

**Title:** *Global treatment outcomes of extensively drug-resistant tuberculosis in adults: a systematic review and meta-analysis*

**Background:** In recent years, drug-resistant tuberculosis has become an increasing cause of concern with the most advanced example being extensively drug-resistant tuberculosis (XDR-TB). While treatment options are available for XDR-TB, only a few studies have previously estimated the overall global treatment outcomes of XDR-TB patients. In this systematic review and meta-analysis, we aimed to calculate an updated estimate of the pooled proportion of individuals who achieved a successful outcome on a global scale.

**Methods:** We searched PubMed/MEDLINE, Scopus, Web of Science, and Embase (January 2005 to June 2022). Eligible studies reported treatment outcomes of pre-XDR- and/or XDR-TB patients according to the definitions provided by the World Health Organization, or adaptations hereof. Pooled proportions of treatment outcomes were calculated using a random-effects model. Subsequently, a series of sensitivity and subgroup analyses were performed.

**Results:** Among 4 692 studies screened, we included 86 studies from 26 different countries that reported treatment outcomes for 8 623 individuals with XDR-TB. The overall pooled proportion of successful outcomes was 43.7% (95%CI: 37.4-50.3). All sensitivity analyses yielded similar estimates. Subgroup analyses showed a significantly lower proportion of successful outcomes in studies with higher a prevalence of diabetes compared to studies with a lower prevalence (21.0%, 95%CI: 14.2-29.8 vs. 35.9%, 95%CI: 23.2-51.0,  $p = 0.029$ ), and in studies where tobacco usage was more prevalent compared to studies where tobacco usage was less prevalent (19.2%, 95%CI: 12.1-29.2 vs. 36.3%, 95%CI: 22.8-52.5,  $p=0.009$ ). There was also a significant difference across subgroups based on five-year intervals of the first year of inclusion, with a tendency towards improved outcomes after 2013 ( $p<0.000$ ).

**Conclusion:** The results of our systematic review and meta-analysis have shown a 43.7% success rate among individuals treated for XDR-TB globally which is still discouragingly far away from the WHO's goal of a 75% success rate. However, reassuringly there seems to be a tendency towards better outcomes in more recent studies.

## XDR-TB outcomes by subgroups

Category	Treatment success			Pooled proportion, % (95%CI)*		
	Studies, n	Pooled proportion, % (95%CI)	Studies, n	Failure	LTFU	Died
<b>Drug resistance</b>						
XDR	86	43.7 (37.4-50.3)	43	22.2 (16.6-29.1)	12.4 (10.1-15.2)	18.8 (13.7-25.3)
Pre-XDR	21	60.6 (49.3-70.9)	11	14.6 (6.9-28.3)	11.6 (6.1-21.0)	14.3 (8.5-23.2)
<b>First year of inclusion</b>						
1993-1997	6	57.7 (35.4-77.2)	3	10 (0.4-96.6)	6.9 (0.1-78.8)	11.8 (0.1-93.1)
1998-2002	12	38.4 (24.3-54.8)	7	23.4 (10.2-45.0)	13.0 (9.0-18.6)	16.4 (8.2-30.3)
2003-2007	17	38.4 (24.9-54.0)	10	26.8 (11.6-50.7)	11.3 (7.8-15.9)	16.9 (7.7-33.0)
2008-2012	31	35.8 (27.1-45.6)	16	19.5 (12.9-28.4)	12.2 (7.8-15.9)	25.1 (14.1-40.8)
2013-2017	16	61.7 (44.2-76.6)	5	22.5 (4.3-65.1)	9.4 (7.5-11.8)	11.8 (4.9-25.8)
2018-now	1	86.6 (77.3-92.4)	-	-		-
<b>Mean age, years</b>						
< 39.5	11	46.6 (26.3-68.0)	9	16.2 (8.4-9.0)	15.4 (9.5-24.1)	21.7 (9.3-42.6)
≥ 39.5	11	28.7 (18.1-42.4)	7	38.7 (20.0-61.4)	13.6 (7.2-24.3)	14.8 (7.0-28.4)
<b>Median age, years</b>						
< 36	8	25.9 (11.9-47.4)	5	16.2 (11.5-22.3)	11.7 (3.1-35.4)	40.9 (11.4-78.8)
≥ 36	8	41.9 (20.3-67.0)	6	34.8 (10.0-72.0)	8.7 (6.3-12.0)	15.1 (8.0-26.5)
<b>Males</b>						
< 62.5%	24	37.7 (26.2-64.8)	14	24.5 (12.5-42.3)	10.3 (7.0-14.9)	22.9 (11.3-41.0)
≥ 62.5%	25	34.7 (27.2-43.0)	19	24.0 (16.2-34.1)	16.3 (12.2-21.5)	20.1 (14.3-27.5)
<b>BMI, kg/m<sup>2</sup></b>						
< 18.5	5	32.5 (0.15-99.4)	2	9.4 (3.9-26.6)	12.15 (5.2-26.0)	44.3 (0.1-99.9)
≥ 18.5	2	22.7 (10.8-41.5)	4	41.8 (10.8-81.0)	11.1 (7.2-16.9)	15.1 (3.5-46.5)
<b>Diabetes</b>						
< 8.6%	10	35.9 (23.2-51.0)	9	22.6 (13.5-35.3)	13.5 (9.2-21.5)	19.6 (8.2-40.1)
≥ 8.6%	10	21.0 (14.2-29.8)	8	39.7 (15.9-69.8)	11.4 (6.1-20.5)	16.7 (7.9-31.9)
<b>HIV</b>						
No HIV-infected	17	35.5 (42.1-49.0)	13	34.6 (19.5-53.6)	13.8 (9.3-20.0)	13.9 (8.0-23.1)
< 43.6%	13	35.5 (25.6-47.2)	9	15.1 (7.6-27.8)	11.5 (5.9-21.3)	28.1 (13.8-49.0)
≥ 43.6%	11	47.1 (26.8-68.4)	5	17.2 (13.0-22.5)	14.4 (7.0-27.3)	42.1 (19.4-68.7)
<b>Tobacco use</b>						
< 18.4%	6	36.3 (22.8-52.5)	3	21.5 (1.3-84.8)	13.2 (2.7-45.3)	19.7 (1.5-79.9)
≥ 18.4%	6	19.2 (12.1-29.2)	6	35.7 (9.1-75.6)	9.4 (3.6-22.7)	20.1 (4.3-58.7)
<b>Previous TB treatment</b>						
< 80.7%	20	36.4 (24.9-49.8)	14	27.6 (13.5-48.1)	10.3 (6.7-15.5)	15.8 (9.1-26.2)
≥ 80.7%	21	36.9 (27.5-47.6)	15	22.0 (15.2-30.7)	14.1 (10.6-18.5)	26.0 (15.5-40.2)
<b>TB manifestation</b>						
PTB only	7	34.0 (15.4-59.4)	5	29.0 (11.0-57.6)	16.0 (9.0-26.9)	16.0 (6.1-35.8)
PTB and EPTB	12	38.6 (28.5-49.7)	10	19.6 (9.2-37.0)	12.8 (7.3-21.6)	21.7 (12.5-34.8)
<b>WHO regions**</b>						
African	15	42.1 (24.2-62.5)	7	14.7 (11.4-18.7)	12.3 (6.8-21.4)	50.1 (29.4-70.8)
Americas	7	38.4 (18.2-63.6)	3	6.0 (0.7-85.9)	10.4 (0.2-88.5)	33.6 (5.4-81.8)
South-East Asia	6	31.6 (12.6-59.3)	5	14.9 (4.7-38.2)	17.2 (6.1-39.8)	46.6 (27.7-66.6)
Europe	21	44.8 (33.0-57.3)	10	24.7 (13.4-40.9)	15.6 (10.1-23.2)	14.9 (10.5-20.7)
Eastern Mediterranean	2	40.6 (38.4-42.9)	1	14.9 (11.7-18.7)	7.7 (5.5-10.7)	36.9 (32.3-41.7)
Western Pacific	28	47.0 (34.2-60.1)	14	32.0 (18.0-50.3)	15.6 (10.1-23.2)	10.2 (6.4-15.8)

Abbreviations: CI, confidence interval. LTFU, lost to follow-up. XDR, extensively drug-resistant. BMI, body mass index. HIV, human immunodeficiency virus. TB, tuberculosis. PTB, pulmonary TB. EPTB, extrapulmonary TB. WHO, the World Health Organization.

\*Pooled proportions of died, failure and LTFU were only computed for studies where all outcomes for successful and unsuccessful were stratifiable (n=43), \*\*Countries for each WHO region is available from <https://www.who.int/countries>, red: significant subgroup differences, yellow: border significant subgroup differences.