Official journal of the Spanish Society of Chemotherapy

Systematic review

Revista Española de Quimioterapia
doi:10.37201/req/029.2022

Shruti Subhash Shiromwar[1]
Amer Hayat Khan[1]
Vijay Chidrawar[2]

A systematic review on extensively drug-resistant tuberculosis from 2009 to 2020: special emphases on treatment outcomes

[1]Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia (USM)
[2]Raghavendra Institute of Pharmaceutical Education and Research, India

Article history
Received: 17 March 2022; Revision Requested: 25 May 2022; Revision Received: 24 September 2022; Accepted: 4 October 2022; Published: 9 December 2022

ABSTRACT

Objectives. Extensively drug-resistant tuberculosis (XDR-TB) has raised a great threat to human health globally, especially in developing countries. The objective of the present study is to collate and contrast the proportions of treatment outcome in the previously published XDR-TB articles.

Material and methods. By considering inclusion criteria and search engines, a total of 22 articles were enrolled.

Results. Our findings revealed that the overall favorable treatment outcome was 24.04%. From the cohort of enrolled studies 19.76% (397) and 43.35% (871) patients were cured and died respectively. In 90.9% of enrolled articles, the investigators performed drug-susceptibility testing at the baseline. The overall treatment outcome was improved by the use of new drugs (linezolid, bedaquiline, ciprofloxacin, clofazimine) in the treatment regimen of XDR-TB showing linezolid and bedaquiline better results i.e. 59.44 and 78.88%, respectively. Moreover, use of antiretroviral treatment in XDR-TB patients with HIV infection have not shown any significant difference in the treatment outcome.

Conclusions. XDR-TB treatment success can be achieved by implying standardized definitions, upgraded diagnostic procedures, and novel drugs.

Keywords: Extensively Drug-Resistant tuberculosis (XDR-TB), Multidrug-resistant tuberculosis (MDR-TB), Treatment Outcomes, Systematic Review.

Una revisión sistemática sobre la tuberculosis extremadamente resistente de 2009 a 2020: énfasis especial sobre los resultados del tratamiento

RESUMEN

Objetivos. La tuberculosis extremadamente resistente (XDR-TB) ha planteado una gran amenaza para la salud humana a nivel mundial, especialmente en los países en desarrollo. El objetivo del estudio es recopilar y contrastar las proporciones del resultado del tratamiento en los artículos de XDR-TB publicados.

Material y métodos. Teniendo en cuenta los criterios de inclusión y los motores de búsqueda un total de 22 artículos fueron incluidos.

Resultados. Nuestros hallazgos revelaron que el resultado total del tratamiento favorable fue del 24,04%. De la cohorte de estudios inscritos, el 19,76% (397) y el 43,35% (871) de los pacientes se curaron y murieron, respectivamente. En el 90,9% de los artículos, los investigadores realizaron pruebas de sensibilidad. El resultado total del tratamiento mejoró mediante el uso de nuevos medicamentos (linezolid, bedaquilina, ciprofloxacino, clofazimina) en el régimen de tratamiento de XDR-TB, mostrando linezolid y bedaquilina los mejores resultados, 59,44 y 78,88%, respectivamente. Además, el uso del tratamiento antirretroviral en pacientes con XDR-TB y con infección por VIH no mostró ninguna diferencia significativa en el resultado del tratamiento.

Conclusiones. El éxito del tratamiento de la XDR-TB se puede lograr implicando definiciones estandarizadas, procedimientos de diagnóstico mejorados y nuevos medicamentos.

Palabras clave: XDR-TB, tuberculosis multirresistente (MDR-TB), resultados del tratamiento, revisión sistemática.

Correspondence:
Shruti Subhash Shiromwar,
Research Scholar, School of Pharmaceutical Sciences,
Universiti Sains Malaysia (USM), Pulau Pinang, Malaysia.
E-mail: shrutishiromwar@gmail.com

INTRODUCTION

As per the Global TB Report 20, tuberculosis (TB) remains a major cause of illness and death in the 21st century. It is caused by infection of *Mycobacterium tuberculosis* (MTB). TB persists as the disease of public health importance, influencing approximately 10.4 million individuals, and is one of the leading causes of death, with a mortality rate of 1.8 million/year globally, with further approximately 484,000 people developing rifampicin resistant tuberculosis (RR-TB)/multidrug resistant tuberculosis (MDR-TB) [1,2]. MTB resistant to at least rifampin and isoniazid, which are the 2 most powerful first-line drugs called as MDR-TB. XDR-TB a subcategory of MDR-TB, defined as MTB resistant to isoniazid and rifampicin) i.e., multidrug resistance TB as well as to any fluroquinolone (FQ) and to at least one of the second line injectable drugs (SLID) kanamycin, amikacin, or capreomycin [1,3]. Such resistance threatens global TB control efforts. MDR-TB patients need easy access to treatment, require longer treatment with potent medications, and exhibit a low probability of positive outcome. Pre-XDR-TB is defined as TB caused by MTB resistant to isoniazid, rifampicin and any one of FQ, or one of the SLID but not both [1, 3].

According to WHO 2016 report, a total of 58 countries and territories have reported 7234 XDR-TB cases which were on SLID therapy. Among them, the highest number of cases were reported from India (2,130), Ukraine (1,206), the Russian Federation (1,205), and South Africa (719). By the end of 2015, a total of 74 countries reported 7,579 XDR-TB cases [4]. The global emergence and spread of XDR-TB reflect the shortcomings of global TB management. XDR-TB cases have limited therapeutic options available for them, which are more toxic, more costly, and less effective compared to other TB patients, and consequently, exhibit poorer treatment outcomes as well as higher mortality rate [5-8].

Treatment modalities of MDR-TB and XDR-TB cases comprise heavy, ineffective, and poorly-tolerated second-line anti-TB agents, with recommended treatment courses of 24 months or more [9] besides, even those MDR-TB patients who have completed their treatment often exhibit poor treatment outcomes with a success rate of only 50% by the end of the treatment course [10]. Response rates among XDR-TB patients are even worse, owing to their extensive drug resistance to even the most potent second-line anti-TB drugs, which warrants the urgent need for superior therapeutic regimens for such patients [11].

Despite the growing public awareness regarding TB-drug resistance, the essential variables that play a key role in progression of XDR-TB are not systematically collected, analyzed, and reported in published studies. The essential parameters, such as clinical and epidemiological analysis, demographic features of enrolled cases, details of drug-susceptibility testing (DST) along with implemented methods, treatment regimens, treatment efficacy endpoints, treatment outcomes, recording of adverse events, and drug resistance, have not been studied or only minimally studied in the previous studies [12]. To the current authors' knowledge, despite its clinical and public health interest no systematic review article on this topic had been published at the time of writing (March, 2022).

The present study aims to systemically review the available literature on XDR-TB to assess the various modes of operational challenges. This review also assesses the existing facts and recommends a course of action to accumulate comprehensive knowledge on the treatment outcomes and efficacy of XDR-TB. Moreover, the study evaluates the laboratory analysis and clinical epidemiology of XDR-TB of earlier studies that can be helpful to improve our expertise to regulate and circumvent the global threat to public health.

MATERIAL AND METHODS

Search strategy. The present study is a systematic review of published English literature search between 2009 and 2020 on the clinical epidemiology, diagnosis, management, and treatment outcomes of XDR-TB, as per the PRISMA guidelines [13].

A manual search approach was implemented to identify the research articles based on the proposed subject. Original articles published in peer-reviewed journals on clinical epidemiology, clinical management, and treatment outcomes of XDR-TB were identified through the computerized search of the following database: Science Direct, PubMed (advance search)/Medline, and Google Scholar database/search engine links were principally reviewed The combination of keywords and phrases were used to assess the purpose of the search include 'Extensive drug-resistant Tuberculosis', 'Treatment outcome', and 'XDR-TB treatment outcomes.' The relevant articles were fetched along with the lists of the references.

Inclusion and exclusion criteria. All articles were extensively studied, and selected for this review based on the inclusion and exclusion criteria.

i) Inclusion criteria: 1) Mentioned XDR-TB cases 2) Evaluated on the basis of epidemiology, laboratory diagnostics as well as treatment outcome and regimen, and 3) Were published in-between 2009 and 2020 (the resistance was high in this era even though new drugs were introduced). 4) The included articles should estimate both successful and unsuccessful treatment outcomes in XDR-TB cases who started treatment, including cured, completed treatment, died, patients lost to follow-up, those transferring out and/or those for whom outcomes were not reported.

ii) Exclusion criteria: 1) The studies that included pregnant women with XDR-TB and 2) The studies were excluded if the key outcome variables are not reported or did not have relevant data. 3) The articles which contained duplicate information. 4) The articles with no accessible full text and also review articles were excluded.

Each article was systemically studied with respect to adopted methods and regimen settings, objectives, result and finally evaluated for treatment outcomes (Figure 1).

Quality assessment. The quality assessment of the ar-

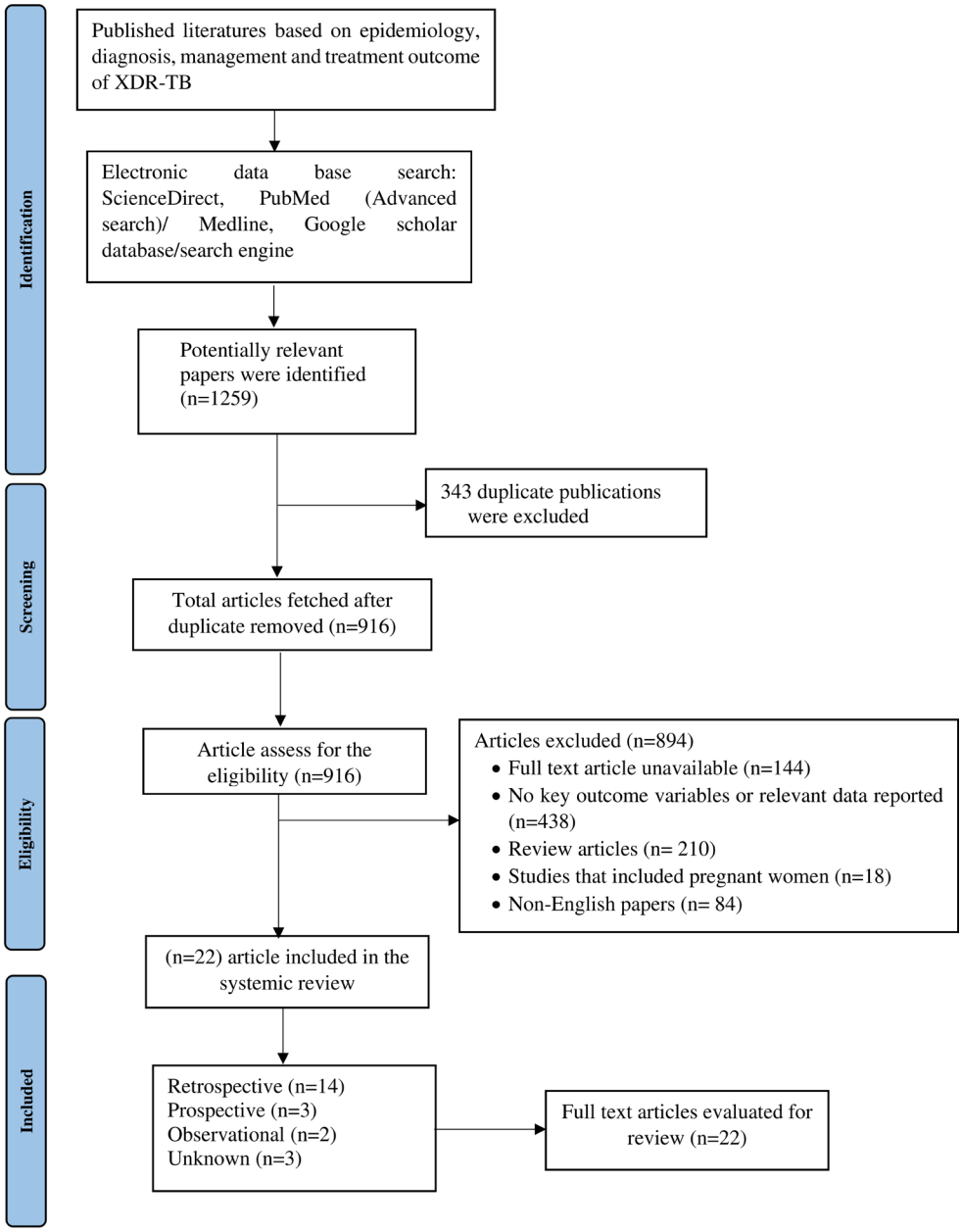

Figure 1 Systematic review flow diagram

ticles for the present review done by all the authors independently by evaluating the abstract and full text of the eligible articles. The final inclusion of the study was decided through consensus of all authors.

Outcome measures and definitions. MDR-TB covers the patients who are resistant to at least isoniazid and rifampin whereas, MDR-TB patients with additional resistance to the fluroquinolones and a second line injectable drugs are classifies as XDR-TB.

The treatment outcome of XDR-TB cases was determined in percentages of successful and unsuccessful treatment outcomes among all the patients who were on the therapy, measured according to the WHO and International Union Against Tuberculosis and Lung Disease (IUATLD) guidelines [14,15].

"Cured" was defined as one who had completed treatment and had been consistently culture negative (with at least 5 results) for the final 12 months of TB treatment. Patients who completed treatment but did not meet the definition for cure

Table 1 **Clinical and epidemiological analysis of cases enrolled in the review studies**

Study	First author (year) [reference]	Total Subject enrolled (n)	Location	Study duration	Year of publication	Total XDR-TB patients (n)	Previously treated case (%)	Previous treatment regimen > 1 month	No. of drugs resistant to MTB	Cohort prevalence of HIV	Study concerning HIV/ non-HIV patients	New drugs	Definitions
1	Kashongwe (2020) [35]	40	Kinshasa, Democratic Republic of the Congo	January 1, 2015 to December 31, 2017	2020	3	Yes	-	R, H, E, S	Yes	Both	Bdq	Global tuberculosis report 2019. Geneva: WHO, 2019.
2	Li (2019) [40]	325	Zhejiang Province, China	Between March 2012 and December 2015	2019	24	Yes	Yes	H, R	No	-	Cs	Shah NS, Wright A, Bai GH, et al. 2007
3	Nkurunziza (2018) [3]	86	Johannesburg, South Africa	From January 2008 and December 2010	2018	53	-	-	-	Yes	Both	Lzd	Zignol M, Van Gemert W et. al. 2012
4	Yuengling (2018) [17]	110	KwaZulu-Natal Province, South Africa	August 2009 through July 2011	2018	105	No	-	-	Yes	Both	-	WHO, tuberculosis fact sheet 2017
5	Ndjeka (2018) [23]	200	South Africa,	March 2013 to March 2015	2018	87	No	-	-	Yes	Both	Lzd, Bdq, Cfx	WHO, 2017
6	Gallo (2018) [39]	313	State of Sao Paulo, Brazil	Between January 2011 & December 2013	2018	32	Yes	-	Am, Cm, S, H, E, Km, Ofx, Z, R	Yes	Both	-	-
7	Prajapati (2017) [33]	112	Gujarat, Western India	From January 2012 to October 2016	2017	112	Yes	-	H, R, Km, Ofx	Yes	Both	Lzd	RNTCP, 2012
8	He (2017) [34]	144	Shandong Province, China	Between January 2008 and December 2015	2017	144	Yes	Yes	R, H	-	Non-HIV patients	-	Shah NS et al. 2007, Raviglione MC et Al. 2007, Gandhi NR et al. 2006
9	Kvasnovsky (2016) [22]	355	Eastern Cape Province, South Africa KwaZulu-Natal Province, South Africa	Eastern Cape Province: during October 1, 2006–January 31, 2008 & April 1–July 1, 2008 KwaZulu-Natal Province: during October 1, 2006–January 31, 2008.	2016	229 126	Yes	Yes	5 (4–6) #	Yes	Both	-	WHO, Global tuberculosis report, 2015
10	Pietersen (2015) [16]	310	South Africa	Between August, 2002 & October 2012	2015	178	Yes	-	-	-	-	-	S1.1 in S1 Definitions and Methods)
11	Pietersen (2014) [18]	114	South Africa	Between August 2002 & February, 2008	2014	107	Yes	-	R, H, Ofx, Am, Eto, Km, Cm, AMG, PAS	Yes	Both	-	WHO, Oct 17, 2006
12	Lytvynenko (2014) [25]	484	Kiev (Ukraine) Europe	Between 1 January 2006 & 31 December 2011.	2014	114	Yes	-	-	Yes	Both	-	WHO, 2013
13	O'Donnell (2013) [19]	130	KwaZulu-Natal Province, South Africa	During December 1, 2006 to October 31, 2007	2013	114	Yes	-	-	Yes	Both	-	-
14	Roongruangpitayakul (2013) [26]	24	Central Chest Institute, Thailand (CCIT)	From 2009 to 2012	2013	7	Yes	-	H, R, E, S, Km, Cm, Ofx, Eto, Cs, PAS	-	-	Lzd	Guideline for the programmatic management of MDR-TB. 2008; Banerjee R, et al. 1993-2006
15	Tang (2013) [41]	586	China	From July 2006 to June 2011	2013	169	Yes	Yes	H, R, S, E, Ofx, Cm, Am	No	Non-HIV	-	WHO 2008, WHO 2011
16	Koh (2012) [27]	51	Seoul, South Korea	From September 2007 to December 2009	2012	26	Yes	Yes	H, R, E, S, Km, Cm, Am, Ofx, Mfx, Pto, Cs, PAS, Rfb	-	-	Lzd	Chiang CY, et al. 2009, Sotgiu G et al. 2009
17	Liu (2011) [28]	3,270	Beijing, China	During 1996 - 2009	2011	51	Yes	Yes	H, R, E, S, Z, Ofx, Lfx, Km, PAS	No	Non-HIV	-	Beijing Municipal Bureau of Statistics. Beijing statistical year book 2007. Beijing: China Statistics Press, 2007. WHO 2008
18	Leimane (2010) [30]	1,027	Riga, Latvia	From January 1, 2000 to December 31, 2004	2010	48	Yes	-	Km, Cm, Pto, Ofx, H, R, E, PAS, T, Z, S	Yes	Both	-	CDC, 2007. WHO, 2006
19	Masjedi (2010) [31]	105	Iran	Between 2002 and 2006	2010	7	Yes	-	Ofx, Cfx , Cs, Am, Km, Eto, PAS, Cm, Z, E	-	-	-	CDC. Revised definition XDR-TB 2006, WHO, 2006, Dorman S. et al. 2007
20	Jeon (2009) [32]	176	Masan, South Korea	From January 2001 to December 2005	2009	158	Yes	Yes	H, R, E, Z, S, Km, Ofx, PAS, Pto, Cs	-	HIV uninfected	Lzd	CDC. Revised definition XDR-TB 2006
21	Kliiman (2009) [24]	1,109	Estonia, European country	From January 2003–December 2005	2009	54	Yes	-	H, R, S, Z, E, Km, Cm, Am, Ofx, Pto	Yes	HIV uninfected	-	XDR-TB: recommendations for prevention and control, 2006
22	O'Donnell (2009) [20]	6127	KwaZulu-Natal, South Africa	Between 1 December 2006 and 31 May 2007	2009	60	Yes	-	-	Yes	Both	-	CDC, 2006

CDC: Centers for Disease Control and Prevention. Median: #, H: Isoniazid, R: Rifampicin, E: Ethambutol, Z: Pyrazinamide, FQs: Fluroquinolones, Eto: Ethionamide, Pto: Protionamide, Cs: Cycloserine, AMG: Aminoglycoside, Ofx: Ofloxacin, Lfx: levofloxacin, Cfx: Ciprofloxacin, Am: Amikacin, Cm: Capreomycin, S: Streptomycin, PSA: Para amino-salicylic acid, Km: kanamycin, Trd: Terizidone, Rfb: Rifabutin, T: Thiacetazone

Table 2 **Laboratory diagnosis in the studies reviewed**

Study	First author (year) [reference]	Drugs to which strains were resistant (n) (Mean/Median)	100% SRL QA DST	DST for First line drug	DST for Second line drug	Both or All drug tested	Method Used	Sputum smear positive at baseline	HIV +ve Patients	HIV Patients receiving ART
1	Kashongwe (2020) [35]	R, H, E, S	Yes	Yes	Yes	Both	-	Yes	Yes	-
2	Li (2019) [40]	H, R	Yes	Yes	Yes	Both	Löwenstein–Jensen medium or MGIT 960 Proportion method,	Yes	No	No
3	Nkurunziza (2018) [3]	-	Yes	Yes	Yes	Both	MGIT proportion method, Geno Type@ MTBDR plus polymerase chain reaction assay	Yes	Yes	Yes
4	Yuengling (2018) [17]	-	Yes	Yes	Yes	Both	BACTEC MGIT 960 Fluorometric system Modified proportional growth method	Yes	Yes	Yes
5	Ndjeka (2018) [23]	-	-	-	-	-	-	Yes	Yes	Yes
6	Gallo (2018) [39]	Am, Cm, S, H, E, Km, Ofx, Z, R	Yes	Yes	Yes	Both	BACTEC MGIT 960 system.	Yes	Yes	-
7	Prajapati (2017) [33]	H, R, K, O	Yes	-	Yes	-	-	Yes	Yes	-
8	He (2017) [34]	-	Yes	Yes	Yes	Both	Proportion method with Löwenstein–Jensen (L-J) medium.	Yes	No	-
9	Kvasnovsky (2016) [22]	-	-	-	-	-	-	Yes	Yes	Yes
10	Pietersen (2015) [16]	R, H, FQs, Am and Eto, Cm, AMG and Trd	Yes	-	Yes	-	Genotype Phenotype (for second line drug) Standard proportion method on Middlebrook 7H10-agar	-	Yes	Yes
11	Pietersen (2014) [18]	R, H, Am & Ofx	Yes	-	-	-	-	Yes	Yes	Yes
12	Lytvynenko (2014) [25]	-	Yes	Yes	Yes	Both	Conventional culture (Löwenstein-Jensen) BD BACTEC™ liquid culture	Yes	Yes	-
13	O'Donnell (2013) [19]	-	Yes	Yes	Yes	Both	BACTEC MGIT 960 fluorometric system Modified proportional growth method on 7H11 agar	Yes	Yes	Yes
14	Roongruangpitayakul (2013) [26]	H, R, E, S, Km, Cm, Ofx, Eto, Cs & PAS	Yes	Yes	Yes	Both	Sputum smear AFB by fluorescein microscopy, Culture with Lowenstein Jensen medium, proportional method	Yes	No	No
15	Tang (2013) [41]	H, R, S, E, Ofx, Cm, Am	Yes	Yes	Yes	Both	Sputum by optical microscopic analysis of Ziehl-Nielsen–stained smears and culture on Lowenstein-Jensen medium and the BACTEC (MGIT) 960 system	Yes	No	No
16	Koh (2012) [27]	H, R, E, S, Cm, Am, Km Ofx, Mfx,,Pto, Cs, PAS, Rfb	Yes	Yes	Yes	Both	Absolute concentration method with Lo¨wenstein–Jensen medium	Yes	No	No
17	Liu (2011) [28]	6 # (Range 4–9)	Yes	Yes	Yes	Both	Proportion method and Lo¨wenstein-Jensen medium, AFB smear by microscopy was assessed by Ziehl-Neelsen staining, The BACTEC 960 system	Yes	No	No
18	Leimane (2010) [30]	Km, Cm, Pto, Ofx, H, R, E, Z, S	Yes	Yes	Yes	Both	Conventional Lowenstein–Jensen solid media or the BACTEC rapid growth method	Yes	Yes	-
19	Masjedi (2010) [31]	Ofx, Cfx, CS, Am, Km, Eto, PAS, Cm, Z, E	Yes	Yes	Yes	Both	-	-	-	-
20	Jeon (2009) [32]	H, R, E, PZA, S, Km, Ofx, PAS, Pto, Cs	Yes	Yes	Yes	Both	Absolute concentration method	Yes	No	-
21	Kliiman (2009) [24]	7.0 # (Range 5–10)	Yes	Yes	Yes	Both	Cultures by conventional Lo¨wenstein–Jensen solid media and in BACTEC broth media using a radiometric BACTEC 460 or a fluorometric BACTEC MGIT960 system. Proportion method	Yes	Yes	-
22	O'Donnell (2009) [20]	-	Yes	Yes	Yes	Both	Culture by BACTEC Mycobacteria Growth Indicator Tube 960 fluorometric system Proportional growth method on 7H11 agar	Yes	Yes	Yes

SRL: Supranational reference laboratory, Median: #, QA: Quality assurance; DST: Drug susceptibility testing. AFB: Acid-fast bacilli,H: Isoniazid, R: Rifampicin, E: Ethambutol, Z: Pyrazinamide, FQs: Fluroquinolones, Eto: Ethionamide, Pto: Protionamide, Cs: Cycloserine, AMG: Aminoglycoside, Ofx: Ofloxacin, Lfx: levofloxacin, Cfx: Ciprofloxacin, Am: Amikacin, Cm: Capreomycin, S: Streptomycin, PSA: Para amino-salicylic acid, Km: kanamycin, Trd: Terizidone, Rfb: Rifabutin, T: Thiacetazone

Table 3 Treatment characteristics of the studies reviewed

Study	First author (year) [reference]	Standard / individualized treatment	Drugs used				Surgery reported	Adverse events reported	Rate of Adverse events	Nature of adverse events
			Drugs in treatment regimen	Commonly used drugs	Availability of new drug	Name of new drug				
1	Kashongwe (2020) [35]	Individualized	-	Bdq, Am, km, Lfx, Lzd, Cfz, PAS, Cs, High-dose H, Z, Pto.	Yes	Bdq Lzd	-	Yes	Yes	Vomiting, Skin rash, Anemia and peripheral neuropathy, Diarrhea, Hyperuricemia, Nausea, Hypokalemia, Abdominal pain, Otovestibular toxicity, Depression, Thrombocytopenia, Fear of heights, QT prolongation, Optic neuropathy, Blurred vision, Gastritis, Hepatotoxicity, Hyperglycemia.
2	Li (2019) [40]	Both	-	FQs, AMG, Z, Pto, PAS	Yes	Cs	-	Yes	Yes	Gastrointestinal effects (Nausea and vomiting), Arthralgia, Liver injury, Hypokalemia, Headache, Seizure, Depression, Anxiety
3	Nkurunziza (2018) [3]	Both	-	Mfx, PAS, Trd, High-dose H, Z, Cfz, Cm	Yes	Lzd	No	-	-	-
4	Yuengling (2018) [17]	Standardize	Yes	Z, E, Mfx, PAS, Trd, Cm	-	-	-	-	-	-
5	Ndjeka (2018) [23]	Individualizes		Cfz, Lzd,,Z, E, High-dose H, PAS, Cm, Km, Lfx, Eto or Trz, Bdq	Yes	Bdq, Lzd, Cfz	-	Yes	-	Corrected QT interval by Fredericia increase >50 ms from baseline, Paroxysmal atrial flutter, Anemia, Peripheral neuropathy, Ototoxicity
6	Gallo (2018) [39]	Individualized	-	Am, Cm, S, H, E, Km,Ofx, Z, PZA, R	-	-	-	-		
7	Prajapati (2017) [33]	Standardize	Yes	Cm, PAS, Mfx, High-dose H, Cfz, Lzd,, Amx + Clv.	Yes	Lzd	No	Yes	Yes	Gastrointestinal system, Decrease in hearing, Jaundice.
8	He (2017) [34]	Not mentioned	-	-	-	-	-	-	-	-
9	Kvasnovsky (2016) [22]	Individualized	Yes	E, Z, High-dose H, Cm, PAS, Mfx, Cs, Trd, Amx + Clv, Clr	-	-	-	-	-	-
10	Pietersen (2015) [16]	Individualized	Yes	Cm, Mfx, Amx + Clv., Am, Km, Cfx, Ofx, E, Eto, Z, PAS, Cfz, D, T, Trd/Cs	No	No	No	Yes	-	Renal failure
11	Pietersen (2014) [18]	Individualized	Yes	High-Dose H, H, Z, E, Eto, Ofx, Mfx, S, Am, Cm, D, Amx + Clv, PAS, Cfz Azm ,Rfb, Clr, Trd (Cs Derivative)	-	-	-	-	-	-
12	Lytvynenko (2014) [25]	Individualized	-	-	-	-	-	Yes	-	Gastrointestinal toxicity, Vestibular toxicity
13	O'Donnell (2013) [19]	Individualized	Yes	Cm, PAS, Z, Eto , E, Cs or Trd, Mfx, Lfx	-	-	-	Yes	Yes	Psychosis or Severe psychiatric illness Hypokalemia or Hypomagnesemia
14	Roongruangpitayakul (2013) [26]	Individualized	Yes	Lzd, Cm, New generation FQs, Cs, Cfz, Mfx, E, Km, Eto, PAS	Yes	Lzd	Yes	Yes	-	Peripheral neuropathy, Optic neuropathy, Transient visual impairment, Anemia, Thrombocytopenia, Eosinophilia, Vertigo, Increase creatinine >2 mg %, Transient hearing loss, Arthralgia
15	Tang (2013) [41]	Individualized	Yes	Am or Cm, Lfx, Gfx, Mfx, PAS, Pto, Z, Clr, E	-	-	-	No	-	No
16	Koh (2012) [27]	Individualized	Yes	-	Yes	Lzd	Yes	Yes	Yes	Peripheral neuropathy, Optic neuropathy, Eucopenia, Thrombocytopenia

Table 3 Treatment characteristics of the studies reviewed (cont.)

Study	First author (year) [reference]	Standard / individualized treatment	Drugs used				Surgery reported	Adverse events reported	Rate of Adverse events	Nature of adverse events
			Drugs in treatment regimen	Commonly used drugs	Availability of new drug	Name of new drug				
17	Liu (2011) [28]	Individualized	-	S or E, H, R, Z, Am, Cm, T, Z, Ofx, Lfx, Mfx, Cfx,, Rpt, Rfb	No	No	-	-	-	-
18	Leimane (2010) [30]	Individualized	Yes	Eto, Z, Ofx, Km, Cm, Pto, Cs, PAS, T, Amx + Clv ,Clr	-	-	Yes	Yes	Yes	Nausea, Vomiting, Diarrhoea, Abdominal pain.
19	Masjedi (2010) [31]	Standardized	-	Cs, Pto, Am, Ofx, Eto, Z	-	-	-	Yes	-	Neurological adverse effect
20	Jeon (2009) [32]	Individualized	-	Lzd, Mfx, Clr, Amx + Clv, IFN-γ, H, E, R, S,Km, PAS, Cs, Pto, Z, Ofx	Yes	Lzd	Yes	-	-	-
21	Kliiman (2009) [24]	Individualizes	Yes	R, H, S, E, Z, Cm, Am, Km, Eto, Pto, Ofx	-	-	-	-	-	-
22	O'Donnell (2009) [20]	Individualizes	Yes	-	-	-	-	Yes	Yes	Electrolyte abnormalities

Cfz: Clofazimine, Lzd: Linezolid, Z: Pyrazinamide, E: Ethambutol, H: Isoniazid, PAS: Para-amino salicylic acid, Cm: Capreomycin, Km: Kanamycin, Lfx: Levofloxacin, Eto: Ethionamide or Trz: Terizidone, Bdq: Bedaquiline,, Am – Amikacin, S: Streptomycin, Ofx: Ofloxacin , Lfx: Levofloxacin, R: Rifampicin, FQs: Fluroquinolones, Cs: Cycloserine , T: Thiacetazone, Pto: Protionamide, Rfb: Rifabutin, AMG: Aminoglycoside, Amx + Clv: Amoxicillin and Clavulanic acid, Clr: Clarithromycin, Azm: Azithromycin, Gfx: Gatifloxacin, Rpt: Rifapentine, IFN-γ: Interferon gamma, D: Dapsone.

because of lack of bacteriological results were considered as "completed treatment". Patients who did not receive treatment for ≥ 2 consecutive months were defined as "defaulted treatment". "Treatment Failure" was defined as ≥ 2 positive cultures recorded in the final 12 months or if any one of the final three cultures was positive. "Transferred out" means anyone who transferred to another institution and for whom the treatment outcome was unknown. "Death" was defined as mortality during treatment period due to any cause.

In the present review, the patients who are 'cured' or 'completed treatment' are categorized as successful treatment outcome whereas, the others were categorized as unsuccessful treatment outcome.

Evaluation criteria. All the selected articles were evaluated based upon the following criteria:

i) Clinical and epidemiological analysis of cases enrolled in the review study

All selected studies were reviewed to extract the data related to the clinical and epidemiological analysis for XDR-TB, included total number of subjects enrolled, study location, year of patient enrolled in the study, study duration, year of publication and number of XDR-TB patients. The patients' clinical history includes previously treated cases, previous treatment regimen for more than 1 month, number of drugs resistant to MTB, cohort prevalence of HIV, study concerning HIV/non-HIV patients, new drugs involved in the study, and the definition of XDR-TB.

ii) Laboratory diagnosis

All selected studies were reviewed to extract the data regarding microbiological diagnosis for XDR-TB, including the drugs to which the strain was resistant, 100% Supranational reference laboratory (SRL)/Quality Assurance (QA)/DST, DST for first-line/second-line or both, methods used for DST, sputum smear-positive at baseline, HIV-positive patient, and HIV patient receiving ART (antiretroviral therapy).

iii) Characteristics of treatment

All the selected studies were studied to extract their data including treatment modality (standard/individualized), availability of 1st line/2nd line drugs to the center, number of drugs in the treatment regimen, commonly used drugs, availability of new drugs (yes/no), surgery, and adverse events reported/not (if reported, the frequency and nature of adverse events).

iv) Treatment efficacy endpoints

All the selected studies were reviewed to extract the data related to the clinical success end-points of the evaluated cases associated with treatment regimens, time to sputum smear and culture conversion [sputum conversion is the time the culture is smear-positive (from the sputum is cultivated) to smear negative status after the drug treatment], total duration of treatment, and intensive/contentious phase/follow-up/additional post-treatment follow-up.

We also assessed the comparative treatment outcome for HIV/non-HIV patients, use of surgery, success rate (surgery/drugs + surgery), significant association in-between XDR-TB and poor treatment, and tabulation of success rate/overall success rate. Moreover, we examined the relative death risk, and multivariate analysis factor associated with treatment outcome. We differentiated DST at baseline, and references of other definitions of treatment outcomes, such as cure, treatment failure, and default.

v) Treatment outcome

We assessed the favorable treatment outcomes, including cure and completed treatment, and unfavorable treatment outcomes, including death, lost to follow-up, failed to complete treatment, transfer out defaulter insufficient information, and not evaluated.

Data abstraction and statistical analysis. Data abstraction and quality assessment of the article was performed by all

Table 4 Treatment efficacy end points of the studies reviewed

Study	First author (year) [reference]	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	Kashongwe (2020) [35]	1 to 4 months	-	300.8 ± 270.5 days	-	12 months	Yes	WHO, 2018 WHO, 2019	-	-	Yes - D	-	-	Yes	Yes
2	Li (2019) [40]	31 days vs 61 days #	-	6 months	18 months	-	Yes	Euro surveillance editorial team. Revised definitions and reporting framework for tuberculosis, 2013	-	-	Yes - D	-	Yes	-	Yes
3	Nkurunziza (2018) [3]	6 months	24 months	6 months	18 months	-	Yes	Laserson K F, et. al 2005	Yes	No	Yes - D	-	Yes	-	Yes
4	Yuengling (2018) [17]	67 days #	24 months	-	18.1 months	12 months	Yes	WHO, Updated 2014, Gunther G, 2016	No	No	-	-	Yes	Yes	Yes
5	Ndjeka (2018) [23]	-	-	-	-	-	-	-	Yes	No	Yes - D	-	Yes	-	Yes
6	Gallo (2018) [39]	-	-	-	-	-	Yes	-	Yes	-	-	-	Yes	-	No
7	Prajapati (2017) [33]	3 months	24-30 months	-	-	-	Yes	RNTCP Guidelines	No	No	-	-	Yes	-	-
8	He (2017) [34]	-	-	-	12.3 to 109.4 months	-	Yes	WHO and International Union Against Tuberculosis and Lung Disease IUATLD guidelines	-	No	-	Yes	Yes	-	-
9	Kvasnovsky (2016) [22]	4 to 8 months	24 months	-	-	-	Yes	Laserson K F, 2005 O'Donnell MR et al ,2013	Yes	-	-	-	Yes	-	Yes
10	Pietersen (2015) [16]	-	-	-	-	-	Yes	S1.1 in S1 Definitions and Methods	-	-	-	-	-	-	Yes
11	Pietersen (2014) [18]	8·7 months	60 months	-	-	-	-	Laserson K F, et. al 2005	Yes	No	No	No	Yes	-	Yes
12	Lytvynenko (2014) [25]	140.56 ± 11.75 days	-	6-8 months	12–18 months	-	Yes	Ukraine Ministry of Health 2012	Yes	No	No	No	Yes	-	Yes
13	O'Donnell (2013) [19]	6 months	24 months	-	-	-	Yes	Laserson K F et. al,2005	No	-	-	-	Yes	-	Yes
14	Roongruangpitayakul (2013) [26]	52.1 days #	19.1 months #.	-	average of 10.6 months	-	Yes	WHO, 2008	_	Yes	Yes - D	-	Yes	-	No
15	Tang (2013) [41]	-	24 months	6-12 months	-	-	Yes	WHO, 2008 WHO, 2011 Laserson KF, et. al, 2005	No	No	No	Yes	Yes	-	Yes
16	Koh (2012) [27]	55 days	-	-	-	-	Yes	Laserson KF, et. al, 2005	No	Yes	Yes - D	-	-	-	Yes
17	Liu (2011) [28]	-	20.6–23.4 months #	8.9 months #	18 months	-	Yes	WHO, 2008 CDC, 2006	-	-	-	-	Yes	-	Yes
18	Leimane (2010) [30]	-	525 days (323–680 days)	-	-	-	Yes	WHO, 2008	No	Yes	-	-	Yes	-	Yes
19	Masjedi (2010) [31]	-	approx. 24 months	-	-	-	Yes	-	No	-	-	-	-	Yes	No
20	Jeon (2009) [32]	-	-	-	25 months #	-	Yes	WHO, 2006	No	Yes	Yes – D, S	-	Yes	Yes	Yes
21	Kliiman (2009) [24]	-	12–18 months	-	-	-	Yes	Laserson KF, et. al 2005	-	No	-	-	Yes	-	Yes
22	O'Donnell (2009) [31]	90 (69–118) days #	-	-	183.5 (44–267) days #	-	Yes	Laserson KF, et. al 2005	-	-	-	-	-	-	No

1: Time to conversion (Mean/Median in days or Months, 2: Total duration of treatment, 3: Duration of hospitalization, 4: Follow-up Duration, 5: Additional post treatment follow-up, 6: DST at baseline, 7: References of other definition of treatment outcome (like cure/failure /default) (according to who /other), 8: Treatment outcome comparison between HIV+/HIV- patients, 9: Use of surgery, 10: Success rate depend on Surgery/New drug, 11: Significant association between XDR-TB/poor treatment, 12: Treatment success rate/overall success rate mentioned (Yes) or not (No), 13: Relative death risk, 14: Multivariate analysis factor associated with treatment outcome, # : Median, CDC: Centers for Disease Control and Prevention, S: Surgery, D: Drug, RNTCP: Revised National TB Control Program

Table 5 Treatment Outcome of the studies reviewed

Study	First author (year) [reference]	Favorable treatment outcome n (%)	Cured n (%)	Completed treatment n (%)	Unfavorable treatment outcome n (%)	Died n (%)	Lost to follow-up n (%)	Defaulter n (%)	Failed to complete treatment n (%)	Transfer out n (%)	Insufficient information n (%)	Not evaluate n (%)	Total XDR patients	Overall treatment outcome	
														Favorable treatment outcome n (%)	Unfavorable Treatment outcome n (%)
1	Kashongwe (2020) [35]	1 (33.33)	1 (33.33)	-	2 (66.66)	2 (66.66)	-	-	-	-	-	-	3	1 (33.33)	2 (66.66)
2	Li (2019) [40]	11 (45.83)	11 (45.83)	-	13 (54.16)	1 (7.6)	-	-	-	-	-	-	24	11 (45.83)	13 (54.16)
3	Nkurunziza (2018) [3]	11 (21)	7 (13)	4 (8)	42 (79)	14 (26)	12 (23)		7 (13)	9 (17)	-	-	53	11 (21)	42 (79)
4	Yuengling (2018) [17]	33 (31.4)	27 (25.7)	6 (5.7)	72 (68.6)	43 (41)	17 (16.2)	-	12 (11.4)	-	-	-	105	33 (31.4)	72 (68.6)
5	Ndjeka (2018) [23]	70 (80.5)	70 (80.5)	-	17 (19.5)	8 (9.2)	5 (5.7)	-	4 (4.6)	-	-	-	87	70 (80.5)	17 (19.5)
6	Gallo (2018) [39]	15 (48.4)	13 (86.6)	2(13.33)	16 (51.6)	14 (45.2)	-	-	-	-	-	-	32	15 (48.4)	16 (51.6)
7	Prajapati (2017) [33]	29 (25.89)	17 (15.17)	12 (10.71)	83 (74.1)	58 (51.78)	1 (0.91)	11 (9.82)	10 (8.92)	3 (2.67)	-	-	112	29 (25.8)	83 (74.1)
8	He (2017) [34]	21 (14.6)	8 (5.6)	13 (9)	123 (85.4)	12 (8.3)	-	6 (4.2)	66 (45.8)	39 (27.1)	-	-	144	21 (14.6)	123 (85.4)
9	Kvasnovsky (2016) [22]	34 (10.3)	21 (6.4)	13 (3.9)	296 (83.3)	211 (63.9)	24 (7.3)	-	61 (18.5)	-	-	-	355	34 (10.3)	296 (83.3)
10	Pietersen (2015) [16]	53 (31)	53 (31)	-	111(62.3)	93 (53)	-	18 (34)	-	-	-	-	179	53 (29.7)	111 (62.3)
11	Pietersen (2014) [18]	56 (54)	23 (23)	33(31)	372 (269)	262 (245)		22 (22)	72 (64)		19 (18)	-	107	12 (11)	95 (89)
12	Lytvynenko (2014) [25]	24 (21)	23 (20)	1 (1)	90 (80)	12 (11)	19 (17)	-	40 (35)	-	-	19 (17)	114	24 (21)	90 (80)
13	O'Donnell (2013) [19]	25 (12)	15 (3.2)	10 (8.8)	89 (78)	48 (42.0)	-	19 (16.7)	22 (19.3)	-	-	-	114	25 (21.9)	89 (78)
14	Roongruangpitayakul (2013) [26]	4 (80.0)	4 (57.41)	-	3 (42.82)	0 (00)	-	-	1 (14.28)	-	-	2 (28.57)	7	4 (57.41)	3 (42.82)
15	Tang (2013) [41]	22 (13)	8 (4.7)	14 (8.3)	147 (87)	8 (4.7)	-	10(5.9)	124 (73.4)	5 (3.0)	-	-	169	22 (13)	147 (87)
16	Koh (2012) [27]	21 (53)	21 (53)	-	5 (45)	5 (45)	-	-	-	-	-	-	26	21 (80.7)	5 (19.3)
17	Liu (2011) [28]	14 (29.2)	5 (10.4)	9 (18.8)	34 (70.8)	3 (6.3)	-	9 (18.7)	21 (43.8)	1 (2.1)	-	-	51	14 (27.4)	34 (66.6)
18	Leimane (2010) [30]	18 (38)	18 (38)	0 (0)	30 (62)	4 (8)	-	3 (6)	23 (48)	-	-	-	48	18 (38.5)	30 (62.5)
19	Masjedi (2010) [31]	2 (28.6)	2 (28.6)	--	5(71.4)	2 (28.5)	-	-	1 (14.2)	-	-	2	7	2 (28.5)	5 (71.5)
20	Jeon (2009) [32]	28 (17.72)	23 (15)	5 (3)	130 (82.27)	36 (23)	--	15 (9)	63 (40)	16 (10)	-	-	158	28 (17.72)	130 (82.27)
21	Kliiman (2009) [24]	23 (42.6)	22 (40.7)	1 (1.9)	31 (57.4)	10 (18.5)	-	8 (14.8)	13 (24.1)	-	-	-	54	23 (42.6)	31 (57.4)
22	O'Donnell (2009) [20]	12 (20)	5 (45)	-	48 (80)	25 (42)	-	6 (10)	-	-	-	17 (27)	60	12 (20)	48 (80)

authors independently by evaluating the abstract and full text of the eligible articles. When there was disagreement, the relevant paper was reviewed and differences were resolved and final inclusion of the study was decided by consensus. Microsoft Excel 2016 (version 1210), Microsoft word software 2016 (version 1210), and GraphPad Prism 7 were used for data entry and analysis. Study characteristics and treatment outcomes were summarized in tables. Data related to treatment outcomes were pooled from published studies as described above. We pooled the proportion of favorable outcome like cure, completed treatment as well as unfavorable treatment outcome including death, default, transfer of care, and failure across studies. In addition, we have also investigated the effects of the potential heterogeneity factors in the proportions of treatment outcomes by subgroup analysis for continuous variables.

RESULTS

A total of 1,259 articles on clinical epidemiology, clinical management, and treatment outcome of XDR-TB were extracted from Science Direct, PubMed (advance search)/Medline, and Google Scholar database/search engine. Among these, only 22 articles met our inclusion criteria and were considered for our study. Out of 22 studies, 14 were retrospective, 3 were prospective, and 2 were observational, while in 3 articles, study type was not specified.

Clinical and epidemiological features of included cases: The overall patient sample size of 15198 patients were calculated in 22 enrolled studies, in which a total of 2009 XDR-TB patients' data was separated and analyzed.

Retreatment cases were reported in 19 studies (86.36%). Only seven studies (31.81%) included cases undergoing previous treatment regimens shorter than 1 month. Fifteen (68.18%) out of 22 studies reported the 'number of drugs' to which MTB strains were resistant; in one study, a 'median number' of such drugs was provided; whereas in the remaining studies, the names of resistant drugs were clearly mentioned.

Of the 22 studies, 13 studies mentioned the cohort prevalence of HIV patients; in six studies, information regarding the inclusion of HIV patients was not provided; whereas in

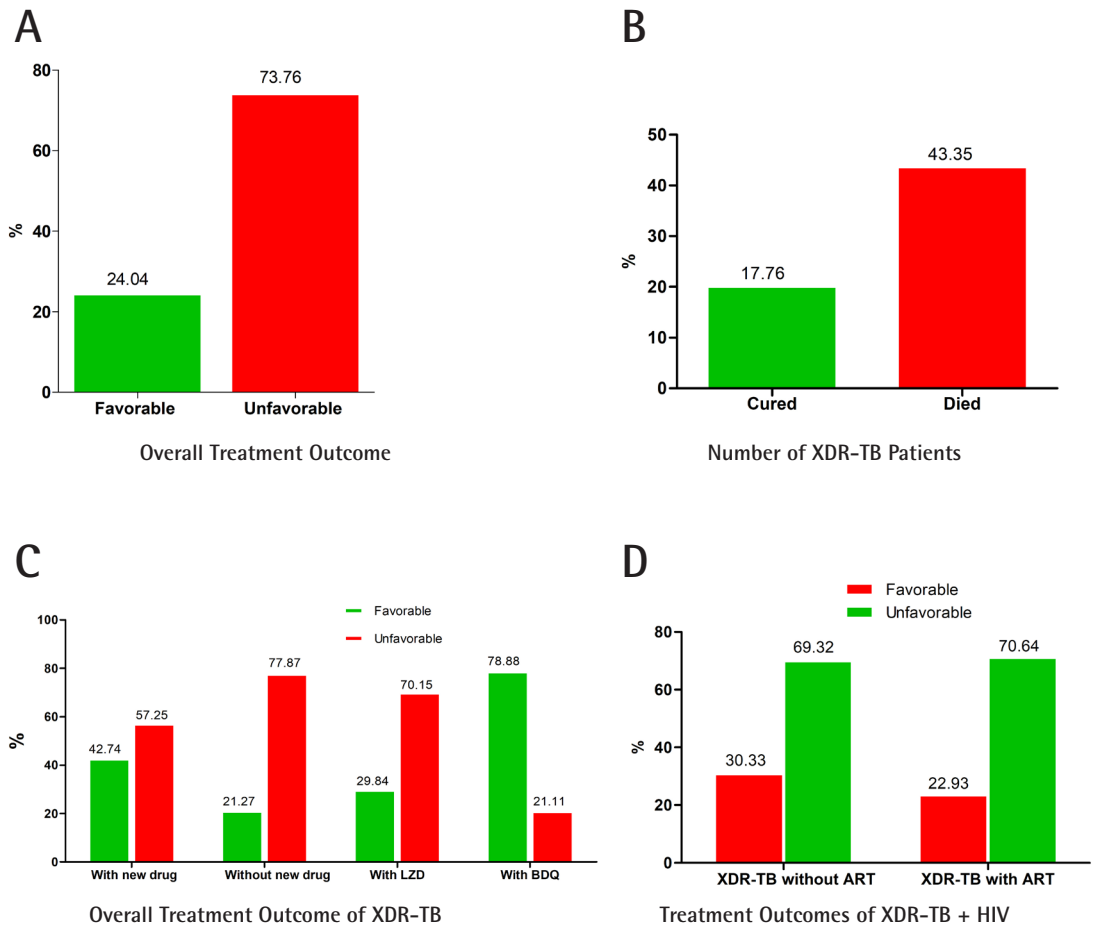

Figure 2 | **Treatment Outcome: 2A. Overall treatment outcome. 2B. Number of XDR-TB patients 2C. Overall treatment of XDR-TB. 2D. Treatment outcome of XDR-TB + HIV patients**

the remaining three articles, HIV patients were not included. HIV/non-HIV status of the patients was specified in 12 articles, while in remaining articles it's not mentioned clearly.

Linezolid (LZD) was used as therapeutic agent in five studies, bedaquiline (BDQ) was mentioned in one study, while one article specified the combination of LZD, BDQ, and ciprofloxacin (CIP). Surprisingly, out of 22 studies, cycloserine (CYC) was used in only one study. Fourteen studies did not mention the use of any new drug in their treatment regimen. Among 22 studies, 10 studies stated the current WHO definition of XDR-TB. Another 10 articles referred to other sources for XDR-TB definition. In remaining 2 articles didn't mention any reference to define XDR-TB (Table 1).

Laboratory diagnosis. Out of 22 studies, in 17 (77.27%) studies, the investigators performed DST on first- and second-line drugs, whereas in 2 (9.09%) studies no DST was performed either on first line or second line drug. Only second line drugs DST was performed in 1(4.54%) study.

Out of 22 articles included in this review, 15 studies used culture media for the diagnosis of XDR-TB. BACTEC alone was used in five studies, LJ (Lowenstein-Jensen) alone was used in only two studies, and BACTEC and LJ both were used in four studies. The combination of LJ, Acid Fast Bacillus (AFB), and BACTEC (Bacteriology Bactec Automated Blood Culture System) was used in two studies and LJ and AFB were used in only one study. In the remaining 7 articles, the diagnostic technique was not specified. In 20 (90.9%) articles, sputum smear-positive was observed at the baseline.

Out of all included studies, 14 (63.6%) studies comprised HIV positive patients, out of which only in eight (57.1%) studies, HIV-positive patients were receiving ART treatment along with the anti-TB regimen (Table 2).

Treatment characteristics. Out of 22 articles, the standardized 3 (13.63%), individualized 16 (72.72%), and both 3 (13.63%) treatment types were used. The treatment regimens was mentioned in 12 (54.54%) articles. Moreover, eight (36.36%) studies used novel drugs for the treatment while two (9.09 %) studies used the conventional drugs.

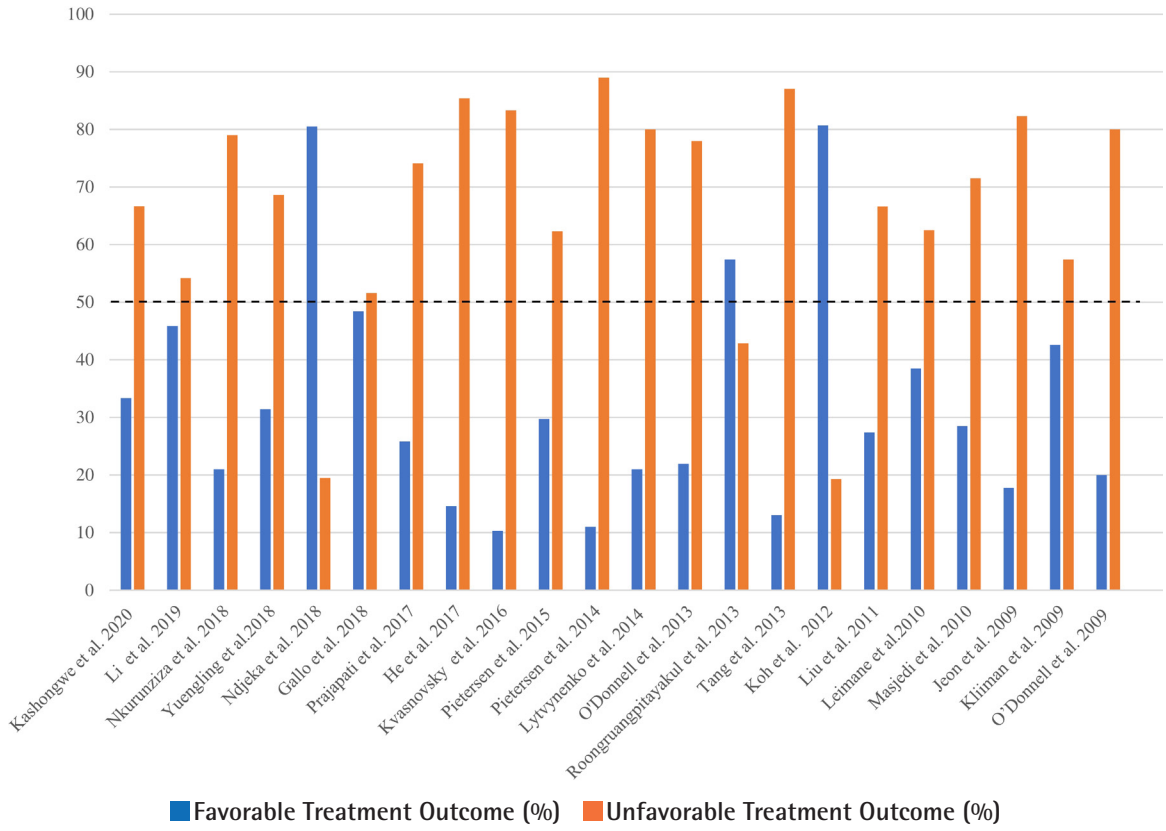

Figure 3 | **Individual treatment outcome of the studies reviewed**

The combinations of new drugs like LZD, BDQ and CFZ were used in two articles (9.09%) while single new drug like CYC was used in one (4.54 %) article and linezolid in five studies (22.72%).

Surgery (either resection and/or lobectomy) during the treatment was reported in four studies (18.18 %) while in 12 (54.54 %) studies reported adverse drug events and the rate of adverse events (%) was specified in seven (31.81%) articles. (Table 3).

Treatment efficacy endpoints. Out of 22 articles, the time of sputum conversion specified in 12 (54.5%) articles. In 12 (54.5%) studies 24 months were considered as the total duration of treatment and the duration of hospitalization were specified in just 6 (27.2%) articles. Duration of treatment follow-up was mentioned in 9 (40.9%) studies whereas additional duration of treatment follow-up was mentioned only in 2 (9.09%) studies.

Out of 22 articles, in 20 (90.9%) studies DST was carried out at the baseline. In 15 (68.18%) articles references for other definitions of treatment outcome were followed according to WHO, and Laserson *et al.* (2005) whereas in 4 (18.18%) studies referred to other sources.

The comparison of treatment outcome in-between HIV vs non-HIV patients was mentioned in 6 (27.27 %) articles. Seven (31.81%) studies reported the study success rate was due to the use of new drugs like CFZ, BDQ, and LZD. 'Significant association' and 'no significant association' in-between XRD-TB and poor treatment outcome were reported in 2 (9.09 %) studies each out of 22 enrolled studies.

By considering all 22 articles, a figure concerning 'treatment success rate' or 'overall success rate' was provided in 17 (77.27 %) studies.

The multivariate analysis factor associated with the treatment outcome was mentioned in 16 (%) studies while 'no' association was mentioned in 4 (18.18 %) studies (Table 4).

Treatment outcome. In 22 included XDR-TB studies the overall cohort size was 2009. The overall treatment outcome was favorable 24.04% (483) and unfavorable 73.76 % (1,482) (Figure 2A). In 3 studies [5,14,16] the favorable treatment outcomes was observed above 50% while in 19 studies unfavorable treatment outcome was more than 50%. The weakest (80% unfavorable) treatment outcome was observed in 7 studies [8,9,11,12,15,20,22) (Figure 3).

Out of 2009 patients XDR-TB patients, 19.76% (397) were cured while 43.35% (871) were died (Figure 2B). Pietersen et al. 2015 [16] reported XDR-TB treatment outcomes between

August 2002 to October 2012 in South Africa. Nkurunziza et al. 2018 [3], Yuengling et al. 2018 [17], Pietersen et al. 2014 [18] O'Donnell et al. 2013 [19], and O'Donnell et al. 2009 [20] has also reported XDR-TB treatment outcomes in South Africa-based studies. The results of this study were overlapped with study dates of Pietersen et al. 2015 [16]. We reanalyzed summery statistics of favorable treatment outcome by eliminating the small sample size studies. The results show only <1% change i.e., from 23.62% to 24.35%.

Out of 22 studies, in 14 studies, where the new drugs were not incorporated in the treatment regimen, the favorable treatment outcome was just 21.27% whereas in 8 studies, new drugs (LZD, BDQ, CIP, CFZ) were used the favorable outcome almost double (42.74%). Out of 8 studies (where the new drugs were incorporated) in 5 studies a single new drug, LZD was used with total sample size of 258 XDR-TB patients and the favorable outcome was 77 (29.84%) while in 2 studies BDQ was used in the sample size of 90 patients, the favorable treatment outcome was 71 (78.88%) (Figure 2C).

Among 22 XDR-TB studies, 14 studies include the condition HIV of the patients. Among the 14 studies, 6 were patients with XDR-TB treatment without ART and had an unfavorable outcome of 69.38%. In the remaining 8 studies, the patients treated as XDR-TB also received ART and in these cases the unfavorable outcome was 70.64%. The difference was less than 1%. This comparison represents ART plays a minor role in treatment outcome of XDR-TB (Figure 2D).

DISCUSSION

XDR strains of MTB have now been identified in 77 countries with 88% cases were reported by WHO in European and South-East Asia regions. After the preliminary statement of an association of XDR-TB with very high mortality in the patients co-infected with MTB and HIV in the rural area of South Africa in 2006, the public became rapidly conscious about the risk due to emerging drug resistance of MTB [21,22]. The clinical illustration of XDR-TB is gradually becoming more comprehensible, with several research teams inspecting clinical and epidemiological factors along with the treatment outcomes of patients infected with XDR-TB. To the best of our knowledge, this is the first systematic review of the clinical epidemiology, laboratory diagnosis, and treatment outcome of XDR-TB patients.

Methodological problems in XDR-TB study. In the present review, variety of study designs does not allow the collection of all valuable parameters. The small sample size of XDR-TB cases (range 3-355), lack of DST facilities and quality assured DST results, flexible treatment regimens for XDR-TB (like individualized or standardized or both) making it difficult for health workers to choose either single/combined therapy. Moreover, variations in treatment outcome definitions make it difficult to compare the results of all enrolled studies (Table 1 and 4)

Unexpectedly, the number of previous treatment regimens lesser than 1 month was not specified in about 75% of enrolled articles. The number of drugs to which the patients are resistant to anti TB drugs (to categorize them as XDR-TB) was specified in 15 studies [3,16, 17,19,20,23-32]. All the included data is necessary to define the epidemiological summary and to accurately interpret the statistics (Table 1).

Laboratory diagnosis of XDR-TB is the most challenging part, according to WHO, second-line DST for fluoroquinolone and all three injectable agents is necessary to categories XDR-TB patients, but in the majority of settings it is not feasible due to lack of DST laboratory facilities, and/or unavailability of second-line drugs in the country [18,20,26,30,31,33].

Nowadays, standardized procedures were made available to test second-line drugs, but still, it's lacking in many developing countries [18,30,33]. Even after many laboratory developments and implementation of surveillance at the national level the precision in results of second-line DST has not been guaranteed.

In most of the studies, the patient received individualized treatment based on DST results; however, in many articles data regarding drug treatment regimen is not available but the commonly used drug is mentioned in 18 articles [18,25,27,34].

Till date, in a few selected studies new drugs (LZD, BDQ, CIP, CFX) were added to the treatment regimen while others reported lack of availability (Table 3).

Half of the enrolled studies reported adverse drug events that may be attributed to poly-pharmacy, patients with other comorbidities like HIV, diabetes, drug use without precise patients' examination, improper use of new drugs [18,30,35]. In one study, the use of LZD was associated with most frequent adverse events [15]. Most of the adverse events were peripheral and optic neuropathy, anemia, thrombocytopenia, fear of heights, blurred vision, hyperglycemia [23,26,36]. QT interval prolongation was especially observed in BDQ-treated patients, while other common adverse events in other studies were gastrointestinal and vestibular toxicity, vertigo, vomiting, hearing loss [23,26,35].

The whole assessment of treatment outcomes as proposed by Laserson et al. or, WHO, was not specified in all studies, which focus on the risk of potential mistake in a meta-analysis of the data [1,15,36]. The present review also covers the clinical and epidemiological characteristics, laboratory evidence, treatment characteristics, treatment outcomes, adverse events of XDR-TB. It excludes extreme selection bias situation, but the 100% coverage cannot be substituted when the prevalence of the disease requirement needs to be determined [36-38].

By considering all these factors, the optimization of the XDR-TB management policies, including early diagnosis, availability of second-line anti-tuberculosis drugs, and improved management of the adverse event is the key for better evaluation of results as well as framing new queries for further research.

Treatment challenges in XDR-TB. The treatment modality of patients with XDR-TB involves use of second-line drugs. These drugs are more costly, less potent, and more toxic than

first-line TB drugs. Designing of personalized treatment regimens for the patients is extremely challenging due to limited choices of available drugs.

The highest prevalence of XDR-TB was observed in many Asian and European countries. Previous TB treatment, which indicates earlier treatment mismanagement, and present administration of drugs without proper DST or laboratory diagnosis plays an important role in the development of drug resistance [39]. A generalization of DST for all TB patients should be done at the baseline before starting a TB regimen.

Most data points to the fact that at least 4-8 drugs to which the strain is sensitive needs to be used for effective treatment. Although, in one study from South Africa, a very poor treatment outcome was obtained in spite of the use of several effective drugs in XDR-TB regimens [19]. Currently, in many countries novel drugs (LZD, BDQ, CIP, CFX) [3,17,35,40] are incorporated in the treatment regimen of XDR-TB several articles have stated that the success rate of their respective study could be attributed to the use of a novel drug in the treatment regimen [27,26,32]

The use of LZD and BDQ have better results compared to other drugs. An individual comparation between LZD and BDQ shows that BDQ is superior to LZD but difference in the sample size was significant and cannot be ignored.

Potentially most beneficial approach is surgical resection in critical conditions, which cannot be effectively controlled by medical intervention. Out of all the included studies, a few studies carried out surgical interventions such as surgical resection [32,41]. Jeon DS *et al*. 2009 mentioned that the surgery was performed on 16 patients and reported a significantly high treatment success, nine patients cured, four patients failing to cure, and three patients transferred [32]. In another study, two patients underwent lobectomy at 28 and 42 weeks after negative sputum smear showed positive outcomes [26].

A key question is whether ideal trials to compare the efficacy of treatment regimens for XDR-TB can be planned and applied. The treatment regimen for XDR-TB will constantly require to be individualized, which leads to the use of several regimens within a given trial as well as between the trials. In such cases, random treatment allocation will not be possible to reduce relevant bias.

Outcome difficulties with XDR-TB cases. Several studies form America, Europe, and Asia have shown that with personalized treatment regimen (including new drugs/surgery in selected cases), treatment success can still be achieved in XDR-TB.

The outcomes, in the current review, were categorized into favorable outcome (including cured and completed treatment) and unfavorable outcome (including patients died, lost to follow-up, failed to complete treatment, transfer out defaulter)

Majority of the studies analyzed in the current review confirmed that XDR-TB is associated with a higher mortality rate, treatment failure, longer hospitalization, longer treatment duration, delayed microbiological (sputum smear and culture) conversion, adverse drug reactions. The fact that mortality was almost invariably increased among XDR-TB cases indicates that a fraction of truly incurable XDR-TB patients does exist.

The study carried out in China mentioned a significant association between the XDR-TB and poor treatment outcome and reported high lost to follow-up rates, unavailability of free second-line TB drugs routinely, and no routine DST in many hospitals [34].

Usually, XDR-TB patients are resistant to a large number of anti TB drugs; however, it is noteworthy that efficacy of drugs varied significantly within studies. We also observed that some studies reported incomplete and/or inaccurate patient data [24,28,29,40].

Studies from South Africa, China, and other countries recommend that treatment adherence, positive patients' psychology, nutrition, and even financial interventions play an important role in treatment outcome. New approaches early diagnosis before the lung damage, accessibility of second-line as well as use of new drugs, [42,43] effective management of adverse events, and patient support are the key factors to improve the treatment outcome of XDR-TB [23,27,35].

In conclusion, our finding recommends a few areas to reduce XDR-TB cases by improving the current situation like-the use of upgraded methods including appropriate prospective study design, standardized international laboratory diagnostic tests and measures to assess disease severity. The long-term XDR-TB treatment is expensive, less effective and not free from severe adverse effects so more efforts should be made for the frequent use of new drugs with better efficacy and fewer side effects. Moreover, newer drugs should be made available in the TB centers and clinicians are encouraged to become familiar with the use of new drugs and fortified to add new drugs in the treatment regimen of TB patients. Lack of DST facilities promotes drug resistance owe to inappropriate treatment which can be overcome by using economical, rapid testing methods. Moreover, the unsatisfactory outcome of XDR-TB is more a political or structural than the medical problem.

ACKNOWLEDGMENTS

The authors are grateful to the Institute of Postgraduate Studies (IPS) of Universiti Sains Malaysia (USM) for the constant encouragement and support.

FUNDING

None to declare

CONFLICT OF INTEREST

Authors declare no conflict of interest.

REFERENCES

1. WHO consolidated guidelines on tuberculosis (2021). Module 2: Screening – systematic screening for tuberculosis disease. Geneva: World Health Organization; 2021 (https://www.who.int/publications/i/item/9789240022676).
2. Arya A, Singh S, Dwivedi VD, Shakila H. Integration of biometric ID for the effective collection and epidemiological evaluation of antibiotic prescription in tuberculosis and other diseases: A medical hypothesis. J Glob Antimicrob Resist. 2020 Jun;21:439-444. doi: 10.1016/j.jgar.2019.12.003.
3. Nkurunziza J, Karstaedt AS, Louw R, Padanilam X. Treatment outcomes of pre- and extensively drug-resistant tuberculosis in Johannesburg, South Africa. Int J Tuberc Lung Dis. 2018 Dec 1;22(12):1469-1474. doi: 10.5588/ijtld.18.0205.
4. Prasad R, Singh A, Balasubramanian V, Gupta N. Extensively drug-resistant tuberculosis in India: Current evidence on diagnosis & management. Indian J Med Res. 2017 Mar;145(3):271-293. doi: 10.4103/ijmr.IJMR_177_16.
5. Kim HR, Hwang SS, Kim HJ, Lee SM, Yoo CG, Kim YW. et al. Impact of extensive drug resistance on treatment outcomes in non-HIV-infected patients with multidrug-resistant tuberculosis. Clin Infect Dis. 2007 Nov 15;45(10):1290-5. doi: 10.1086/522537.
6. Migliori GB, Lange C, Centis R, Sotgiu G, Mütterlein R, Hoffmann H, et al. Resistance to second-line injectables and treatment outcomes in multidrug-resistant and extensively drug-resistant tuberculosis cases. Eur Respir J. 2008 Jun;31(6):1155-9. doi: 10.1183/09031936.00028708.
7. Shah NS, Pratt R, Armstrong L, Robison V, Castro KG, Cegielski JP. Extensively drug-resistant tuberculosis in the United States, 1993-2007. JAMA. 2008 Nov 12;300(18):2153-60. doi: 10.1001/jama.300.18.2153.
8. Marks SM, Flood J, Seaworth B, Hirsch-Moverman Y, Armstrong L, Mase S, et al. Treatment practices, outcomes, and costs of multidrug-resistant and extensively drug-resistant tuberculosis, United States, 2005-2007. Emerg Infect Dis. 2014 May;20(5):812-21. doi: 10.3201/eid2005.131037.
9. Falzon D, Schünemann HJ, Harausz E, González-Angulo L, Lienhardt C, Jaramillo E et al. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. Eur Respir J. 2017 Mar 22;49(3):1602308. doi: 10.1183/13993003.02308-2016.
10. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis. 2009 Mar;9(3):153-61. doi: 10.1016/S1473-3099(09)70041-6.
11. Sotgiu G, Ferrara G, Matteelli A, Richardson MD, Centis R, Ruesch-Gerdes S, et al. Epidemiology and clinical management of XDR-TB: a systematic review by TBNET. Eur Respir J. 2009 Apr;33(4):871-81. doi: 10.1183/09031936.00168008.
12. Migliori GB, Richardson MD, Lange C. Of blind men and elephants: making sense of extensively drug-resistant tuberculosis. Am J Respir Crit Care Med. 2008 Nov 15;178(10):1000-1. doi: 10.1164/rccm.200809-1380ED.
13. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Open Med. 2009;3(3):e123-30. Epub 2009 Jul 21. PMID: 21603045.
14. Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Geneva: World Health Organization; 2014. PMID: 25320836.
15. Laserson KF, Thorpe LE, Leimane V, Weyer K, Mitnick CD, Riekstina V et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2005 Jun;9(6):640-5. PMID: 15971391.
16. Pietersen E, Peter J, Streicher E, Sirgel F, Rockwood N, Mastrapa B, et al. High frequency of resistance, lack of clinical benefit, and poor outcomes in capreomycin treated South African patients with extensively drug-resistant tuberculosis. PLoS One. 2015 Apr 24;10(4):e0123655. doi: 10.1371/journal.pone.0123655.
17. Yuengling KA, Padayatchi N, Wolf A, Mathema B, Brown T, Horsburgh CR, et al. Effect of Antiretroviral Therapy on Treatment Outcomes in a Prospective Study of Extensively Drug-Resistant Tuberculosis (XDR-TB) HIV Coinfection Treatment in KwaZulu-Natal, South Africa. J Acquir Immune Defic Syndr. 2018 Dec 1;79(4):474-480. doi: 10.1097/QAI.0000000000001833.
18. Pietersen E, Ignatius E, Streicher EM, Mastrapa B, Padanilam X, Pooran A et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. Lancet. 2014 Apr 5;383(9924):1230-9. doi: 10.1016/S0140-6736(13)62675-6.
19. O'Donnell MR, Padayatchi N, Kvasnovsky C, Werner L, Master I, Horsburgh CR Jr. Treatment outcomes for extensively drug-resistant tuberculosis and HIV co-infection. Emerg Infect Dis. 2013 Mar;19(3):416-24. doi: 10.3201/eid1903.120998.
20. O'Donnell MR, Padayatchi N, Master I, Osburn G, Horsburgh CR. Improved early results for patients with extensively drug-resistant tuberculosis and HIV in South Africa. Int J Tuberc Lung Dis. 2009 Jul;13(7):855-61. PMID: 19555535.
21. Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, Zeller K et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006 Nov 4;368(9547):1575-80. doi: 10.1016/S0140-6736(06)69573-1.
22. Kvasnovsky CL, Cegielski JP, van der Walt ML. Treatment Outcomes for Patients with Extensively Drug-Resistant Tuberculosis, KwaZulu-Natal and Eastern Cape Provinces, South Africa. Emerg Infect Dis. 2016 Sep;22(9):1529–36. doi: 10.3201/eid2209.160084. Erratum in: Emerg Infect Dis. 2016 Nov;22(11):2028. PMID: 27538119.
23. Ndjeka N, Schnippel K, Master I, Meintjes G, Maartens G, Romero R et al. High treatment success rate for multidrug-resistant and extensively drug-resistant tuberculosis using a bedaquiline-containing treatment regimen. Eur Respir J. 2018 Dec 20;52(6):1801528. doi: 10.1183/13993003.01528-2018.
24. Kliiman K, Altraja A. Predictors of poor treatment outcome in multi- and extensively drug-resistant pulmonary TB. Eur Respir J. 2009 May;33(5):1085-94. doi: 10.1183/09031936.00155708. Epub 2009 Jan 22. PMID: 19164345.

25. Lytvynenko N, Cherenko S, Feschenko Y, Pogrebna M, Senko Y, Barbova A et al. Management of multi- and extensively drug-resistant tuberculosis in Ukraine: how well are we doing? Public Health Action. 2014 Oct 21;4(Suppl 2):S67-72. doi: 10.5588/pha.14.0035.
26. Roongruangpitayakul C, Chuchottaworn C. Outcomes of MDR/XDR-TB patients treated with linezolid: experience in Thailand. J Med Assoc Thai. 2013 Oct;96(10):1273-82. PMID: 24350407.
27. Koh WJ, Kang YR, Jeon K, Kwon OJ, Lyu J, Kim WS et al. Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients. J Antimicrob Chemother. 2012 Jun;67(6):1503-7. doi: 10.1093/jac/dks078.
28. Liu CH, Li L, Chen Z, Wang Q, Hu YL, Zhu B et al. Characteristics and treatment outcomes of patients with MDR and XDR tuberculosis in a TB referral hospital in Beijing: a 13-year experience. PLoS One. 2011 Apr 29;6(4):e19399. doi: 10.1371/journal.pone.0019399.
29. Velayati AA, Masjedi MR, Farnia P, Tabarsi P, Ghanavi J, ZiaZarifi AH et al. Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in iran. Chest. 2009 Aug;136(2):420-425. doi: 10.1378/chest.08-2427.
30. Leimane V, Dravniece G, Riekstina V, Sture I, Kammerer S, Chen MP et al.TH. Treatment outcome of multidrug/extensively drug-resistant tuberculosis in Latvia, 2000-2004. Eur Respir J. 2010 Sep;36(3):584-93. doi: 10.1183/09031936.00003710.
31. Masjedi MR, Tabarsi P, Baghaei P, Jalali S, Farnia P, Chitsaz E et al. Extensively drug-resistant tuberculosis treatment outcome in Iran: a case series of seven patients. Int J Infect Dis. 2010 May;14(5):e399-402. doi: 10.1016/j.ijid.2009.07.002.
32. Jeon DS, Kim DH, Kang HS, Hwang SH, Min JH, Kim JH et al. Survival and predictors of outcomes in non-HIV-infected patients with extensively drug-resistant tuberculosis. Int J Tuberc Lung Dis. 2009 May;13(5):594-600. PMID: 19383192.
33. Prajapati K, Mishra V, Desai M, Solanki R, Naik P. Treatment outcome of patients having extensively drug-resistant tuberculosis in Gujarat, India. Int J Mycobacteriol. 2017 Jul-Sep;6(3):289-295. doi: 10.4103/ijmy.ijmy_59_17.
34. He XC, Tao NN, Liu Y, Zhang XX, Li HC. Epidemiological trends and outcomes of extensively drug-resistant tuberculosis in Shandong, China. BMC Infect Dis. 2017 Aug 9;17(1):555. doi: 10.1186/s12879-017-2652-x.
35. Kashongwe IM, Mawete F, Mbulula L, Nsuela DJ, Losenga L, Anshambi N et al. Outcomes and adverse events of pre- and extensively drug-resistant tuberculosis patients in Kinshasa, Democratique Republic of the Congo: A retrospective cohort study. PLoS One. 2020 Aug 4;15(8):e0236264. doi: 10.1371/journal.pone.0236264.
36. Barrera L, Cooreman E, de Dieu Iragena J, Drobniewski F, Duda P, Havelkova M et al.. Policy Guidance on Drug-Susceptibility Testing (DST) of Second-Line Antituberculosis Drugs. Geneva: World Health Organization; 2008. PMID: 26290924.
37. Aziz MA, Wright A, Laszlo A, De Muynck A, Portaels F, Van Deun A, et al. Epidemiology of antituberculosis drug resistance (the Global Project on Anti-tuberculosis Drug Resistance Surveillance): an updated analysis. Lancet. 2006 Dec 16;368(9553):2142-54. doi: 10.1016/S0140-6736(06)69863-2.
38. Laserson KF, Thorpe LE, Leimane V, Weyer K, Mitnick CD, Riekstina V, et al. Espinal M. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2005 Jun;9(6):640-5. PMID: 15971391.
39. Gallo JF, Pinhata JMW, Simonsen V, Galesi VMN, Ferrazoli L, Oliveira RS. Prevalence, associated factors, outcomes and transmission of extensively drug-resistant tuberculosis among multidrug-resistant tuberculosis patients in São Paulo, Brazil: a cross-sectional study. Clin Microbiol Infect. 2018 Aug;24(8):889-895. doi: 10.1016/j.cmi.2017.11.015.
40. Li Y, Wang F, Wu L, Zhu M, He G, Chen X et al. Cycloserine for treatment of multidrug-resistant tuberculosis: a retrospective cohort study in China. Infect Drug Resist. 2019 Mar 29;12:721-731. doi: 10.2147/IDR.S195555.
41. Tang S, Tan S, Yao L, Li F, Li L, Guo X, et al. Huang J. Risk factors for poor treatment outcomes in patients with MDR-TB and XDR-TB in China: retrospective multi-center investigation. PLoS One. 2013 Dec 5;8(12):e82943. doi: 10.1371/journal.pone.0082943.
42. Caminero, JA, Deun AV, Monedero I, Fujiwara PI, Chiang C, Rieder HL, et al. "Guidelines for clinical and operational management of drug-resistant tuberculosis." Paris: International Union Against Tuberculosis and Lung Disease 2013; 1-232.
43. The Use of Bedaquiline in the Treatment of Multidrug-Resistant Tuberculosis: Interim Policy Guidance. Geneva: World Health Organization; 2013. PMID: 23967502.