

## Epidemiological perspective of drug resistant extrapulmonary tuberculosis

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### Abstract

Tuberculosis (TB) remains one of the leading infectious diseases causing significant morbidity and mortality worldwide. Although, pulmonary TB is the most common presentation and is the main transmissible form of the disease, extrapulmonary TB

also significantly contributes to the burden of disease and can cause severe complications and disabilities. At present, the most serious issue with TB control programme is emergence of multi and extensively drug resistant *Mycobacterium tuberculosis* strain worldwide. As the number of drug resistant pulmonary TB is increasing around the world, the number of drug resistant TB with extrapulmonary manifestations are also on rise. However, there is surprisingly scant information in medical literatures on prevalence and impact of extrapulmonary drug-resistant TB. Here, we appraise the recent epidemiological studies that underpin the status and impact of drug resistance in TB cases with extrapulmonary manifestations.

**Key words:** Extrapulmonary tuberculosis; Tuberculosis; Epidemiology; *Mycobacterium tuberculosis*; Drug resistance

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**Core tip:** The emergence of highly drug resistant (DR) *Mycobacterium tuberculosis* and human immunodeficiency virus epidemic has paved the way for resurgence of tuberculosis (TB). Extrapulmonary tuberculosis (EPTB), accounts for a significant proportion of all notified TB cases, is a persistent global health issue. Although DR-EPTB is uncommon, but the increasing rate of DR-pulmonary TB around the world has heightened our concern for DR-EPTB too. Unfortunately, systematic surveillance data on DR-EPTB is lacking, however, sporadic information from different countries has begun to accumulate. Here, we aim to provide current understanding on epidemiological scenario of DR-EPTB and also to address some of the key challenges associated with diagnosis, control and management of DR-EPTB.

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## INTRODUCTION

Despite the availability of effective treatment for many decades, tuberculosis (TB) remains an enormous global health problem, responsible for about 1.5 million deaths annually<sup>[1]</sup>. *Mycobacterium tuberculosis* (MTB), the causative agent, usually affects the lungs [pulmonary TB (PTB)], however it may spread through lymphatic or hematogenous dissemination to virtually any organs and tissues of body resulting in the development of extrapulmonary TB (EPTB). In last few decades, extensive information has been gathered describing the clinical pictures of different common and rare forms of EPTB. The distribution of various types of EPTB may vary among different populations and countries. However, the most common sites of EPTB includes peripheral lymph nodes, pleura, genitourinary sites, bones and joints, abdomen (peritoneum and gastrointestinal tract), and the central nervous system<sup>[2,3]</sup>. A detailed discussion on clinical aspect of each form of EPTB is beyond the scope of this review but can be found elsewhere<sup>[2,3]</sup>.

The existence of EPTB is centuries old however the prime attention of global TB control programme has been principally focused on contagious pulmonary TB. Indeed, EPTB is milder and less contagious as compared to PTB it cannot be overlooked as it constitutes about 20% of all form of TB among immuno-competent adults<sup>[2]</sup>. Moreover, EPTB result in significant morbidity and mortality dependent on the organs affected (like central nervous system) and also due to various difficulties encountered in achieving a timely and definite diagnosis<sup>[4]</sup>. EPTB became more common worldwide since the advent of human immunodeficiency virus (HIV) infection. Consequently, a significantly high predisposition to the development of EPTB can be found in patients with concurrent acquired immune deficiency syndrome and TB<sup>[3]</sup>. Younger age is another potential risk factor for developing EPTB and even some aggressive form of TB like tubercular meningitis or miliary TB are commonly reported in children<sup>[5,6]</sup>. Such mounting significance of EPTB is suggestive to consider EPTB as much a public health priority as pulmonary TB (Table 1).

At present, the global emergence of multi-drug resistant (MDR) and even extensively drug resistant (XDR) TB is a great challenge to success of global TB control efforts. MDR-TB is usually caused by spontaneous genetic mutation in MTB that confers resistance to the two main first line antimicrobials rifampicin (RIF) and isoniazid (INH). Mutation in a hotspot region (81-bp) of *rpoB* gene (encoding beta-subunit of DNA dependent RNA polymerase) is responsible for rifampicin resistance

**Table 1 Drug resistant-extrapulmonary tuberculosis: Reasons to worry**

Drug resistance (including MDR) in cases of EPTB is increasing and now it cannot be considered as rare  
Accurate and timely diagnosis and drug susceptibility testing are very difficult and may result into high morbidity and mortality  
DR-EPTB is often difficult to treat due to poor penetration of some key anti-tubercular drugs into extra-pulmonary sites (especially in CSF)  
HIV and young age are independent key risk factors  
Although not contagious but it may co-exist with highly contagious pulmonary manifestation

MDR: Multi-drug resistant; DR-EPTB: Drug resistant-extrapulmonary tuberculosis; CSF: Cerebrospinal fluid; HIV: Human immunodeficiency virus.

while INH resistance is largely conferred by mutations in *katG* gene and *inhA* gene<sup>[7]</sup>. When MDR MTB develops additional resistance to a fluoroquinolone and a second line injectable drug (*i.e.*, amikacin, kanamycin or capreomycin), it is termed as XDR. Although, drug resistance in PTB has been extensively studied on various aspects, status of drug resistant (DR) EPTB is not clear. While some presentations of EPTB may be life threatening, the involvement of drug resistant MTB strain may amplify the risk of mortality. Thus, in the present era of HIV pandemic coupled with global emergence of MDR and XDR MTB, DR-EPTB represents as a real and new significant challenge to public health that is yet to receive serious attention. In this review, we aim to provide an epidemiological overview of drug resistant EPTB and to discuss some of key challenges associated with diagnosis and control of disease.

## EPIDEMIOLOGICAL SCENARIO

As many population based TB surveys of different countries are more confined to smear positive PTB especially in adult populations, the knowledge of the global epidemiology of EPTB is rather limited. Despite this, surveys from different parts of world have accumulated that demonstrate substantial increase of global burden of EPTB in both developed and developing countries, particularly in regions where the prevalence of HIV infection is high. In the areas where adequate diagnostic and reporting systems are available, EPTB accounts for 20%-25% of reported cases<sup>[8]</sup>. Recent estimate of WHO showed that among 5.4 million new TB cases, 0.8 million had EPTB of which a significant proportion (about 70%) were localized into Southeast and African regions<sup>[1]</sup>. In developed countries, 10%-15% of TB cases have extra-pulmonary involvement, but this rate is much higher in patients belonging to high TB burden countries<sup>[3]</sup>. India ranks first in having maximum number (about 0.35 million) of EPTB among new cases<sup>[1]</sup>. The successful TB control program in many developed countries resulted into a declining trend of incidence of pulmonary TB; however the rate of EPTB has remained constant or increased

Table 2 Drug resistant extrapulmonary tuberculosis in different parts of world

Region	Type of EPTB	Study period	Culture positive cases/total cases analyzed	Prevalence of drug resistant MTB	DST method	Concomitant Pulmonary TB cases/ total cases analyzed	HIV positive cases/ total cases tested	Treatment outcomes	Ref.
Argentina	TBM	1996-2004	101	Any DR: 51.5% MDR: 41.6%	E	Not stated	101/101	64/101 died during hospitalization	Cecchini <i>et al</i> <sup>[49]</sup>
Australia	Various sites (including pulmonary)	2007	871 <sup>2</sup> (culture proven PTB/EPTB cases with available DST result)	MDR: 25% (6/24) of all MDR-TB cases	E	Not stated	Not stated	Not stated	Lumb <i>et al</i> <sup>[50]</sup>
Bangladesh	Various sites	2011	152 (culture proven TB cases)	Any DR: 45.4% MDR: 11.2%	C	Not stated	Not stated	All cured	Afroz <i>et al</i> <sup>[51]</sup>
Brazil	TBM	1999-2007	108 (DST result available for 90 cases)	Any DR: 40% MDR: 9%	D	Not stated	108/108	31/108 died during hospitalization	Croda <i>et al</i> <sup>[54]</sup>
Canada	Various sites	1995-2002	126/214	Any DR: 19% INH-R: 7.9%	G	0/214	4/126	Not stated	Yang <i>et al</i> <sup>[52]</sup>
China	Spinal TB	2005-2010	127/249	Any DR: 30.7%	A	9/35	0/35	No death; 33/35 cases cured	Li <i>et al</i> <sup>[47]</sup>
	Spinal TB	2006-2011	(35 DR cases studied in detail) 76/152	Any DR: 30.3%	A	Not stated	Not stated	No death; 19/19 cases cured	Xu <i>et al</i> <sup>[53]</sup>
	TBM	2009-2010	(19 DR cases studied in detail) 30 (culture proven TB cases)	Any DR: 66.7% MDR: 32.1%	B	20/30	0/30	Not stated	Duo <i>et al</i> <sup>[54]</sup>
Denmark	TBM	2000-2008	41/50	INH-R: 4% MDR: 2%	D	23/50	5/50	9/50 cases died	Christensen <i>et al</i> <sup>[55]</sup>
Ethiopia	Tuberculosis lymphadenitis	2012	225/437	Any DR: 6.7% MDR: 1.3%	D	Not stated	Not stated	Not stated	Biadlegne <i>et al</i> <sup>[56]</sup>
France	Various sites (including pulmonary)	1992-1999	264 MDR-TB cases (207 PTB cases, 19 EPTB cases and 38 EPTB cases with concomitant PTB)	Any DR: 6.7% MDR: 1.3%	D	38/264	55/224	Not stated	Robert <i>et al</i> <sup>[16]</sup>
India	Various EP sites	2007-2010	227/756 (165 isolates confirmed as MTB)	Any DR: 39.9% MDR: 13.5%	C	Not stated	3/165	Not stated	Maurya <i>et al</i> <sup>[58]</sup>
	TBM	Not stated	51/370	Any DR: 33.3% MDR: 1.9%	D	Not stated	Not stated	Not stated	Jain <i>et al</i> <sup>[57]</sup>
	Abdominal TB	2008-2013	31/61	Any DR: 14.3% MDR: 5.4%	A	0/61	0/61	Not stated	Samant <i>et al</i> <sup>[58]</sup>
	Various EP sites	2010	(DST analyzed for 18 isolates) 150/547 (14 cases excluded)	MDR: 33%	A	Not stated	16/547	Not stated	Vadwai <i>et al</i> <sup>[59]</sup>
	Various EP sites	2007-2011	125/419	Any DR: 20.8% MDR: 12%	A	Not stated	7/125	Not stated	Sankar <i>et al</i> <sup>[62]</sup>
	Various EP sites	2002-2006	338 (culture proven TB cases)	Any DR: 52.7% MDR: 11.8%	D	Not stated	Not stated	Not stated	Sethi <i>et al</i> <sup>[19]</sup>
	Various EP sites	2010-2011	18 (culture proven TB cases)	MDR: 5%	D	Not stated	0/18	Not stated	Desikan <i>et al</i> <sup>[60]</sup>
	TBM	2004-2005	22/100	MDR: 18.2%	C	Not stated	1/4 MDR cases	All 4 MDR cases died	Baveja <i>et al</i> <sup>[61]</sup>
	TBM	2000-2003	256/2325	Any DR: 19% MDR: 1.5%	C	Not stated	Not stated	Not stated	Venkataswamy <i>et al</i> <sup>[22]</sup>
	TBM	2001-2005	(DST analyzed for 205 isolates) 366 (culture proven TB cases)	Any DR: 17.8% MDR: 2.4%	C	Not Stated	48/107	Not Stated	Nagarathna <i>et al</i> <sup>[62]</sup>
	Spine TB	2004-2007	25 (culture proven MDR-TB cases)		E	Not Stated	2/25 MDR cases	19/25 MDR-EPTB cases cured; rest 6 cases not concluded	Pawar <i>et al</i> <sup>[63]</sup>

Kazakhstan	Osteoarticular TB	2007-2009	76/285	MDR: 54.4%	I	Not stated	Not stated	Tutkyshbaev and Amanzholova <sup>[64]</sup> Cho <i>et al</i> <sup>[65]</sup>
Korea	Various sites	2008-2010	168 (culture proven TB cases)	Any DR: 8.9%	E	52/168 (5 cases had DR-TB; 43 cases had disseminated TB)	4/168	Not stated
Nepal	Various sites	2004	54/513 (48 isolates confirmed as MTB)	MDR: 1.8%	F	Not stated	Not stated	Gurung <i>et al</i> <sup>[66]</sup>
Pakistan	Various sites	2000-2002	98/460 (88 isolates confirmed as MTB)	Any DR: 62.9%	H	Not stated	Not stated	Butt <i>et al</i> <sup>[67]</sup>
Russia	Tuberculous spondylitis	2008-2011	107 (culture proven TB cases)	MDR: 12.6%	I	66/107	25/107 (15 HIV cases had MDR)	Vyazovaya <i>et al</i> <sup>[30]</sup>
South Africa	TBM (in children)	1992-2003	362/6781	MDR: 69.1%	E	Not stated	6/8 MDR cases	Padayatchi <i>et al</i> <sup>[68]</sup>
Taiwan	Various sites	1999-2002	350/6762 (Only MDR cases studied)	Any DR: 11.6%	E	14/30	17/30 MDR cases died (rest cases survived with disability)	Patel <i>et al</i> <sup>[20]</sup>
Turkey	Various sites	2000-2010	798 (culture proven TB cases)	MDR: 2%	D	Not stated	Not stated	Lai <i>et al</i> <sup>[71]</sup>
United States	Various EP sites	2001-2007	103 (culture proven TB cases)	MDR: 8.6%	A/C	Not stated	Not stated	Gunal <i>et al</i> <sup>[69]</sup>
	Various sites	1993-2006	31633/47293	MDR: 0.9%	E	Not stated	Not stated	Peto <i>et al</i> <sup>[13]</sup>
	Pleural TB	1993-2003	4215/7549	Any DR: 9.9%	E	264/7549 (sputum positive by culture)	679/7549 (9% cases died during treatment)	Baummann <i>et al</i> <sup>[15]</sup>
	Various sites	1993-2003	197/239 (in an ethnic group)	INH-R: 6%; MDR: 1%	D	41/239	One MDR case died; 169/186 (91%) cases completed treatment	Rock <i>et al</i> <sup>[23]</sup>
	TBM	1993-2005	1614/1896 (from CSF samples)	Any DR: 18%	E	468/777 (sputum positive by culture)	43/123 INH resistant cases died	Vinnard <i>et al</i> <sup>[24]</sup>
Vietnam	TBM	2004-2005	51/58 (DST result available for 46 cases)	MDR: 3%	D	Not stated	39/58 cases died; 11/58 cases survived; 8 cases lost to follow-up	Torok <i>et al</i> <sup>[27]</sup>
	TBM	2001-2003	222 (culture proven TB cases)	INH-R: 6%	D	Not stated	24/35 TBM cases (HIV co-infected) died	Caws <i>et al</i> <sup>[28]</sup>
	TBM	2000-2003	180 (culture proven TB cases)	Any DR: 54.3%	A	Not stated	60/180 cases (including 29 DR cases) died; 49/180 cases disabled; rest recovered well	Thwaites <i>et al</i> <sup>[20]</sup>

Besides the reports tabulated here, some case studies as well as studies with very low sample size have also been reported from different countries but could not be addressed in this review. <sup>1</sup> Cases with unknown HIV status are excluded from total number of cases tested; <sup>2</sup> Isolates recovered from both pulmonary and extra-pulmonary sites. DST methods: A: BACTEC MGIT 960 system; B: PCR and Genotype MTBDRplus line-probe assay; C: BACTEC 460 TB system; D: Conventional DST using proportion method; E: Method not specified; F: Conventional DST using minimum inhibitory concentration method; G: Middlebrook 7H10 agar using proportion method; H: BacT/Alert 3D system; I: Conventional DST using absolute concentration method. DR: Drug resistance to any one first line anti-tuberculosis drugs; MDR: Multi-drug resistance; DST: Drug susceptibility test; MGIT: Mycobacterial growth indicator tube; MTB: *Mycobacterium tuberculosis*; EPTB: Extra-pulmonary tuberculosis; P.TB: Pulmonary tuberculosis; INH: Isoniazid; HIV: Human immunodeficiency virus; R: Resistant; CSF: Cerebrospinal fluid; TBM: Tubercular meningitis; TB: Tuberculosis.

substantially. In USA, EPTB ratio has increased from 8% to 17.5% during year 1964 to 1986<sup>[9]</sup>. Similarly, an increase in prevalence of EPTB had been reported as 21% in Western Europe and 10% in Eastern Europe<sup>[10]</sup>. Recently, the incidence of EPTB is reported as 22% and about 50% of all diagnosed TB cases in United States and the United Kingdom, respectively<sup>[11,12]</sup>.

Unlike pulmonary TB, systematic drug resistant surveillance for EPTB has not been conducted. Furthermore, drug susceptibility testing for EPTB is not routinely

undertaken in many resource-limited countries, thus no authentic estimates on prevalence of drug resistant EPTB could be made available. However, sporadic information mostly derived either from retrospective cohort studies or TB surveillance data is now available from different parts of world and is summarized in Table 2. As per data accrued thus from different countries, the prevalence of MDR may lie between 1%-69% of total of EPTB cases; whereas, the proportion of resistant cases to any one anti-tuberculosis drug is about 10%-75% (Table 2). The wide variation in proportion of drug resistant EPTB among different studies is probably due to variation in study settings, burden of MDR-TB and quality of medical services in particular region, demographic characteristic and HIV status of patients, types of EPTB cases investigated, sample size and its selection criteria *etc.*. The comprehensive public health surveillance data of United States showed that about only 1% of total EPTB cases studied during 1993-2006 were MDR-EPTB<sup>[13]</sup>. On the other hand, some studies were published from high TB burden countries with much higher rate of DR-EPTB (Table 2). However in most of these studies data were collected from a cohort in a specific programmatic setting, mostly tertiary health care facility/hospitals that serves underprivileged population. In addition to this, the prevalence estimates in most of the tabulated studies collected from only a subset cases *i.e.*, culture confirmed EPTB cases. Looking at these potential limitations the prevalence figures may not be truly representative to that particular region or country; nonetheless, these studies are definitely concerning. Further, it is worth-while to note that the deadly combination of drug resistance among cases of tubercular meningitis (TBM) has been reported increasingly in many countries (Table 2). Recently, the rare possibility for the presence of XDR strain in extrapulmonary site has also been documented in India<sup>[14]</sup>.

Although, the behavior of the mycobacterium does not differ from site to site, drug resistance including MDR-TB is less common in cases of EPTB as compared to PTB. Studies from different countries have compared the drug resistance profiles between MTB isolates recovered from pulmonary and extra-pulmonary sites and showed negative association of EPTB with anti-TB drug resistance<sup>[14-17]</sup>. This is due to the fact that the selective multiplication of resistant mutants of MTB in caseous focal lesions of extrapulmonary sites is much less than in cavitary lesions of pulmonary sites. The development of DR-EPTB is mainly acquired through previous improper anti-tuberculosis regimen, poor patient compliance, a prolonged diagnosis of drug resistance and the spreading of drug-resistant strains. Drug resistance in EPTB is more common in previously treated patients<sup>[18]</sup>. Recently, a high level drug resistance among treatment failure PTB (48.1%) and EPTB cases (52.7%) from north India was reported<sup>[19]</sup>. Similarly, in another study, about 73% patients with drug resistant

TBM had a history of prior exposure to anti-tuberculosis drugs<sup>[20]</sup>.

The heterogeneous nature of extrapulmonary samples is another factor that not only contributes the variability in sensitivity values of various diagnostics but may also contribute to variation in drug resistance profile. In a study conducted in Taiwan, drug resistance profile of MTB isolates in specimens derived from various extrapulmonary sites was compared. In this study, isoniazid-resistant (or resistant to any first line drugs) MTB was more common in genitourinary and pleural sites followed by skin and soft tissue, peritoneum and lymphnode<sup>[17]</sup>. Cerebrospinal fluid, a preferred sample for diagnosis of TBM was not included in this study but drug resistance among TBM cases have been reported relatively high in different countries. Different Indian studies investigated the cerebrospinal fluid (CSF) collected from the cases of TBM and a high prevalence of drug resistant strain (MDR: about 2%; Resistance to any one first line drugs: 18%-33%) were found. Previous studies from different parts of the world showed a predominant resistance to INH in EPTB cases especially in TBM<sup>[17,21-23]</sup>. Among the first line drugs, INH is the only bactericidal agent that easily crosses the blood-brain barrier and is known to penetrate freely into the CSF. Therefore, INH resistance is a potential threat to the successful treatment and causes significant mortality in EPTB especially when meningeal involvement is present<sup>[24,25]</sup>.

EPTB is more common in HIV infected individuals and it may be undiagnosed until advance stages of the disease<sup>[26]</sup>. In addition to this, recently it is found that HIV status may also influence the incidence of drug resistance among cases of EPTB especially in TBM. Studies from Vietnam demonstrated that a significantly higher proportion (> 50%) of CSF mycobacterial isolates from TBM patients were resistant to one or more first-line anti-tuberculous drugs<sup>[27,28]</sup>. In contrast, no significant association between HIV infection and drug resistance among TBM cases were seen in some other studies<sup>[21,24]</sup>.

Recent studies suggest that different lineages of MTB may have different clinical manifestation. Indo-Oceanic and East-African Indian lineages were associated with exclusively extrapulmonary tuberculosis disease<sup>[29]</sup>. Interestingly, a strong association between "Beijing genotype" lineage, drug resistance, and HIV infection in a cohort of TBM patients has been shown<sup>[28]</sup>. Similarly, a Russian study also observed prominent association of Beijing genotype with multi-drug resistance (out of 80 Beijing genotype isolates, 90.5% were multi-drug resistant) in cases of tuberculous spondylitis<sup>[30]</sup>. However, it seems that such association may be influenced by variable distributions of MTB lineages in different parts of world. Despite this possibility, the Beijing family of MTB is considered highly virulent and associated with drug resistance in several settings<sup>[31,32]</sup>.

## CHALLENGES IN DIAGNOSIS, TREATMENT AND MANAGEMENT

Respiratory tract infections caused by pathogens other than *Mycobacteria* is often implicated by physician. But the treatment failure and recurrence or persistence of symptoms led to suspicion and investigation of PTB. Despite this initial delay, the definite diagnosis and effective treatment management of PTB is feasible. Unlike PTB, the diagnosis of EPTB is a major challenge for clinician. As the clinical manifestation of EPTB is highly heterogeneous, many of patients are examined by different specialists with little awareness in TB diagnosis thus may cause significant delay in including the EPTB into differential diagnosis panel. Data from many countries shows that 20%-50% cases of EPTB are diagnosed post-mortem<sup>[33]</sup>; which not only highlights our limited ability to diagnose the EPTB but also provide a possible reason for lower incidence of EPTB in many countries. Lack of strong laboratory backup at peripheral health facility level in many high TB burden countries also contribute significantly for excess delay and difficulty to establish EPTB.

It is believed that a small amount of tubercle bacilli even sensitive to anti-tubercular drugs often cause great damage in some aggressive form of TB like TBM. Therefore, diagnostic delay in EPTB poses great risk of mortality. Previous studies demonstrated, a delay of 3 d between TBM presentation and initiation of anti-tuberculous therapy among pediatric as well as adult cases is associated with increased risk of death<sup>[34,35]</sup>. Further, drug resistance may severely complicate the situation because a twofold increase in mortality was observed recently among the isoniazid drug resistant TBM cases<sup>[36]</sup>. The various hurdles making the diagnosis of DR-EPTB an issue are highlighted in Table 3.

Although, EPTB is not considered as contagious but concomitant contagious PTB may spread the infection to others. European TB surveillance report<sup>[37]</sup> showed that about 1/4<sup>th</sup> of all EPTB cases had also pulmonary involvement. Thus the presence of EPTB does not exclude the pulmonary involvement, even though such cases are nevertheless classified as contagious PTB<sup>[1]</sup>. Recent studies have found that even with a normal chest radiograph, the concomitant pulmonary involvement may be present in considerable proportion (up to 18%) of patients<sup>[38,39]</sup>. However still in routine practice, the existence of PTB in cases of EPTB is not generally ruled out.

For a definite diagnosis of EPTB, WHO recommends that it should be on the basis of culture-positive specimen and/or positive histology and/or strong clinical evidence consistent with active EPTB<sup>[1]</sup>. A cautious investigation of clinical, radiological and histopathological representations in different form of EPTB may provide some clues to achieve the diagnosis even than seeking the laboratory based diagnosis is important to establish the disease. Although laboratory testing for EPTB follows the same principles as for PTB, but it is very difficult and

negative test result does not rule out the EPTB.

The multiplication of tubercle bacilli is generally hindered within the caseous foci lesion/tissues of extrapulmonary sites due to low availability of oxygen as well as acidic pH, and the presence of toxic fatty acids<sup>[40]</sup>. Therefore under these stress condition, EPTB is generally found in pauci-bacillary that may be skipped to be detected by conventional diagnostic tests. Direct visualization of acid-fast bacteria is still the first and most preferred microbiological test but it is far from being sensitive to diagnose EPTB<sup>[41]</sup>. At present, microbiological confirmation (either by solid or liquid culture method) of MTB in samples from the affected sites of EPTB is considered as gold standard which also gives the opportunity to identify the *Mycobacterium* species and to perform phenotypic drug-susceptibility tests as well as genotyping for molecular epidemiology studies. However, the main drawback of culture is long turn-around time and compromised sensitivity due to lower and non-uniform distribution of bacillary load at extrapulmonary sites as well as compromised quality and quantity of specimen. It has been demonstrated that concentration of large volumes of sampled fluid (CSF, ascites, etc.) and repeated analyses can increase the diagnostic yield<sup>[42]</sup>. However, it is often too difficult to get additional and adequate amount of samples from the patients.

As discussed above, delay in diagnosis may not be acceptable in the management of aggressive TB cases like TBM or HIV-associated EPTB, a rapid and sensitive diagnosis and DST method is always pre-requisite. In the same regard, several nucleic-acid amplification tests (NAAT) are now available that can detect MTB and can also determine the drug resistance to some key drugs. Of the various NAAT, Xpert MTB/RIF seems most promising as it is fully automated cartridge-based real-time PCR based test that efficiently detects both TB and resistance to rifampicin in less than 2 h. WHO reviewed a set of studies and concluded into an excellent sensitivity and specificity of Xpert MTB/RIF from pooled data on samples collected from various extrapulmonary sites (CSFs, gastric fluids and biopsies)<sup>[43]</sup>. Unfortunately, this system does not determine the isoniazid resistance which is known to be significantly associated with mortality among TBM cases. The cost of the test, dependency on electric supply, the cartridge supply and storage conditions and the difficulty to carry and implement the system in limited resource settings are some other challenges. Nevertheless, Xpert MTB/RIF assay coupled with its speed, simplicity and less biohazard problems could play an important routine role in diagnosis of EPTB.

Like diagnosis, the treatment and management of EPTB is also full of challenges and recently a meta-analysis showed that treatment outcomes were poor in patients with DR-TB<sup>[44]</sup>. This is especially due to poor drug penetration to the affected tissue and the lack of accessibility of tissue/sample for assessing the treatment response by serial cultures. Further, any degree of drug

**Table 3** Key issues in diagnosis of drug resistant-extrapulmonary tuberculosis

<p>Issues in laboratory diagnosis</p> <p>In general, the sensitivity of laboratory tests is often compromised</p> <p>Due to pauci-bacillary nature of EPTB</p> <p>Due to difficulty in obtaining an adequate sample</p> <p>Risk associated with the sampling procedure (<i>e.g.</i>, lumbar puncture, biopsy of deep lymph nodes, <i>etc.</i>)</p> <p>Lack of accessibility of serial samples for monitoring the treatment response</p> <p>Un-availability of reliable host biomarkers that can be analyzed in easily attainable specimens</p> <p>Xpert-MTB-RIF test seems promising diagnostic tool but the negative test result does not rule out EPTB and it can only determine the resistance to rifampicin (not other crucial drugs)</p> <p>Issues at programmatic/administrative level</p> <p>Lack of focused programme (like pulmonary TB) in many high TB burden countries</p> <p>Lack of reliable estimates on impact and magnitude of DR-EPTB</p> <p>Although seeking microbiological, histopathological diagnosis and drug susceptibility testing is crucial, it is however not in routine practice (in many high TB burden countries)</p> <p>Rapid molecular based diagnostic (Xpert-MTB-RIF) is still away from its accessibility at peripheral health care centers in many resource limited countries</p> <p>Wide variation in diagnostic and treatment practices among health service providers (as reported in private sectors of India) that often do not comply with national or international standards</p>
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DR-EPTB: Drug resistant-extrapulmonary tuberculosis; MTB: *Mycobacterium tuberculosis*; RIF: Rifampicin; TB: Tuberculosis; EPTB: Extrapulmonary tuberculosis.

resistance hinders the treatment and may results into poor outcomes especially in severe form of disease. The problem gets compounded among HIV infected individual as it has been shown that MDR-TB at treatment initiation, positive HIV status among EPTB cases are significantly associated with mortality<sup>[24,45]</sup>. WHO recommended the treatment of MDR-EPTB with the same strategy involving the same regimen and duration as pulmonary MDR-TB. However in severe complication, individualized chemotherapy and some other means like surgery, adjunctive corticosteroids, immune-modulators may result into good treatment outcomes<sup>[46,47]</sup>. Owing to increasing incidence of drug resistance and severity of some kinds of EPTB, there is an urgent need for effective short-term regimens with newer drugs having better penetration at various sites in body.

At programmatic management level, EPTB also deserves special attention to ensure access of quality diagnosis, drug susceptibility testing and prompt initiation of appropriate therapy. The political commitment and support in this regard is utmost important. In many high TB burden countries, the peripheral health centers are still devoid of strong laboratory back-up and sensitized medical staff. In India, EPTB is predominantly managed in the private sector and these cases are rarely notified to government agencies. Additionally, in private sector the diagnostic and treatment practices is not firmly followed as per national or international standards and usually treatment is started without having culture confirmation and drug susceptibility testing<sup>[48]</sup>. Taking all these challenges into consideration, it is anticipated that MDR-TB affecting extrapulmonary site may continue to increase.

## CONCLUSION

Drug resistance among cases of EPTB is a definitely

rising problem in most of the countries where ever it has been investigated. Since survey study on similar line begun to accumulate only recently, a continued effort in future will be of exquisite importance to achieve reliable estimates of the incidence in different parts of world. Such information will be imperative in establishment of strategic frameworks for intensified cases finding, effective treatment management and also to garner the resources necessary for the prevention of associated high morbidity and mortality. Further, there is an urgent need for increasing awareness of the clinician to rising incidence drug resistant EPTB and to consider the drug resistance testing before start of therapy for better treatment outcomes. We hope this preliminary review will encourage the future systematic studies to precisely define the epidemiological picture of drug-resistance EPTB.

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