



High prevalence of bedaquiline and linezolid resistance in extensively drug-resistant tuberculosis patients in a Médecins Sans Frontières clinic, Mumbai, India

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Introduction: Context

Since 2015, Médecins Sans Frontières (MSF) has provided treatment for TB patients in Mumbai with extensive resistance patterns, and have limited treatment options under India's National TB Elimination Programme



Background:

- Bedaquiline (BDQ) and linezolid (LZD) are group A drugs and form part of shorter and longer BDQ-based regimens¹.
- Systematic review on acquired BDQ resistance reports 2.2% phenotypic, and 4.4% genotypic resistance².
- Pooled frequency of LZD resistance among drug-resistant tuberculosis (DR-TB) isolates was 4.2% in a meta-analysis³.
- The emergence of resistance to BDQ is concerning as it results in difficulties in constructing regimens and is commonly associated with unsuccessful treatment outcomes⁴.

1. Guidelines for programmatic management of drug resistant tuberculosis in India-2021

2. Mallick JS, Nair P, Abbew ET, Van Deun A, Decroo T. Acquired bedaquiline resistance during the treatment of drug-resistant tuberculosis: a systematic review. *JAC Antimicrob Resist.* 2022 Mar 29;4(2):dlac029. doi: 10.1093/jacamr/dlac029. PMID: 35356403; PMCID: PMC8963286.

3. Azimi T, Khoshnood S, Asadi A, Heidary M, Mahmoudi H, Kaviar VH, Hallajzadeh M, Nasiri MJ. Linezolid resistance in multidrug-resistant mycobacterium tuberculosis: A systematic review and meta-analysis. *Front Pharmacol.* 2022 Aug 30;13:955050. doi: 10.3389/fphar.2022.955050. PMID: 36110536; PMCID: PMC9468755.

4. Assessment of epidemiological and genetic characteristics and clinical outcomes of resistance to bedaquiline in patients treated for rifampicin-resistant tuberculosis: a cross-sectional and longitudinal study

Ismail, Nazir Ahmed et al. *The Lancet Infectious Diseases*, Volume 22, Issue 4, 496 - 506

Objective:

- To determine the proportion of BDQ and LZD resistance in patients who had previously failed on BDQ and LZD-based regimens and their household contacts.
- Among the patients with BDQ and/or LZD resistance:
 - a) To describe the socio-demographic and clinical characteristics
 - b) To determine the duration of exposure and resistance to BDQ and LZD
 - c) To describe the treatment outcome.



Methods

Study conducted at the MSF DRTB clinic in Mumbai, India

- Retrospective descriptive study from Dec 2020 to Feb 2022
- The BDQ DST samples were sent to a nationally accredited lab

The study population was as follows:

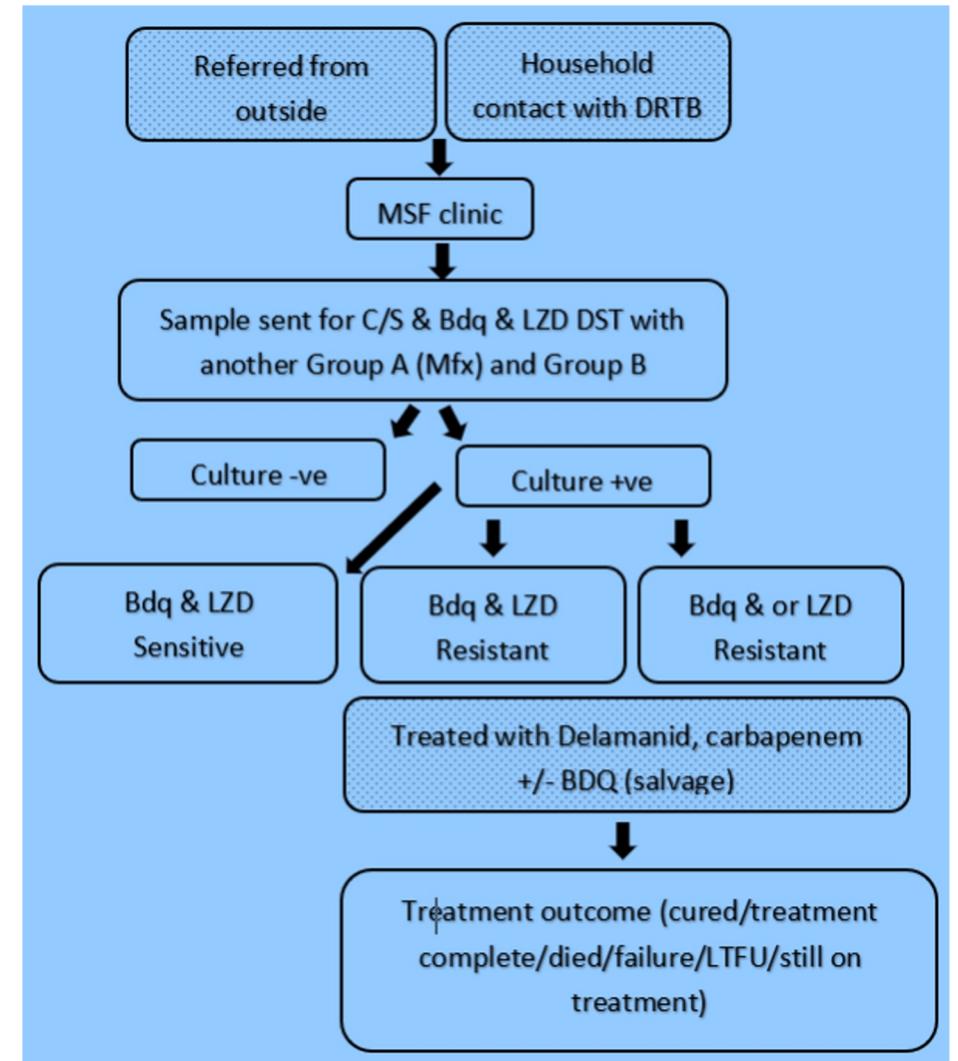
- BDQ and LZD exposed (>1 month) adolescent and adult patients referred to or treated in the MSF clinic with
- Suspected or confirmed failure
- Household contacts of BDQ exposed patients diagnosed with DRTB

Ethics

This research fulfilled the exemption criteria set by the MSF

Ethics Review Board (ERB).

Figure 1- Patient flow in MSF clinic and the samples sent for BDQ & LZD Drug susceptibility test (DST)



Result:

88 culture-positive samples were subjected to BDQ and LZD drug susceptibility testing (DST)

Prevalence
Total BDQ resistant = 20 (22.7%) Total LZD resistant = 15 (17%)

Only BDQ resistant = 12/88

BDQ + LZD resistant = 8/88

Only LZD resistant = 7/88

27/88

Result: Demography & clinical characteristics

1. Equal proportions male and female
2. Mean exposure to BDQ: 6 Months
3. Mean exposure to LZD: 16 Months
4. Pulmonary TB : 85% (23/27)
5. Bilateral lung involvement: 74% (20/27)
6. Cavities in lung: 67% (18/27)

Table 1: Description of the BDQ, LZD & concomitant BDQ+LZD resistance cohort

Category	Variables	Only BDQ-Res(n=12)	BDQ + LZD Res (n=8)	Only LZD - Res(n=7)
Demographic	Age in yrs (median)	26	23	33
	Male	6 (50%)	5 (63%)	2 (29%)
	Female	6 (50%)	3 (38%)	5 (71%)
Site of TB	Pulmonary	10 (83%)	6 (75%)	7 (100%)
	Disseminated	2 (17%)	2 (25%)	-
Lung involvement & co-morbidity	Bilateral	8 (67%)	6 (75%)	6(73%)
	Unilateral	4 (33%)	2 (25%)	1 (27%)
	Diabetes	2 (8%)	1 (13%)	3 (43%)
Outcome	Successful (completed & cured)	-	-	2 (29%)
	Died	6 (55%)	3 (38%)	3 (40%)
	Failure	2 (18%)	2 (25%)	1 (14%)
	Lost to follow-up	1 (9%)	-	-
	On treatment	2 (18%)	2 (25%)	1 (14%)
	Refused treatment	1	1	-

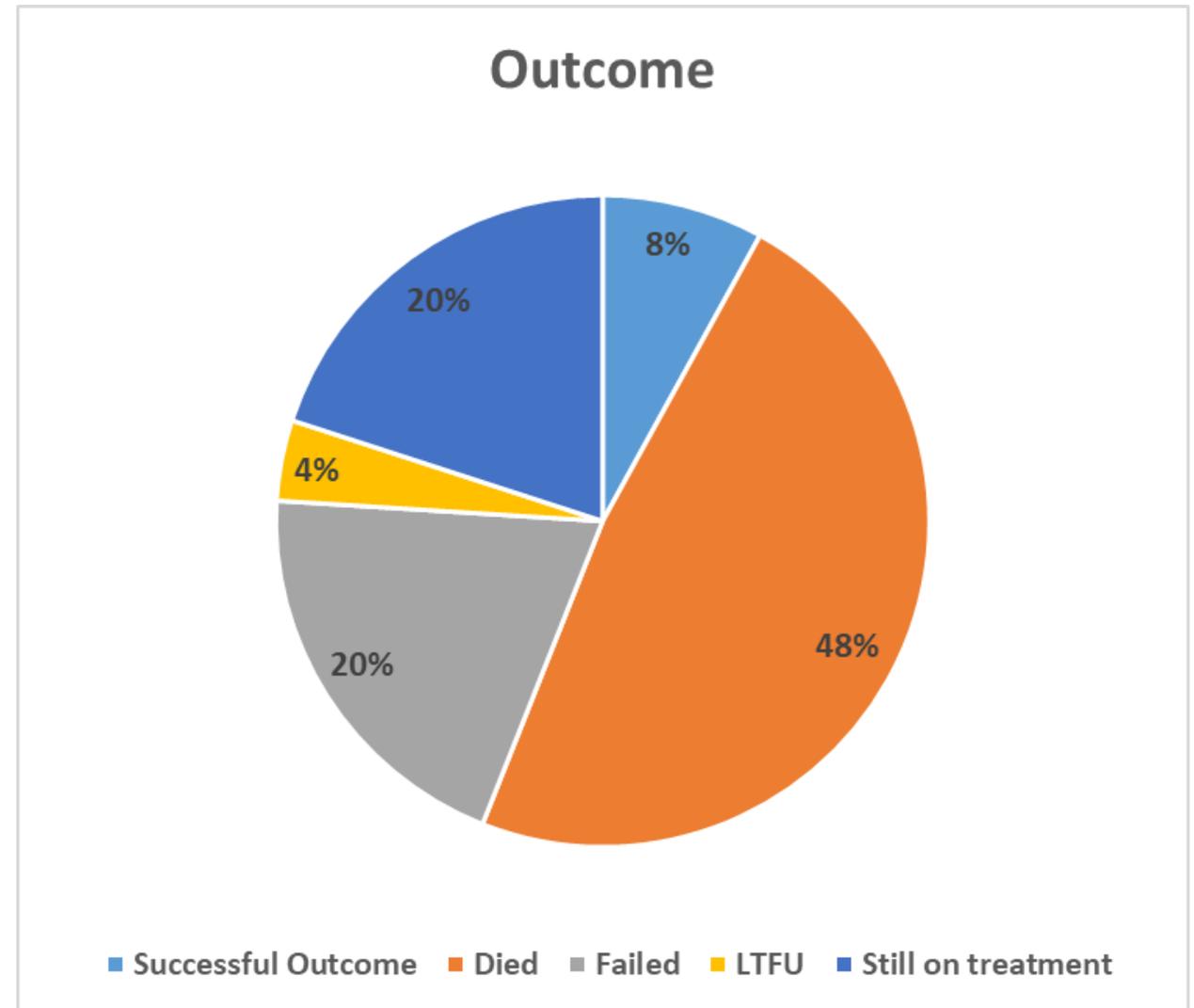
Result: Outcome

Out of 25 patients starting treatment

- 8% (2/25) successfully completed treatment
- 48% (12/25) died
- 20% (5/25) failed
- 4% (1/25) were lost to follow-up
- 20% (5/25) were still on treatment

- Of the **5 patients still on treatment patients, 2** culture-converted and **3** are still culture-positive after three months of treatment.

Figure 2- Treatment outcome of the BDQ & or LZD resistance cohort treated with salvage regimen





Conclusion:

- High proportion of BDQ and LZD resistance in patients who previously failed on BDQ and LZD-based regimens.
- High mortality and unsuccessful outcomes in treating such cases.

Recommendation:

- We urgently recommend increased programmatic access to BDQ DST for early diagnosis of BDQ resistance
- Establishment of systematic surveillance of BDQ and LZD resistance.
- Need for individualised treatment regimens based on DST, exposure history, adverse drug reaction and co-morbidity profile with optimised clinical and laboratory follow up



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