adults were diagnosed with MDR TB in many settings. HIV coinfection was found to be in close association with pediatric MDR TB in South Africa invariably due to the high prevalence of HIV in this area.

2.1. Genesis of MDR TB

Drug-resistant TB has microbial, clinical, and programmatic causes [21]. It manifests when there is a selective growth of resistant mutants among the actively multiplying bacillary population in the presence of drugs, thus making the drug ineffective against mutant bacilli. Microbiologically, the emergence of drug resistance depends upon the frequency of drug-resistant mutants in the susceptible bacillary population, the size of the actively multiplying bacillary population in the lesions, and the antimicrobial quality of the drugs used [22]. The

frequency of spontaneous mutations that can be developed to each drug are believed to be of the following magnitude: Streptomycin 1 in 10^6 , Isoniazid 1 in 10^6 , Rifampicin 1 in 10^8 , Ethambutol 1 in 10^7 , Pyrazinamide 1 in 10^6 , Fluoroquinolones 1 in 10^{6-8} [23]. When these drug-resistant mutants occur in large bacterial population, they have a tendency to further multiply depending on the corresponding clinical treatment regimen the patient receives. This varies from one program to the other and will depend on what drugs are available to a treatment program and the ease of access the patients have to these drugs.

Administered therapy may be inadequate in the following instances: monotherapy, poor adherence to treatment protocols, erratic or even interrupted treatment, or low drug quality. When there is inadequate treatment, resistance develops because bacilli with drug-resistant mutation proliferate and become the dominant strain in the infected individual. Inadequate treatment of susceptible TB can lead to drug resistance to first-line drugs (MDR TB), which is a marker of a failing susceptible TB treatment program. Likewise, inadequate treatment of MDR TB will lead to drug resistance to second-line drugs (XDR TB), which is a marker of failing MDR TB treatment programs.

Drug resistance of the *Mycobacterium tuberculosis* isolated from patients may be categorized based on length of previous anti-TB drug therapy they had received prior to the diagnosis of resistance. Acquired drug resistance is described in those who have been inadequately treated for 1 month or more; Relapse in cases previously completed treatment and reported cured; while that of patients who have never been treated previously or treated for less than 1 month is called Primary drug resistance or resistance in new case. The patients grouped as relapse or as new infections which are found to be drug resistant are grouped together as transmission cases; 82% of MDR TB are reported to be transmission cases. The other 18% are acquired cases, which are mostly adult populations. The acquired cases provoke and sustain MDR TB epidemics in both developed and undeveloped countries [24].

2.2. Epidemics of MDR TB

During the late 1980s and early 1990s, epidemics of MDR TB occurred in North America and Europe killing about 80% of those who were infected. Today, the greatest number of cases is in India and China [25-26], although smaller epidemics have been described due to migrations [27]. The convergence of the following were believed to precipitate MDR TB epidemics especially that of XDR TB: High TB burden, high HIV prevalence, suboptimal TB control practices, and introduction of second-line TB drugs into low- and middle-income countries [28-29]. Among the pediatric age group, there is global paucity of data on MDR TB epidemics. Most data obtained have been reported from South Africa [30]. Some of the identical issues that were identified in all these epidemics were that there was delayed diagnosis of MDR TB cases for over 6 weeks to 6 months due in turn to delayed turnaround time for mycobacterial culture and DST. This invariably led to very high mortality rates which first called attention to the need for DST. In the XDR TB epidemic reported in South Africa [29], there was prominence of associated HIV coinfection in most patients who were transmission cases. Another feature was poor observance of infection control precautions such as: inadequate patient

isolation and airflow regulation within wards, which made the wards conducive for transmission between patients in contact with MDR TB cases. There was also notable direct transmission from patients to health care workers, which was evident by Tuberculin Skin Test (TST) conversion as well as later linkage mappings that correlated the strains in the patients' samples with those of the health workers [29].

2.3. Implications of transmission versus acquired cases

In the high-burden countries, there are reportedly 20-35.2% of new cases and 54-62% of relapse cases that develop MDR TB, accounting for 82% of all incidences of MDR TB [1]. Thus, high burdens of MDRTB and XDR TB are eventually perpetuated from direct transmission within communities. In cases where TB-HIV coinfections are also prevalent, this significantly favors direct transmissibility [31]. Direct transmission is therefore the most common way drug-resistant TB is spread and this must be stemmed to arrest the imminent global health threat from TB.

3. MDR TB diagnosis: Clinical versus laboratory methods

Bacteriological confirmation of TB and Drug sensitivity Testing (DST) of patients presenting with clinical features of Tuberculosis is targeted as universal standard for patient care in TB [1]. When this is incorporated into routine clinical care package and results are available for periodic analysis, it forms a strong database for information about drug resistance in that area.

3.1. Clinical criteria

WHO global TB report [1] revealed that only 2.8 million (58%) of the 4.9 million incident pulmonary TB patients notified in 2013 were bacteriologically confirmed (smear- or culture-positive according to a WHO-recommended rapid diagnostic such as Xpert MTB/RIF). The remaining 42% notifications were diagnosed clinically (symptoms, signs, chest X-ray abnormalities, or suggestive histology). Notifications of new cases are mainly from the high-burden countries, majority of which are low- and middle-income economies. Their capacity for confirmatory testing and DST is limited. Although almost half of notified global TB diagnosis is by clinical methods, this form of diagnosis is attended by poor specificity and false-positive diagnosis. Low laboratory rates, on the other hand, may suggest underdiagnosis of true TB cases and contribute to the gap noticed between notified and estimated incident TB cases [1]. The need for skilled health care workers who can make presumptive diagnosis to improve notification while laboratory methods are being scaled-up, especially in the high-burden countries cannot be overemphasized.

However, the drawback of clinical criteria alone to make a diagnosis in MDR TB is obvious. Detection of TB without investigating drug sensitivity potentially can lead to inadequate treatment and this could lead to spread of MDR TB.

3.2. Laboratory diagnosis – Screening and confirmatory tools

The field of TB diagnosis has been dynamic, changing constantly with the new challenges posed by the bacilli: from being fully susceptible to multidrug therapy to the appearance of MDR TB and now XDR TB. Whereas the need to have accurate bacteriological diagnosis and appropriate drug sensitivity has not changed, the tools to achieve these have continued to evolve as newer and hopefully equally or more effective diagnostic technologies are developed. Diagnosis of MDR TB requires culture to confirm TB and drug susceptibility testing or molecular testing. The challenges faced in achieving these include:

- Laboratory challenges with technical capacity, biosafety, cost, slow growth
- Patient challenges in access to adequately testing facilities – communication, transportation of specimen, and reporting remain critical to success
- Policy challenges in who should be tested and when to test given limited public health resources

Increasingly, molecular technologies are being incorporated into drug resistance surveys to simplify logistics. By 2009, the EXPAND –TB (Expanding Access to New Diagnostics for TB) was launched to accelerate access of MDR TB high-risk populations in high TB burden countries to sophisticated but rapid diagnostic molecular techniques and provide laboratory services. The 27 high MDR TB burden countries were equipped with 97 new or refurbished laboratories and line probe assays (DNA strip test that allows simultaneous molecular identification of TB and the most common genetic mutations causing resistance to Rifampicin and Isoniazid) in reference laboratories which can diagnose MDR TB in two days. By December 2010, the WHO issued a policy on the use of another molecular diagnostic test Xpert MTB/RIF as an initial diagnostic test for cases at risk of MDR TB with negative sputum. The Xpert test, a cartridge-based automated diagnostic test that can identify *Mycobacterium tuberculosis* DNA and resistance to Rifampicin by nucleic acid amplification technique was a sputum only test for pulmonary TB [32].

A review of WHO policy followed in 2013 that Xpert MTB/RIF should be used rather than conventional microscopy, culture, and DST as the initial diagnostic test in adults and children suspected of having MDR TB or HIV associated TB. It may be used for diagnosis of drug-susceptible TB, smear-negative individuals and cases of extra-pulmonary TB testing using non-respiratory specimens such as lymph nodes. By the end of June 2014, 108 countries had benefitted from procurement of Gene Xpert machines. GenoType® MTBDRplus (Hain Lifescience, Germany) was used in the national survey completed in 2012 in Nigeria and is currently being used in the national survey in Sudan. In Pakistan, Xpert® MTB/RIF (Cepheid USA) identified additional cases missed by culture in the national survey completed in 2014. In ongoing surveys in Papua New Guinea and Senegal, Xpert MTB/RIF is being used to screen specimens for rifampicin resistance and identify those requiring further testing at national or supranational TB reference laboratories. Surveys planned in 2014–2015 in Côte d'Ivoire, the Democratic Republic of the Congo, Indonesia, and Zimbabwe will adopt the same testing algorithm [1].

This approach greatly reduces the workload for laboratories and decreases the cost of national surveys. It may also result in the detection of cases that would otherwise have been missed by culture and conventional DST, particularly in settings with delays in transporting sputum samples to laboratories for testing. Although not a complete surrogate for MDR-TB, particularly in settings where levels of drug resistance are low, rifampicin resistance is the most important indicator of MDR-TB and has serious clinical implications for affected patients.

It is noteworthy that the supply of these technologically advanced diagnostics though now in more countries cannot serve the total at-risk populations, because these machines are kept strategically in reference laboratories. There is a critical need to develop within each country a framework that would address the accessibility to reference centers. In the Western Pacific and Eastern Mediterranean regions, it is reported that there was less than one reference center per 100,000 population. In Nigeria, a high TB burden country and the fourth highest African country with MDR TB, there are only 9 reference centers which are inadequate for the whole at-risk population of 170 million.

There is therefore need in the high TB burden areas to still supplement the recent high-tech diagnostic tools with sputum smear microscopy as an initial screening tool and as such be placed in such a way that these can be accessible to all. Improvements in microscopy using fluorescent light emitting diode microscopy, which is more sensitive than light microscopy, has been proposed and adopted in South Africa, and less so in Mozambique, Bangladesh, and Nigeria [1].

The other aspect that needs careful attention in laboratory diagnosis is the need for regular quality assurance of the machines. Likewise, regular capacity training for laboratory personnel to ensure optimal standards of diagnosis and DST Xpert MT/RIF Newer areas of research for improved diagnostics is the research for correlates of protective immunity and host biomarkers of TB that could help determine the potential for susceptibility or protection [33].

4. Unrecognised MDR TB populations

4.1. Pediatric MDR TB

Pediatric TB diagnosis has also been largely based on clinical criteria due to the pauci bacillary nature of their disease [3, 34-36]. In the cases of TB HIV coinfection, the diagnosis of TB disease is usually more difficult because the symptom specificity is reduced due to similarity with chronic HIV-related symptoms, and chest radiograph interpretation is complicated by HIV-related comorbidity and atypical disease presentation. In this case, diagnosis involves linking the child with an adult with confirmed pulmonary TB [37]. However, older children producing sputum can have bacteriological confirmation and where facilities are accessible DST is performed [8]. To date, there is still widespread under-diagnosis of MDR TB in younger children. Children are less likely than adults to acquire MDR TB during treatment due to the lower bacillary load and less-frequent cavity formation [38]. Acquisition of strains of MDR TB through primary transmission has been shown to be same for children as for adults [39].

The implication of this is that with increasing adult MDR TB in populations, there would be increasing incidences of pediatric MDR TB. Once a diagnosis of TB is made, MDR TB should be carefully considered by review of household source cases for drug-resistant disease [40]. Child contacts of adults with coinfection of TB HIV should particularly be screened for MDR TB. The recent efforts to improve on MDR diagnostic tests using non-respiratory specimens should be harnessed for the pediatric age populations so that rapid diagnostic tests become the first-line diagnostic tool for pediatric MDR TB. Outcomes of MDR TB in children depend on prompt diagnosis and initiation of appropriate therapy for drug-resistant strain [41].

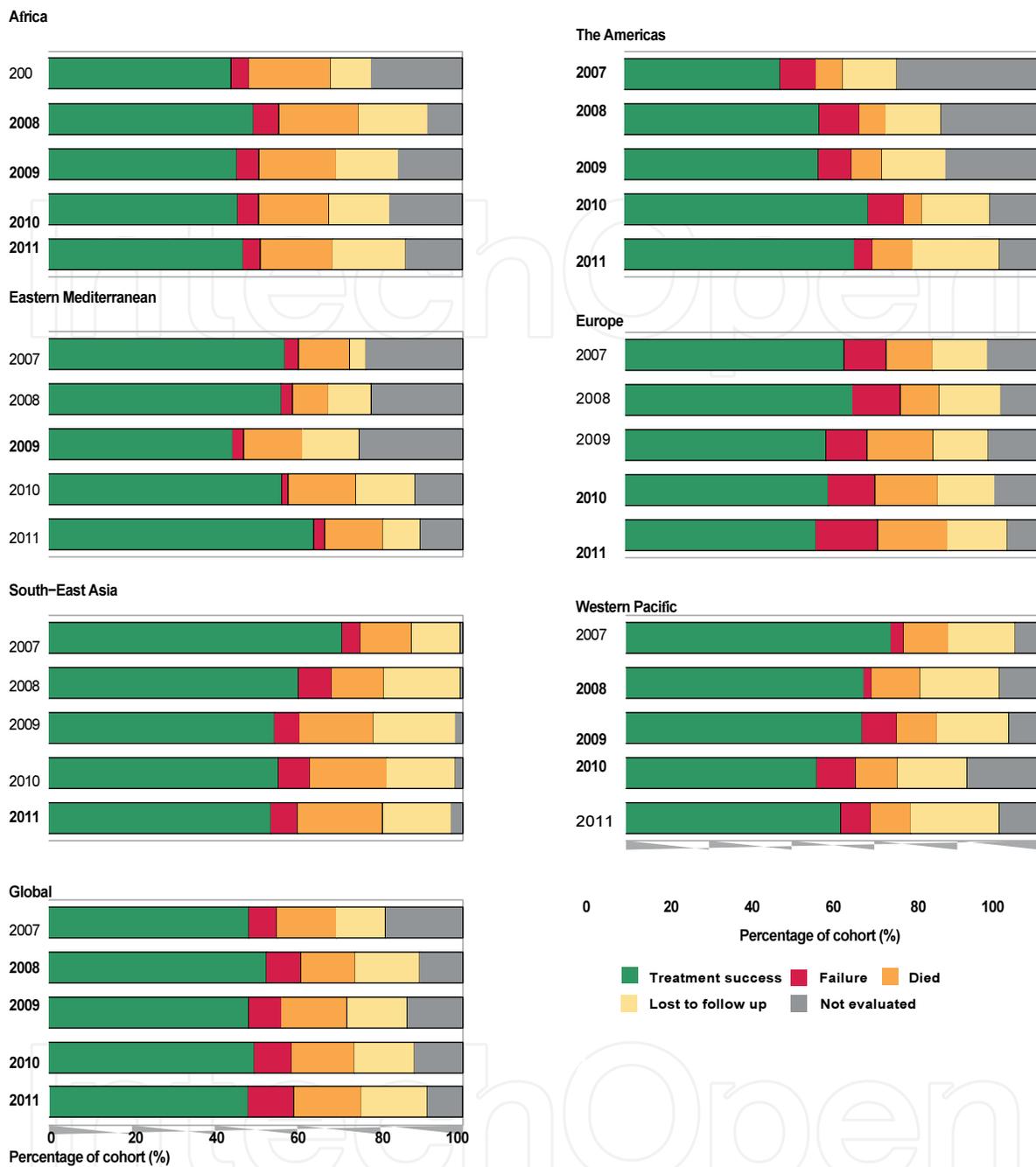
5. Challenges in MDR TB therapy

The Global target of MDR TB treatment is to achieve 75% treatment success by 2015. To achieve success in treatment programs, WHO has published a document which contains the guide to Programmatic Management of Drug-resistant TB (PMDT) which covers all key policies in MDR TB care and control. The numbers of cases treated are usually reported in cohorts that commence therapy within a certain year. In this way it is hoped that treatment outcomes would be clearly understood and modifications where necessary would be implemented. WHO [1] reports increasing numbers of cases enrolled into treatment programs for MDR TB and XDR TB of 47% from 2010 to 2013. In specific terms, however, this increase has been achieved mainly in low TB burden countries. The issue of inadequate notification from weak reporting systems in most high-burden countries is also thought to contribute to only a modest increase despite all efforts made at increasing treatment coverage. Notification still plays a crucial part in the monitoring of treatment outcomes. This depends on systematic record collection, storage, and retrieval by electronic means. All these processes are not uniformly accessible in all parts of the same country and also differ significantly from country to country. Adequately trained personnel to manage this process is crucial and a vital gap.

The treatment target of 75% success outcome has only been reached by 29 out of 126 countries that have reported outcome. Only five of the 27 MDR TB high-burden countries have reached 70% treatment successes (Figure 3). The success recorded in high-burden countries is closely related to the implementation of EXPAND TB project and the scale-up of PMDT in these countries. The identified gaps to achieving treatment include unavailability of second-line TB drugs whose costs are prohibitive in many high-burden countries. This requires substantial financial and health care resources [42]. To ameliorate this, the Global Fund facility which procures TB drugs for the public sector of many countries has increased supply and dropped prices of some MDR TB drugs by 2009 [43].

5.1. Clinical and laboratory monitoring

Drugs used in the treatment of MDR TB are less effective, more toxic (90% experience side effects), used for longer duration (usually more than 2 years' duration), and are more costly than drugs used in susceptible TB (10-100 times more costly) [44]. In the 27 high-burden countries, the expenditure for MDR-TB treatment has increased cost of TB care from an



(Adapted from WHO Global TB Report, 2014)

Figure 3. Treatment outcomes for patients diagnosed with MDR TB by WHO region, 2007-2011 cohorts.

estimated 1.3 billion USD in 2010 to 4.4 billion USD by 2015 [45]. Some of the common adverse effects might also require monitoring such as ototoxicity and renal failure. There is also the need to document improvement by follow-up of bacteriologic cultures. In addition to these, cases need to be monitored because some MDR TB cases are in advanced stages of disease with other end-stage organ failures. MDR TB therapy is often characterized by low treatment completion rates due to death (15%), default (14-23%), and treatment failure (8-9%) [46]. To

achieve increased access, compliance, effective therapy, and retention in care, there is a need for close monitoring. This is traditionally done by hospital-based care at MDR TB referral centers for the initial therapy through health care providers. The model of care involves an initial hospitalization until sputum culture conversion followed by ambulatory phase of treatment in the nearest DOTS facility. However, hospital-based care may serve as an obstacle to access. Ambulatory-based care and community-based care have been proposed in management of MDR TB cases [47]. There have been some successful experiences in some countries using these methods [1]. There would be need for collaboration between these models of care especially when dealing with patients with advanced disease who may benefit for some periods from hospital-based care but would need community- or home-based care for terminal stages. Community and Ambulatory care also serve to ensure adequate contact tracing for cases of MDR and XDR TB, which is of great importance given the role of transmission of disease in spreading the MDR TB epidemic.

When contacts are traced, there is need for DST to identify appropriate second-line drugs. Currently, the diagnostic tools recommended are molecular-based testings: Line probe Assays and Xpert MTB/RIF. There is need, however, to establish quality control measures for these tests to avoid false positives and false negatives. Such tools as would ensure international standards for reference laboratories and other peripheral centers have been developed in some countries. Laboratory monitoring also includes structured assessment tools for TB microscopy, which is shared among laboratory networks.

6. Prevention of MDR TB

To achieve success in the control of MDR TB, there would be a need to strengthen existing TB DOTS programs. To achieve this, some areas that should be focused on are the creation of infection control policies both within and outside institutions. Health education of how transmission of disease occurs from cases to vulnerable groups should be emphasized in communities. Community-based care should be strengthened with recruitment of staff for contact tracing of MDR cases, screening of the contacts, treatment administration, and identification of those who are defaulting on treatment or require institutionalized care. There should be expansion in the teams with involvement of all relevant health care partners to strengthen Public–Private Mix initiatives for TB care and control [48-52].

6.1. Infection control

This aims to prevent transmission from cases to other patients or health care workers. The following means could help to ensure the protection of health care staff: Use of N95 mask by all staff on medical and TB isolation wards and in the HIV clinics [53]; HIV testing of all staff with reallocation of those testing positive to lower-risk positions; Annual Chest Xray screening for TB for all staff [24,54].

Within health care institutions, TB control officers should be hired as well as cough officer in waiting areas who would identify those that are in hospital for other reasons but who may

require TB screening. The duration of hospital admission and stay should be reduced. There should be environmental airflow control to ensure maximal ventilation (natural mechanical ventilation within the ward and the use of outdoor waiting areas for outpatients). MDR TB isolation wards should be created with attention paid to laminar airflow [55].

Infection control programs should be created with plans for intervention should transmission be proved.

7. Conclusions

Underdiagnoses of MDR TB and XDR TB cases pose significant challenge for TB control. The current available means for tracking and monitoring are inadequate since they are reliant on reported data which are usually incomplete. These data overlook transmission to unrecognized populations which sustain MDR TB epidemics. There is also a need to make diagnostic tools more available and accessible for cases and contacts and more reference laboratories provided. These laboratories should be monitored to assure they maintain international standards and produce reliable results. Once diagnosis has been made promptly and accurately, adequate therapy for MDR TB should be instituted. This would require clinical monitoring of cases through collaboration of hospital, community, and ambulatory care services. Control programs should also target health care givers to prevent transmission of MDR TB to them from cases. In essence, routine TB DOTS programs should be strengthened in collaboration with public-private mix initiatives to enhance MDR TB control.

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