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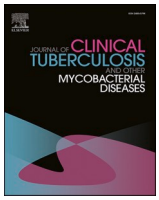

Clinical features, resistance patterns and treatment outcomes of drug-resistant extra-pulmonary tuberculosis: A scoping review

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ABSTRACT

Background: Drug-resistant tuberculosis (DR-TB) is a threat to tuberculosis (TB) control. Extra-pulmonary forms of DR-TB (DR-epTB) are not well characterized. This review summarizes the clinical features, resistance patterns and treatment outcomes of DR-epTB.

Methods: We searched EMBASE to identify studies that reported drug-resistance among extra-pulmonary TB sites. All age groups were included in this review. Studies which did not describe drug-resistance patterns at extra-pulmonary TB sites were excluded. We summarized the proportion of resistance to individual anti-TB drugs as well as multi-drug resistant (MDR), pre-extensively drug resistant (pre-XDR) and extensively drug-resistant (XDR) TB.

Results: Eighteen studies with a total of 10,222 patients with extra-pulmonary TB of whom 1,236 (12.0%) had DR-epTB, were included in this review. DR-epTB was mostly reported in young people aged 28 to 46 years. While TB meningitis is the most commonly studied form, adenitis is the commonest form of DR-epTB reported in 21% to 47%. Central nervous system TB (3.8% to 51.6%), pleural TB (11.3% to 25.9%), skeletal TB (9.4% to 18.1%), abdominal TB (4.3% to 6.5%), and disseminated TB (3.8%) are also encountered. The HIV co-infection rate is reported to be 5.0% to 81.3% while 2.6% to 25.4 % have diabetes mellitus. Clinical symptoms of DR-epTB are consistent with morbidity in the affected body system. Among patients with DR-epTB, the proportion of MDR TB was 5% to 53% while that for pre-XDR TB and XDR TB was 3% to 40% and 4% to 33%, respectively. Treatment success is achieved in 26% to 83% of patients with DR-epTB while death, treatment loss-to-follow up, and treatment failure occur in 2% to 76%, 7% to 15%, and 0% to 4% respectively. Patients with DR-epTB were reported to have poorer outcomes than those with pulmonary DR-TB and extra-pulmonary drug-susceptible TB.

Conclusion: Clinical features of DR-epTB are similar to those observed among people with drug-susceptible EPTB but patients with DR-epTB post worse treatment outcomes.

1. Background

Drug-resistant tuberculosis (DR-TB) is a threat to tuberculosis (TB) control. More than 19 million people have latent multi-drug resistant TB (MDR-TB), a form of *Mycobacterium tuberculosis* that is resistant to rifampicin and isoniazid, and are therefore at risk of MDR-TB reactivation [1]. The incidence, prevalence, death, and disability-adjusted life years of MDR-TB have been declining since the year 2000 [2]. However, about 450,000 people developed MDR-TB/rifampicin-resistant TB (RR-TB) in 2021, which reflected a 3.1% increment from 2020 [3]. It is estimated that 3.6% of new and 18% of global retreatment TB cases in 2021 had MDR/RR-TB [3]. Unfortunately only a third of these cases are initiated on DR-TB treatment and untreated cases continue to propagate community transmission [2].

The treatment of DR-TB has historically been plagued by a high cost of treatment and low treatment success rate owing to long treatment durations, pill burden, less efficacious drugs, and a high incidence of adverse drug events [4]. In countries with the highest burden of MDR-TB, up to 476.5 billion USD were lost and 10 countries lost at least 5% of their gross domestic product in 2018 [5]. By 2050, it is estimated that a total of 16.7 trillion USD will be lost worldwide because of MDR-TB [6]. The emergence of all-oral shorter TB regimens with novel and

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repurposed drugs has revolutionized the management of DR-TB as these promise better safety, patient adherence, and lower cost [7–8]. However, these new regimens are not approved for certain patient categories such as those with severe forms of drug-resistant extra-pulmonary TB (DR-epTB), who constitute a substantial proportion of people with DR-TB [7–8].

While TB predominantly affects the lung parenchyma in more than 80% of people, TB outside the lung parenchyma (extra-pulmonary TB) is often encountered [9–10]. Extrapulmonary TB (EPTB) is neglected in broad approaches to TB control partly because it is thought to be non-transmissible. Patients with EPTB pose a high mortality during TB treatment and after TB treatment completion [11–12]. Therefore, DR-epTB is gaining recognition as a barrier to achieving TB treatment success. About 16 – 20% of EPTB cases have DR – TB of which 8 – 14% have isoniazid resistance, 2.4 – 3.9% have rifampicin mono-resistance and 2 – 10% have MDR-TB [9]. Few studies have described the clinical characteristics and treatment outcomes of DR-epTB. An understanding of the clinical features and outcomes would help clinicians in arriving at a clinical diagnosis and foster close monitoring of patients with DR-epTB.

2. Objectives

1) To describe the clinical features of DR-epTB
2) To describe the drug-resistance patterns in DR-epTB
3) To describe the treatment outcomes in DR-epTB

3. Methods

3.1. Study design

This is a scoping review of studies published on DR-epTB. Our report follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) checklist [13].

3.2. Information sources

We carried out a comprehensive literature search on EMBASE from the inception of the database to 13th October 2022.

3.3. Search strategy

We used this search query: ((((’tuberculosis’/exp OR ’tuberculosis’ OR ’tb’/exp OR ’tb’) AND (’extrapulmonary’ OR ’lymph node’ OR ’meningitis’ OR ’abdominal’ OR ’spine’ OR ’bone’ OR ’pleura’ OR ’urogenital’)) OR (’tuberculous spondylitis’ OR ’pott’ OR ’extrapulmonary tuberculosis’ OR ’eptb’)) AND (’multidrug resistant tuberculosis’ OR ’mdr tb’ OR ’mdrtb’ OR ’extensively drug resistant tuberculosis’ OR ’xdr tb’ OR ’xdrtb’ OR ’drtb’ OR ’dr tb’ OR ’rifampicin resistance’ OR ’rifampicin resistant tuberculosis’ OR ’drug resistance’)) AND (’characteristic’ OR ’symptom’ OR ’sign’ OR ’clinical feature’ OR ’treatment outcome’ OR ’treatment success’ OR ’failure’ OR ’death’ OR ’follow up’ OR ’cure’).

3.4. Eligibility criteria of included studies

3.4.1. Inclusion criteria

We included studies published in English. All age groups were included. Case series, prospective and retrospective cohort studies, cross-sectional studies and clinical trials were included.

3.4.2. Exclusion criteria

Studies that did not report drug resistance profiles in extrapulmonary TB sites were excluded. Further, studies whose full texts were not available were also excluded.

3.5. Selection process

Two reviewers (EM and JBB) screened the titles and abstracts of all the articles retrieved.

3.6. Data collection process

We designed a data extraction form to capture data on study variables (see data items below). One reviewer (EM) extracted the data from each report while a second reviewer (JB) cross-checked the accuracy of the data collected.

3.7. Data items

We collected data on the following variables: first author’s name, publication year, the country in which the study was done, type of study, the start of the study, end of the study, percentage of females/males, rural vs. urban residence, alcohol use disorder, smoking, intravenous drug use, previous TB, imprisonment, contact with TB, site of TB, number with drug-resistance, mean/median age, number of patients with resistance to individual drugs, multi-drug resistance (MDR), pre-extensive drug resistance (Pre-XDR) or extensive drug resistance (XDR). MDR-TB is defined as TB resistant to both isoniazid and rifampicin – the two most effective first-line drugs [8]. Pre-XDR-TB is defined as TB that is resistant to rifampicin and any fluoroquinolone (a class of second-line anti-TB drug) or a second-line injectable aminoglycoside, whereas XDR-TB is TB that is resistant to rifampicin, plus any fluoroquinolone, plus at least one of the drugs bedaquiline, linezolid and a second-line injectable aminoglycoside [8]. We also collected data on comorbidities, symptoms, and signs, diagnostic tests performed, drugs in the treatment regimen, duration of treatment, surgical intervention, cure/completion of treatment, treatment failure, death, loss to follow-up, and no treatment.

3.8. Data analysis and synthesis

We presented the results descriptively. Resistance patterns are presented as proportions of patients with any resistance to a particular drug to the total number of patients with confirmed drug resistance in the study. Similarly, treatment outcomes are presented as proportions. These were computed using R version 4.1.1 [14].

4. Results

4.1. Study selection

There was a total of 1,902 records from our database search. After removing 29 duplicate records, 1,873 records were screened by title and abstract and 35 records were retrieved for detailed evaluation. Of these, 7 records did not have full text available [15–21]. The full texts of 28 records were then screened. Of these, 10 were excluded because drug resistance was not separately reported for extra-pulmonary sites (10/13) [22–31]. Finally, 15 records were included in this review [32–49]. Fig. 1 shows the screening process.

4.2. Study characteristics

The characteristics of the included studies are shown in Table 1. Majority of the studies were from China (6/18) [37,39–40,43–44,48], followed by India (4/18) [33–34] and Vietnam (3/18) [36,41–42]. Most of the studies were retrospective (9/18) [33–34,37–38,44–46], with a few cross-sectional studies (4/18) [32,35,39–40], prospective studies (4/18) [41–42,49–50] and one randomized controlled clinical trial [36].

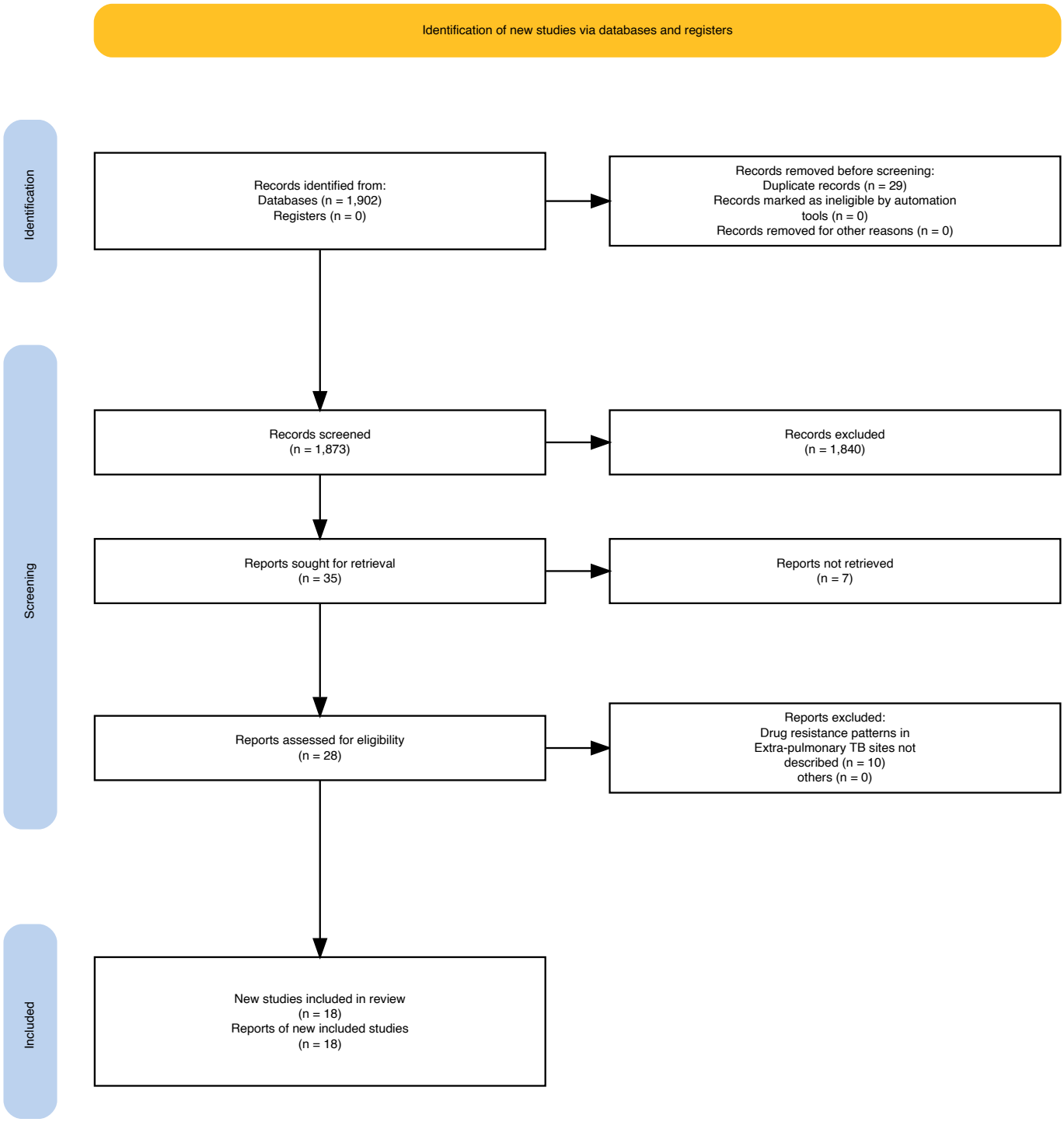

Fig. 1. PRISMA flow diagram showing the results of the data base search and records screening process. Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

4.3. Proportion DR-epTB among patients with EPTB

Of 10,222 patients with EPTB across the 18 studies, 12.1% (1,236/10,222) had resistance to at least one anti-TB drug. Of those, 41.7% (515/1,236) had resistance to isoniazid, 43.4% (536/1,236) had Rifampicin/Multidrug-resistance while 3.5% (43/1,236) had extensively drug-resistant TB.

4.4. Demographic characteristics of patients with DR-epTB

The mean age of patients with DR-epTB ranged from 27.96 [34] to 45.6 [33] years. The proportion of females ranged from 29% [46] to 41.7% [39]. The proportion of DR-epTB with a previous TB episode ranged from 29.2% [39] to 52.6% [37]. In the study by Heemskerk et al., patients with isoniazid- and rifampicin/multidrug resistance were more likely to report a previous episode of TB infection compared to those with no or other forms of resistance (29.1% and 50.0% vs 15.0%, $p < 0.001$) [36]. Ma et al reported a proportion of 60.3% of rural residents

Table 1
Characteristics of the included studies by author, study design, country or countries in which the study was done, period over which their data was collected, Mean (or median) age of the participants in the study and the sample size. *Age is for anti-TB drug resistant cases; median is indicated by '(median)'. #The countries are: Turkey, Slovenia, Serbia, Romania, Hungary, France, Denmark, Croatia and Albania. € Mean age for mono-drug resistant Spinal skeletal TB. ¥ Mean age for mono-drug resistant extra-spinal skeletal TB. ß Median age for isoniazid-resistance. α Median age for streptomycin resistance. Abbreviations: NA, not available; TB, tuberculosis; EPTB, extra-pulmonary Tuberculosis.

First Author (publication year)	Country	Study design	Period of data collection	Number with EPTB (n)	Number with any drug resistance (n)	Mean Age* (years)
Arockiaraj (2018) [36]	India	Retrospective	2006–2013	898	92	$42^{€}$ – $45.6^{¥}$
Desai (2018) [37]	India	Retrospective	2012–2014	76	53	27.96
Diriba (2020) [38]	Ethiopia	Cross-sectional	NA	151	29	NA
Heemskerk (2017) [39]	Vietnam	Randomized Controlled Trial	2011–2014	322	146	NA
Ma (2022) [40]	China	Retrospective	2015–2019	232	232	NA
Krishnakumariamma (2020) [35]	India	Cross-sectional	2018–2020	293	22	NA
Senbayrak (2015) [41]	9 countries#	Retrospective	2000–2012	142	20	NA
Ye (2016) [42]	China	Cross-sectional	2009–2014	193	48	40.79
Duo (2011) [43]	China	Cross-sectional	2009–2010	30	20	NA
Thwaites (2002) [44]	Vietnam	Prospective	1997–2000	56	13	$30^{ß}$ – $39^{α}$ (median)
Torok (2008) [45]	Vietnam	Prospective	2004–2005	58	25	NA
Wang (2021) [46]	China	Retrospective	2014–2020	2884	62	NA
Shi (2016) [47]	China	Retrospective	1999–2013	967	49	NA
Hsu (2011) [48]	Taiwan	Retrospective	1995–2007	64	16	NA
Evans (2022) [49]	Georgia	Retrospective	2013–2018	343	31	40
Korma (2015) [49]	Ethiopia	Prospective	2012–2013	200	37	NA
Udgirkar (2019) [50]	India	Prospective	2014–2017	176	26	NA
Yang (2020) [48]	China	Retrospective	1999–2015	3137	272	31.16

among Rifampicin-resistant/multi-drug resistant extrapulmonary TB [37]. Among patients with drug-resistant TB meningitis, alcohol use disorder was reported in 8%, intravenous drug use was reported in 31% and a history of imprisonment was reported in 25% [46].

4.5. Common sites of infection of DR-epTB

10 studies reported on drug-resistant central nervous system (CNS) TB and TB meningitis was the most studied [32,34,37–38,40–43]. Five studies reported drug-resistant skeletal TB [33,34,37,44,48]. Two studies reported drug-resistant genitourinary TB [39,45]. Other sites were: lymphatic [34,37,43], pleural or chest wall [34,37,43], and abdominal (including peritoneal) [37,43,50]. Among the studies that reported the proportions of DR-ep TB by site of infection [34,37,43], adenitis/lymphatic TB was the commonest form and was reported in 20.7% [37] to 47.2% [34], followed by TB of the central nervous system (3.8% [34] to 51.6% [43]), pleural TB (11.3% [43] to 25.9% [37]), skeletal TB (9.4% [34] to 18.1% [37]), abdominal TB (4.3% [43] to 6.5% [43]), and disseminated TB (3.8% [34]). In the study by Evans et al. [46], those with drug-resistant meningeal TB had significantly more pulmonary co-infection compared to drug-susceptible meningeal TB, (69% vs 15%, p-value < 0.01).

4.6. Comorbidities of DR-epTB

HIV was the most reported comorbidity among 5.0% to 81.3% of people with DR-epTB. In the study by Thwaites, et al [41] and Evans et al. [46], the HIV co-infection rate was 60.0% (15/25) and 50.0% (18/36), respectively. It was 5.0% (1/20) in Senbayrak et al.'s study [38] but was 81.3% among people with meningeal MDR-TB in the study by Heemskerk et al. [36] In the study by Wang et al., only patients with extra-pulmonary TB and HIV co-infection were enrolled [43]. In contrast to the above studies, all patients with DR-ep TB were HIV-negative in the studies by Desai et al. [34], Arockiaraj et al. [33], and Ma et al. [37] The proportion of patients with diabetes mellitus (DM) was 2.6% to 25.4% in three studies [34,37–38]. In the study by Desai et al, 17.11% (13/76) of patients with DR-epTB had comorbidities, including anemia (5.3%), hypothyroidism (2.6%), depression (2.6%) and 1.3% for each of renal failure, mental retardation, elephantiasis, hypertension, urolithiasis, and germ cell testicular tumor [34]. In a population of patients with meningeal DR-epTB, 25.0% (5/20) had at least one comorbidity of chronic kidney disease, HIV, and DM [38]. Hepatitis C was reported in 47.2% of patients with DR-ep TB meningitis in Georgia [46].

4.7. Signs and symptoms

Two studies reported signs and symptoms in patients with drug-resistant compared with drug-susceptible TB meningitis [36,46]. In the study by Evans et al, patients with Drug-resistant TB meningitis presented with more severe disease (grade 3) compared to Drug-susceptible TB meningitis (43% vs 23%, $p = 0.01$) [46]. The commonest symptoms and signs for drug-resistant CNS TB were altered mental status followed in equal frequency by fever, headache and nuchal rigidity. Ye et al., presented symptoms of drug-resistant genitourinary TB [39], where urinary irritation, lumbago and fever were commonly reported in decreasing order of frequency. For drug-resistant spinal skeletal TB, back pain was the commonest presenting symptom (98.5%) while neurological deficits occurred in 30.5% [48]. Other studies did not disaggregate the signs and symptoms for drug-resistant cases from susceptible ones. Table 2 summarizes the frequency of symptoms and signs for CNS and genitourinary DR-epTB.

4.8. Diagnostic tests used in DR-epTB

In almost all studies, drug resistance was confirmed by culture with drug susceptibility testing. Lowenstein-Jensen agar and Mycobacterial growth inhibitor tubes were commonly used. One study did not describe how drug resistance was confirmed [43]. Duo et al found that Polymerase chain reaction (PCR)-based detection of TB in cerebrospinal fluid can be used for the detection of drug resistance when combined with the MTBDRplus line-probe assay, with a shorter turn-around-time compared to classic drug-susceptibility testing (1 day vs 30 to 40 days, respectively) [40]. Heemskerk et al, reported variation in GeneXpert positivity across resistance profiles whereby resistant forms of meningeal TB were less likely to yield positive GeneXpert results (82.2% for No/other resistance vs 78.5% for Isoniazid resistant vs 50.0% for Rifampicin/

Table 2
Signs and symptoms of drug-resistant extra-pulmonary tuberculosis. Abbreviations: DR-epTB, Drug-resistant extra-pulmonary TB.

Site of DR-ep TB	Symptoms and signs	Frequency (%)	Reference
CNS	Altered mental status	89	Heemskerk et al [39]
	Fever	86	
	headache	86	
	Nuchal rigidity	86	Evans et al [49]
	seizures	11	
	Cranial nerve palsy	7.8–17	
	Urinary retention	22	
	paraplegia	2.8–8	
	hemiplegia	6–6.8	
Genito-urinary	Urinary irritation	72.9	Ye et al [42]
	Lumbago	50.0	
	fever	27.1	
	Night sweat	18.8	
	Weight loss	18.8	
Spinal skeletal	Back pain	98.53	Yang et al [48]
	Low fever or/and night sweats	95.59	
	Local percussion pain	94.49	
	Spinal activity limitation	71.32	
	Neurological deficit	30.51	
	Skin ulceration or/and sinus formation	19.49	
	Radicular pain	18.01	
	Numbness	15.81	
	Weakness	13.24	
	Trouble walking	10.29	

Multi-drug resistance, p = 0.02) [36]. Similarly, the odds of culture positivity were significantly lower in DR-epTB compared to pulmonary TB (Odds ratio, 1.43 [95 CI, 1.02 – 2.43], p < 0.01) in the retrospective study of Rifampicin/Multi-drug resistant TB by Ma et al, although there was no difference in the GeneXpert positivity rate (90.9% vs 89.9%, p = 0.24) [37].

4.9. Drug resistance patterns of patients with DR-epTB

We expressed resistance to each anti-TB drug as a proportion of the reported number of patients with resistance to that drug to the total number of patients with DR-epTB. Among patients with DR-epTB, resistance ranged between 0% [41] to 62.5% [39] for rifampicin, 8.1% [49] to 90.0% [40] for isoniazid, 31% [35] for pyrazinamide, 0% [41] to 74.6% [37] for ethambutol, 7.1% [41] to 96.0% [42] for streptomycin, 12.9% [37] for ethionamide, 1.1% [33] to 5.6% [37] for cycloserine, and 3.8% [50] to 39.6% [39] for fluoroquinolones. The proportion of MDR-TB ranged between 10.3% [36] to 52.8% [34] while two studies enrolled only RR/MDR patients [37,48]. The proportion of pre-XDR-TB and XDR-TB, resistance ranged between 3.2% [43] to 39.6% [34] and 0.0% [47] to 33.3% [39] respectively. Table 3 summarizes the patterns of drug resistance.

4.10. Treatment regimens of DR-epTB and their adverse effects

There were varied treatment regimens across the studies. Heemskerk et al randomized 817 patients with TB meningitis, of whom 39.4% (n = 322) had a known drug-resistance profile, to receive the standard treatment or intensified treatment [36]. In the standard treatment, isoniazid (5 mg/kg/day), rifampicin (10 mg/kg/day), pyrazinamide (25 mg/kg/day), and ethambutol (20 mg/kg/day) or streptomycin (20 mg/kg/day) were administered for three months followed by rifampicin and isoniazid at the same doses for 6 months. Intensified treatment consisted of the standard regimen with an additional, weight-based dose of rifampicin (5 mg/kg/day) to achieve a total dose of 15 mg/kg/day, and

Table 3
Resistance patterns in patients with drug-resistant extra-pulmonary tuberculosis. *N is the number of patients who had resistance to any anti-tuberculosis drug. Resistance to each drug is expressed as a percentage of N. Abbreviations: NA, not available; MDR, Multi-drug resistance; Pre-XDR, Pre-extremely drug resistant; XDR, extremely drug resistant. $Enrolled patients with Rifampicin/multi-drug resistance, without reporting the separate proportions. **N here excludes 5 cases of suspected (but unconfirmed) resistance.

First Author (year of publication)	N*	Rifampicin (%)	Ethambutol (%)	Streptomycin (%)	Ethionamide (%)	Cycloserine (%)	Isoniazid (%)	Fluoroquinolones (%)	Pyrazinamide (%)	MDR (%)	Pre-XDR (%)	XDR (%)
Arockiaraj (2017) [33]	92	NA	2.2	26.1	NA	1.1	14.1	NA	NA	35.9	NA	4.3
Desai (2018) [34]	53	NA	NA	NA	NA	NA	NA	NA	NA	52.8	39.6	5.7
Diriba (2020) [35]	29	48.3	10.3	31.0	NA	NA	75.9	NA	31	48.3	10.3	NA
Heemskerk (2017) [36]	146	8.9	3.4	78.8	NA	NA	58.9	NA	NA	10.3	NA	NA
Ma[37§] (2022)	232	100.0	74.6	87.5	12.9	5.6	NA	NA	NA	100.0	30.2	NA
Krishnakumariamma (2020) [32]	22	NA	NA	NA	NA	NA	13.6	NA	NA	NA	NA	NA
Senbayrak (2015) [38]	20	25.0	30.0	35.0	NA	NA	85.0	NA	NA	25.0	NA	NA
Ye (2016) [39]	48	62.5	10.4	NA	NA	NA	79.2	39.6	NA	52.1	NA	33.3
Duo (2011) [40]	20	55.0	NA	NA	NA	NA	90.0	NA	NA	45.0	NA	NA
Thwaites (2002) [41]	13	NA	NA	76.9	NA	NA	69.2	NA	NA	NA	NA	NA
Torok (2008) [42]	25	16.0	NA	96.0	NA	NA	76.0	NA	NA	16.0	NA	NA
Wang (2021) [43]	62	51.6	4.8	50.0	NA	NA	72.6	NA	NA	NA	3.2	16.1
Shi (2016) [44]	49	59.2	22.4	49.0	NA	NA	63.3	NA	NA	49.0	NA	4.1
Hsu (2011) [45]	16	43.8	NA	75.0	NA	NA	87.5	NA	NA	25.0	NA	NA
Evans (2022) [46]**	31	6.5	NA	NA	NA	NA	19.4	NA	NA	22.6	29.0	22.6
Korma (2015) [49]	37	21.6	2.7	5.4	NA	NA	8.1	NA	NA	NA	NA	NA
Udgirkar (2019) [50]	26	19.2	NA	3.8	NA	NA	15.4	3.8	NA	30.8	3.8	0.0
Yang (2020) [48]	272	57.4	NA	41.9	NA	NA	68.8	29.0	NA	100.0	NA	NA

levofloxacin (20 mg/kg/day) for the first 8 weeks of treatment. Both treatment regimens were 9 months long. Isoniazid resistance was treated with a fluoroquinolone and occasionally an aminoglycoside was used early in treatment. However, there was significant heterogeneity in treatment adjustments for drug resistance across centers. The results of the trial showed that intensified treatment was significantly associated with improved 9-month survival in Isoniazid-resistant TB meningitis [36]. In the study by Ma et al, all patients with rifampicin/multi-drug resistance received treatment for at least 18 months with regimens that were individualized according to the WHO guidelines and drug susceptibility testing [37]. In Desai et al., the mean treatment duration for DR-ep TB was 22.22 months although some patients received shorter regimens (mean 15.4 months) due to adverse drug reactions [34]. The generic regimen comprised Kanamycin, Levofloxacin, Ethionamide, Pyrazinamide, Ethambutol, and Cycloserine during the 6 to 9 months of the intensive phase and 4 drugs (Levofloxacin, Ethionamide, Ethambutol, and Cycloserine) during the 18 months of the continuation phase. In this study, resistance to Fluoroquinolones was managed with a substitution for *para*-amino salicylic acid while resistance to kanamycin was managed by replacement with capreomycin [34]. In the study by Arockiaraj et al, the drug combination of pyrazinamide, a fluoroquinolone, an injectable agent, and a bacteriostatic was used to treat multi-drug-resistant skeletal TB for a period of 24 months [33].

Desai et al reported adverse drug effects in two-thirds of patients with DR-ep TB including gastritis (23.6%), psychiatric disorders (19.7%), arthralgia (7.9%), ototoxicity (3.9%), hepatotoxicity (3.9%), hypothyroidism (3.9%) and skin rashes (1.3%) [34]. In Heemskerk et al., isoniazid resistance had a significant association with the combined outcome of new neurological events or death (Hazard Ratio, 1.58 [95% CI, 1.11–2.23]). New onset neurological events were defined as the occurrence of any of the following adverse events after enrollment: cerebellar symptoms; coma/consciousness deterioration or a fall in Glasgow Coma Scale score by $\geq$2 points for $\geq$2 days from the highest previously recorded; cranial nerve palsy; hemiplegia, paraplegia, tetraplegia, or monoplegia; neurological deterioration requiring ventilation; seizures; or cerebral herniation. In MDR spinal skeletal patients, the commonly reported drug-related complications were gastrointestinal symptoms (4.87%) and liver injury (2.21%) [48].

4.11. Surgical interventions in DR-epTB

In the study by Arockiaraj et al, 55% (31/55) of patients with drug-resistant spinal TB underwent surgical interventions while 78% (28/36) with drug-resistant extra-spinal TB had surgery in addition to anti-tuberculous therapy in both cases [33]. The surgical techniques employed included decompression with spine fusion, pigtail drainage of the psoas abscess, knee synovectomy, and bone debridement [33]. Of the drug-resistant skeletal TB cases who received surgical interventions in this study, 87.3% (48/55) went on to heal as per authors' set criteria, 10.9% (7/55) were lost to follow-up and 1.8% (1/55) died [33]. In the study of patients with MDR spinal skeletal TB by Yang et al., 39% (166/272) patients received surgical intervention in addition to chemotherapy [48], 14% (39/272) underwent an anterior approach, 25% (68/272) a posterior approach and 19% (52/272) underwent a combined approach [48]. However, treatment outcomes in terms of cure were not reported. In the study by Ye et al., 23.8% (46/193) of patients with genitourinary TB underwent nephrectomies [39]. Of those who were followed up post-nephrectomy, 95.2% (20/21) recovered after surgery [39].

4.12. Treatment outcomes of DR-epTB

Seven studies reported treatment outcomes as cured/completed treatment, died, or lost to follow-up [33,34,42,38–39], summarized in Table 4. Cure/completion of treatment ranged between 25.8% [46] to 82.6% [33]. Death during treatment ranged between 2.2% [33,37] to 76.0% [42]. Treatment failure ranged between 0% [33] to 3.8% [34] while the loss to follow-up ranged between 6.5% [46] to 15.2% [33]. In a randomized controlled clinical trial by Heemskerk et al, there were increased odds of death in patients with drug-resistant TB meningitis (isoniazid, rifampicin, or multi-drug resistance) compared to those with no or other forms of resistance (95% CI, 3.39–31.36, $p < 0.001$) [36]. In the study of patients with RR/MDR-TB by Ma et al., favorable treatment outcomes (defined as a sum of cure and treatment completion) were less likely in DR-ep TB compared to pulmonary drug-resistant TB (61.2% vs 70.7%, $p < 0.01$) [37]. In addition, patients with DR-ep TB experienced longer delays in mycobacterium tuberculosis detection compared to patients with drug-resistant pulmonary disease (89 days vs 52 days, $p < 0.01$) [37]. Patients with joint/spine and genitourinary RR/MDR-TB also had less favorable outcomes (52.4% and 53.3% respectively) compared to the throat, central nervous system, and lymph node TB (76.2%, 66.7%, and 62.5% respectively) [37]. In genitourinary TB, drug-susceptible TB was significantly associated with good recovery compared to drug-resistant TB (83.6% vs 64.6%, $p = 0.017$) [39].

Table 4
Treatment outcomes among patients with drug-resistant extrapulmonary TB for studies that reported outcomes. *N is the number of patients who had resistance to any anti-tuberculosis drug. Treatment outcomes to each drug are expressed as a percentage of N. Abbreviations: NA, not available. Studies that did not report treatment outcomes are not shown. # 3 patients (6.3%) were not treated while 1 (2.1%) defaulted treatment 4. **N here includes 5 cases of suspected resistance; 5 (14%) had unknown/not evaluated outcome.

Author (year of publication)	N*	cured/ completed treatment (%)	Died (%)	treatment failure (%)	Loss to follow-up (%)
Arockiaraj (2017) [33]	92	82.6	2.2	0	15.2
Desai (2018) [34]	53	79.2	3.8	3.8	13.2
Ma (2022) [37]	232	61.2	2.2	NA	NA
Senbayrak (2015) [38]	20	NA	30.0	NA	NA
Ye (2016) [39]#	48	77.1	4.2	2.1	10.4
Torok (2008) [42]	25	NA	76.0	NA	NA
Evans (2022) [46]**	36	25.8	67.7	0	6.5

5. Discussion

DR-epTB is a mostly ignored form of DR-TB which poses a risk to achieving the End TB strategy [51]. While there are several case reports on DR-epTB forms such as spine TB [52], genital-urinary DR-epTB [53], adenitis [54], and meningitis [55], there are few studies that have systematically reviewed the literature on DR-epTB. In this study, we have reviewed the clinical features and outcomes of 1,236 patients with DR-epTB reported in 18 studies. We found that patients with DR-epTB are mostly young with HIV co-infection and diabetes mellitus. HIV impairs T-cell immune responses that would otherwise contain the *Mycobacterium tuberculosis* infection in the lungs [56]. HIV is therefore an established risk factor for EPTB in several studies [57]. HIV has also been associated with a higher risk for DR-TB, although the mechanisms are not fully understood [58–59]. The high rate of HIV co-infection in our review can therefore partly be explained by the immune suppression associated with HIV and the risk for DR-TB posed by HIV. Similarly, diabetes mellitus has been associated with 97% higher odds of MDR-TB in a *meta*-analysis of 24 studies [60].

TB adenitis was the commonest form of DR-epTB in our review. TB lymphadenitis is also the most common form of EPTB in DS-TB [9]. This is likely because the primary *Mycobacterium tuberculosis* infection spreads to regional lymph nodes in the lung from whence it spread to others regions via the lymphatics [61]. Nonetheless, other forms of DR-

epTB were reported and meningeal DR-epTB was the most frequently studied form. It is unclear whether this overrepresentation of meningeal DR-epTB has to do with the ease of acquiring cerebral spinal fluid specimens for testing as compared to other specimens (such as bone for skeletal TB and gonads for genital TB). It should be explored further whether drug-resistant forms of TB have any predilection to the central nervous system. From our review, it appears that the clinical symptoms and signs of DR-epTB depend on the affected system affected, although few studies described symptoms specific to DR-epTB. It follows that clinical symptoms and signs may not be sufficient to differentiate people with and without drug resistant forms of EPTB. This calls for building diagnostic capacity for biopsy particularly in low-income setting where access to surgery and histopathology services are low. Further, more research is needed to identify non-invasive biomarkers to differentiate patients with DR-epTB for drug sensitive EPTB.

In this review, we found a high proportion of DR-epTB patients with MDR-TB (up to 53%), pre-XDR-TB (up to 40%), and XDR-TB (up to 33%). This is concerning since there are no specific regimens that are optimized for DR-epTB. As such, the composition and duration of the treatment are largely not informed by clinical trials. Interestingly, up to 40% of patients had fluoroquinolone resistance, which is currently recommended as a priority drug group (Group A drugs) in the management of DR-TB [8]. Most studies in our review did not report regimens used in the management of these patients. There was an apparent role of surgery for patients with skeletal TB but the timing of surgery during TB chemotherapy is largely unclear. It is therefore not surprising that treatment outcomes of DR-epTB were very varied: treatment success in up to 83%, death in up to 76%, failure in up to 4%, and loss-to-follow-up in 15%. This is largely due to the lack of a uniform definition of the outcomes for the varied DR-epTB sites in addition to non-standardized treatment regimens. Moreover, patients with DR-epTB might have more severe forms of EPTB and concurrent PTB than those with drug-sensitive EPTB [46]. It follows that there need to be site-specific evidence-based treatment recommendations and outcome definitions for the varied DR-epTB organ sites.

Our review has some limitations. First, there is an overrepresentation of studies from China. The estimates in our study may therefore not be very representative. However, China has one of the highest burdens of DR-TB globally. Therefore, any review is likely to see an over-representation of studies from China. A second limitation is that we're unable to perform pooled analyses for the estimation of all proportions. This could not be performed because of the various DR-epTB organ sites. This would inherently introduce significant heterogeneity in our estimates. A third limitation is that some sites that treat DR-TB may exclude DR-epTB when reporting in the literature or they may report only confirmed RR-TB which comprises a smaller group among patients treated for DR-epTB.

5.1. Conclusion

DR-epTB is common and people with DR-epTB tend to be young with HIV co-infection and/or diabetes mellitus. Adenitis is the commonest form of DR-epTB. DR-epTB posts worse treatment outcomes compared to pulmonary TB and drug-susceptible EPTB. There is a need for site-specific treatment regimens and outcome definitions for DR-epTB.

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7. Data sharing

The data extracted from the studies included in this review as well as the computer code used to generate the figure and tables are available here: https://github.com/MiiroEm/DR-epTB-review.

CRediT authorship contribution statement

Emmanuel Miiro: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Ronald Olum:** Methodology, Writing – original draft. **Joseph Baruch Baluku:** Conceptualization, Methodology, Data curation, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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