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Supplementary appendix

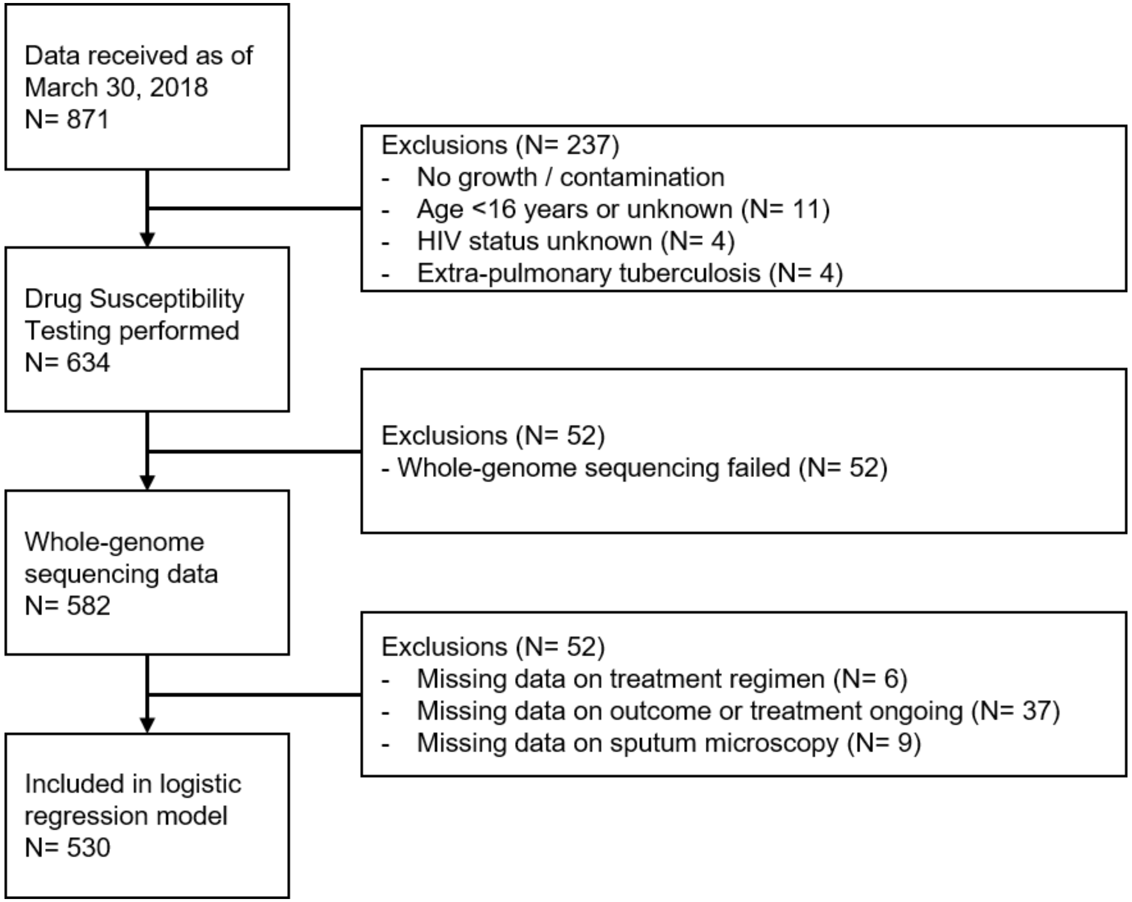
Supplement to: Zürcher K, Reichmuth ML, Ballif M, et al. Mortality from drug-resistant tuberculosis in high-burden countries comparing routine drug susceptibility testing with whole-genome sequencing: a multicentre cohort study. *Lancet Microbe* 2021; published online April 29. https://doi.org/10.1016/S2666-5247(21)00044-6.

Supplementary materials

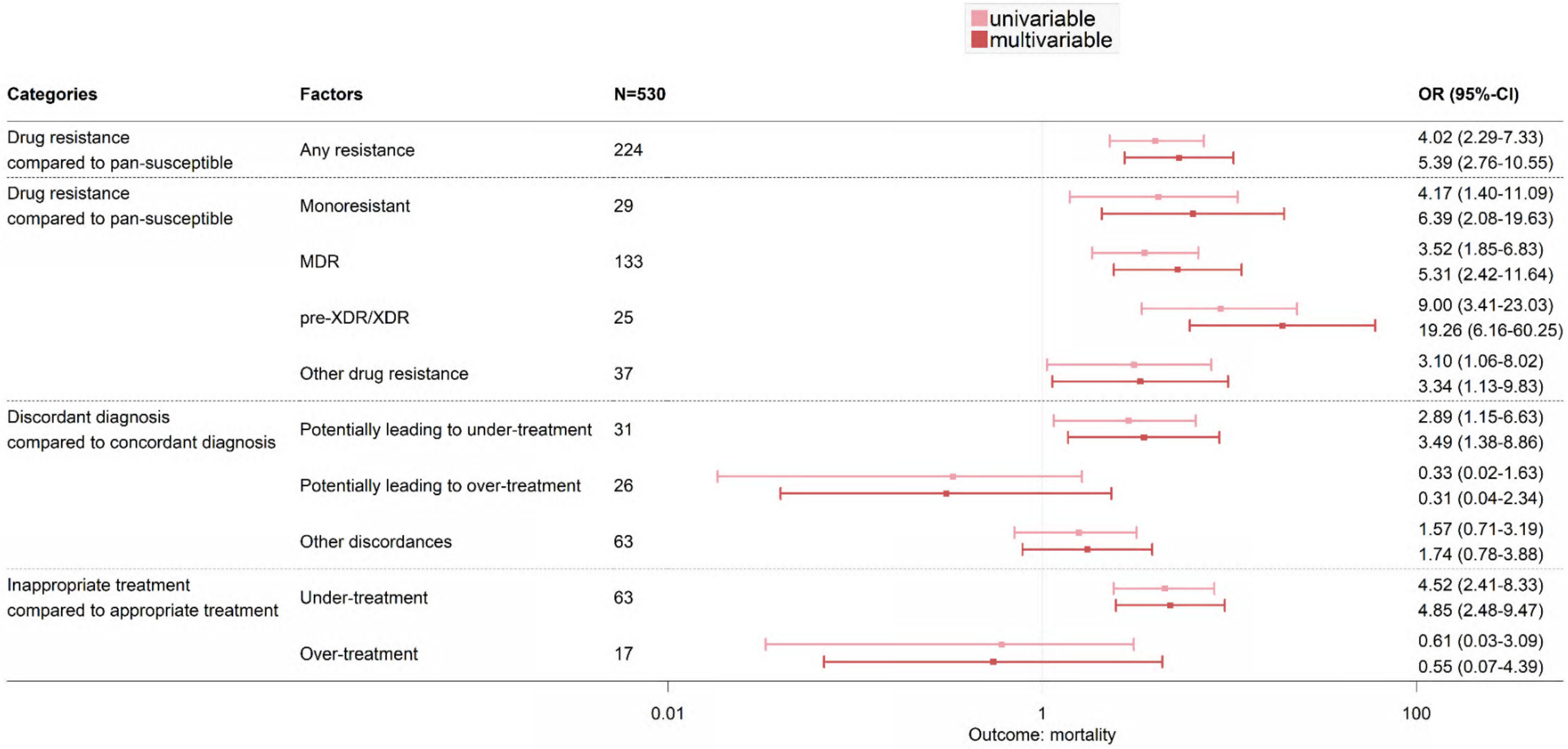
Zürcher et al. Mortality from drug-resistant tuberculosis in high-burden countries comparing routine drug susceptibility testing with whole-genome sequencing: a multicentre cohort study

Lancet Microbe, 2021

Supplementary Figure 1. Selection of the study population.

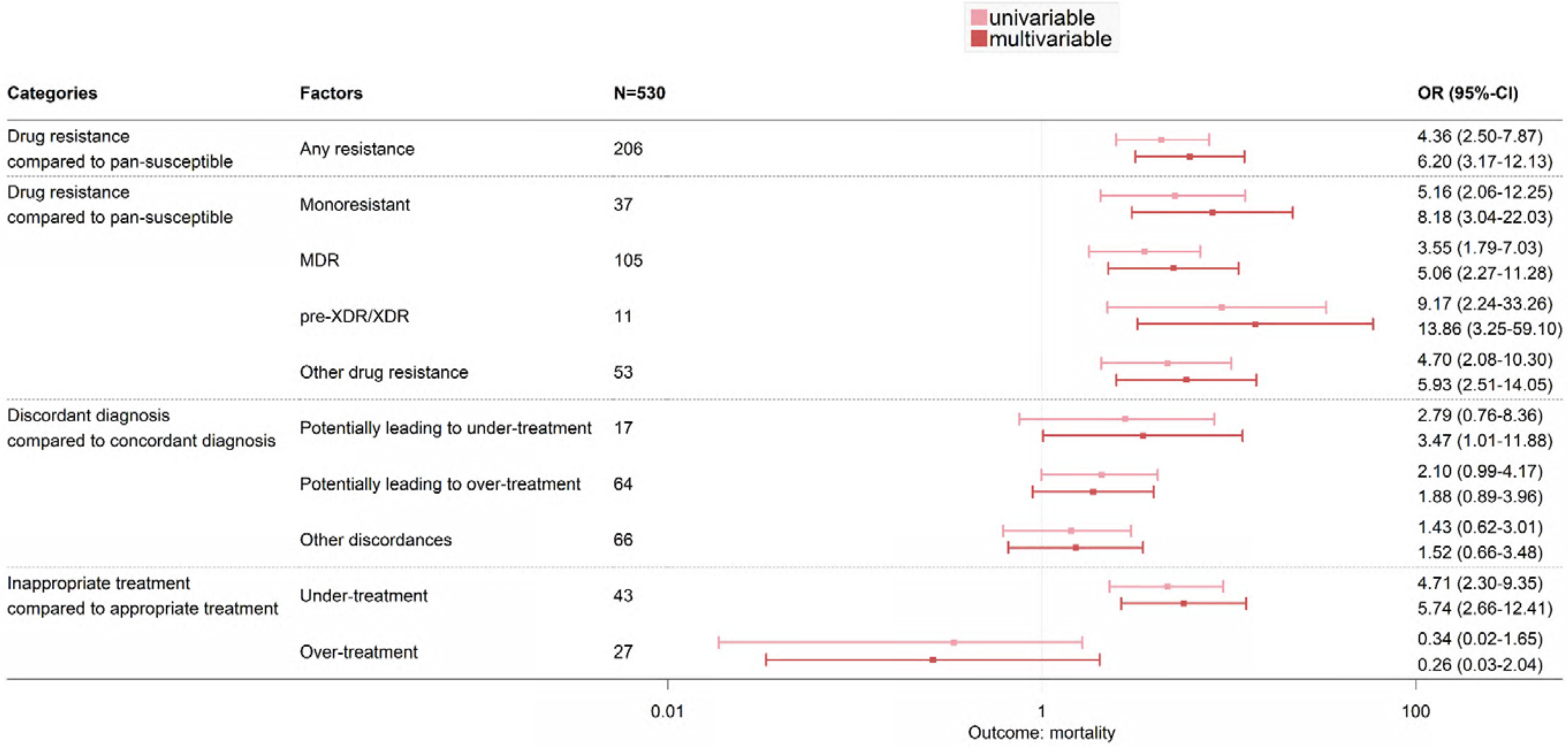


Supplementary Figure 2. Results from sensitivity analysis (using > 0% variant frequency) of four logistic regression models to assess 1) the impact of any drug resistance on mortality, 2) the impact of drug resistance categories on mortality, 3) the impact of diagnosis discordance on mortality, 4) the impact of treatment appropriateness (according to WHO guidelines) on mortality.



The models were adjusted for sex, age, HIV status, history of tuberculosis, sputum microscopy, and country of participating sites was included as random effect on the intercept.
Abbreviations: OR, odds ratio; CI, confidence interval; N, number; WHO, world health organisation; MDR, multidrug-resistant; Pre-XDR/XDR, pre-/ extensively drug resistant.

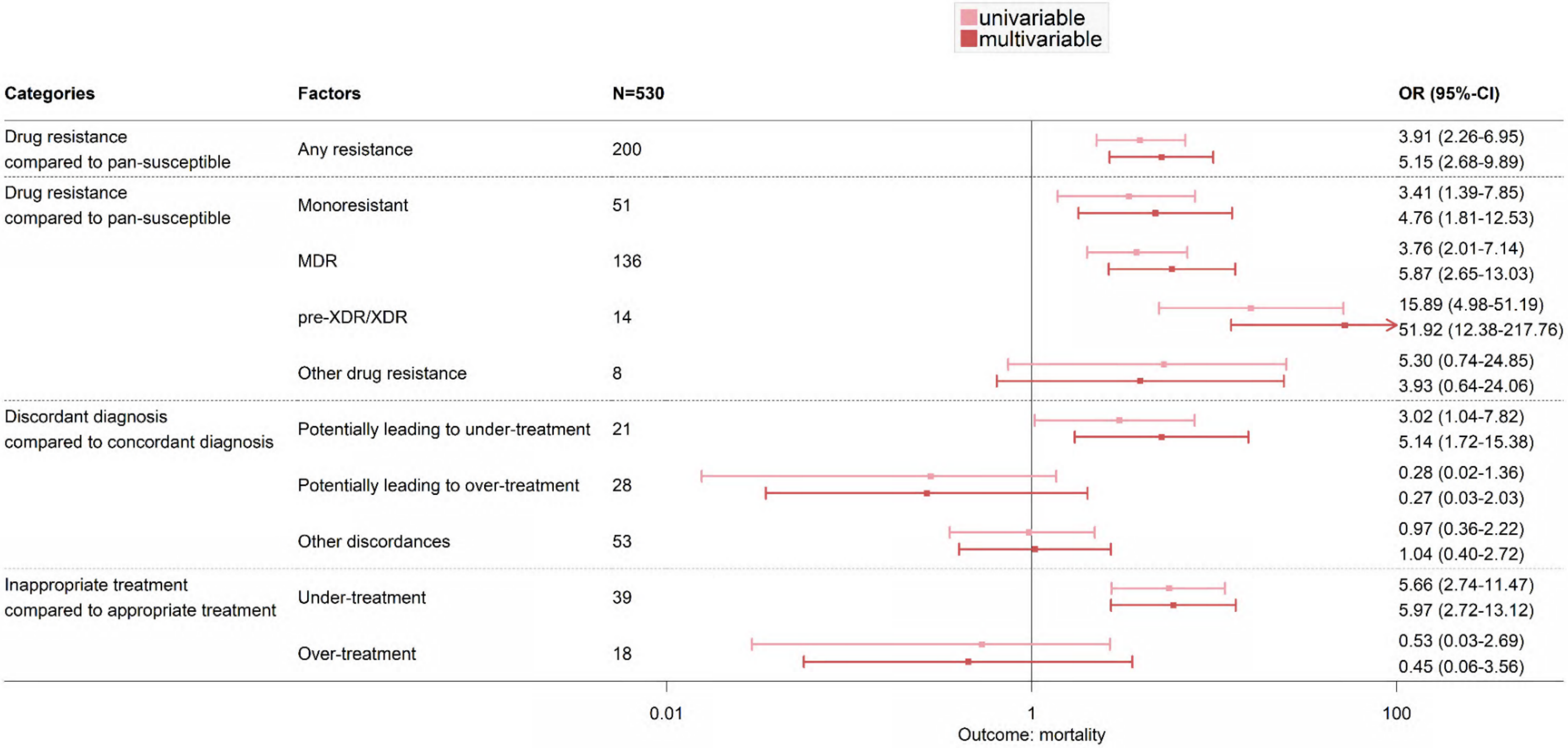
Supplementary Figure 3. Results from sensitivity analysis (using 100% variant frequency) of four logistic regression to assess 1) the impact of any drug resistance on mortality, 2) the impact of drug resistance categories on mortality, 3) the impact of diagnosis discordance on mortality, 4) the impact of treatment appropriateness (according to WHO guidelines) on mortality.



Categories	Factors	N=530	OR (95%-CI)
Drug resistance compared to pan-susceptible	Any resistance	206	4.36 (2.50-7.87) 6.20 (3.17-12.13)
Drug resistance compared to pan-susceptible	Monoresistant	37	5.16 (2.06-12.25) 8.18 (3.04-22.03)
	MDR	105	3.55 (1.79-7.03) 5.06 (2.27-11.28)
	pre-XDR/XDR	11	9.17 (2.24-33.26) 13.86 (3.25-59.10)
	Other drug resistance	53	4.70 (2.08-10.30) 5.93 (2.51-14.05)
Discordant diagnosis compared to concordant diagnosis	Potentially leading to under-treatment	17	2.79 (0.76-8.36) 3.47 (1.01-11.88)
	Potentially leading to over-treatment	64	2.10 (0.99-4.17) 1.88 (0.89-3.96)
	Other discordances	66	1.43 (0.62-3.01) 1.52 (0.66-3.48)
Inappropriate treatment compared to appropriate treatment	Under-treatment	43	4.71 (2.30-9.35) 5.74 (2.66-12.41)
	Over-treatment	27	0.34 (0.02-1.65) 0.26 (0.03-2.04)

The models were adjusted for sex, age, HIV status, history of tuberculosis, sputum microscopy, and country of participating sites was included as random effect on the intercept.
Abbreviations: OR, odds ratio; CI, confidence interval; N, number; WHO, world health organisation; MDR, multidrug-resistant; Pre-XDR/XDR, pre-/ extensively drug resistant.

Supplementary Figure 4. Results from sensitivity analysis (<u>restricting to drug resistance for which sites could test and ≥ 90% variant frequency</u>) of four logistic regression models to assess 1) the impact of any drug resistance on mortality, 2) the impact of drug resistance categories on mortality, 3) the impact of diagnosis discordance on mortality, 4) the impact of treatment appropriateness (according to WHO guidelines) on mortality.



Footnote: The models were adjusted for sex, age, HIV status, history of tuberculosis, sputum microscopy, and country of participating sites was included as random effect on the intercept
Abbreviations: OR, odds ratio; CI, confidence interval; N, number; WHO, world health organisation; MDR, multidrug-resistant; Pre-XDR/XDR, pre-/ extensively drug resistant.

Supplementary Table 1. Drug resistance category potentially leading to under- and over-treatment.

Drug resistance profile obtained with WGS	Drug resistance profile obtained at sites	Drug resistance profile obtained at sites
	Potentially leading to under-treatment	**Potentially leading to over-treatment**
Pan-susceptible	-	INH-, RIF-, or PZA- with EMB- resistance, MDR, or pre-XDR/XDR
Resistance to PZA or EMB	-	INH-, RIF-, or PZA- with EMB- resistance, MDR, or pre-XDR/XDR
Resistance to PZA and EMB	Pan-susceptible, PZA-, or EMB- resistance	INH-, RIF- resistance, MDR, or, pre-XDR/XDR
Resistance to INH	Pan-susceptible, PZA-, or EMB- resistance	RIF- resistance, MDR, or pre-XDR/XDR
Resistance to RIF	Pan-susceptible and resistance without RIF	pre-XDR/XDR
Pre-XDR/XDR	All resistance except pre-XDR/XDR	-

Abbreviations: WGS, whole-genome sequencing; INH, isoniazid; RIF, Rifampicin; PZA, pyrazinamide, EMB, ethambutol; MDR, multidrug-resistance; Pre-XDR/XDR, pre-/extensively drug-resistance.

Supplementary Table 2. Treatment appropriateness according to drug resistance profile.

Drug resistance	Number of effective drugs	Appropriate regimen	WHO guidelines
Pan-susceptible	4	First-line	First-line regimen
EMB- without INH- or RIF-resistance	3-4	First-line	First-line regimen
PZA- without INH- or RIF-resistance	3-4	First-line	First-line regimen
INH-resistance	≥ 4	Second-line	(H-INH) + RIF + PZA + EMB + FQ
RIF-resistance	≥ 4	Second-line	MDR regimen
MDR	≥ 4	Second-line	MDR regimen
Pre-XDR/XDR	≥ 4	Second-line	MDR/XDR regimen

Abbreviations: WHO, World Health Organization; INH, isoniazid; H-INH, high-dose isoniazid; PZA, pyrazinamide; EMB, ethambutol; RIF, rifampicin; MDR, multidrug resistance; Pre-XDR/XDR, pre-/ extensively drug resistance.

Supplementary Table 3. Mutant *Mycobacterium tuberculosis* position and number of strains identified locally as sensitive to a given drug, out of number of strains having the corresponding drug-resistance conferring mutation based on WGS.

Mutations (gene)	**Drug**	**No. of strains identified locally as sensitive, out of total no. of strains with the drug-resistance conferring mutation based on WGS**
c.-10G>A (*eis*)	KM	1/1 (100%)
c.-11A>C (*pncA*)	PZA	1/1 (100%)
c.-11A>G (*ethA*)	ETH	2/2 (100%)
c.-11C>A (*embA*); p.Met306Ile (*embB*)	EMB	0/1 (0%)
c.-12C>T (*embA*)	EMB	1/1 (100%)
c.-12C>T (*embA*); p.Asp1024Asn (*embB*)	EMB	1/1 (100%)
c.-14C>T (*eis*)	KM	1/1 (100%)
c.-15C>T (*fabG1*)	ETH INH	24/40 (60%)
c.-15C>T (*fabG1*); c.65_65del (*ethA*); p.Ala95Thr (*ethR*)	ETH INH	1/1 (100%)
c.-15C>T (fabG1); c.827_827del (*ethA*)	ETH INH	1/1 (100%)
c.-15C>T (*fabG1*); p.Ala381Pro (*ethA*)	ETH INH	1/1 (100%)
c.-15C>T (*fabG1*); p.Ala95Thr (*ethR*)	ETH INH	7/7 (100%)
c.-15C>T (*fabG1*); p.Ile194Thr (*inhA*)	ETH INH	0/5 (0%)
c.-15C>T (*fabG1*); p.Ile194Thr (*inhA*); p.Ala95Thr (*ethR*)	ETH INH	5/5 (100%)
c.-15C>T (*fabG1*); p.Ile21Thr (*inhA*)	ETH INH	3/6 (50%)
c.-15C>T (*fabG1*); p.Ile21Thr (*inhA*); p.Ala381Pro (*ethA*)	ETH INH	1/1 (100%)
c.-15C>T (*fabG1*); p.Ile21Val (*inhA*)	ETH INH	1/1 (100%)
c.-15C>T (*fabG1*); p.Ser315Gly (*katG*)	ETH INH	1/1 (100%)
c.-15C>T (*fabG1*); p.Ser315Thr (*katG*)	INH ETH	1/7 (14%)
c.-16C>G (*embA*)	EMB	1/1 (100%)
c.-16C>T (*embA*)	EMB	1/1 (100%)
c.-16C>T (*embA*); p.Met306Ile (*embB*)	EMB	1/1 (100%)
c.-16C>T (*embA*); p.Met306Val (*embB*)	EMB	1/1 (100%)
c.-16C>T (*thyX*)	PAS	1/1 (100%)
c.-17G>T (*fabG1*)	ETH INH	2/3 (67%)
c.-17G>T (*fabG1*); p.Ala381Pro (*ethA*)	ETH INH	7/7 (100%)
c.-17G>T (*fabG1*); p.Ser315Thr (*katG*)	INH ETH	1/8 (12%)
c.-48G>A (*ahpC*)	INH	0/1 (0%)
c.-54C>T (*ahpC*)	INH	1/1 (100%)
c.-74G>A (*ahpC*)	INH	1/1 (100%)
c.-8T>A (*fabG1*); p.Ser315Thr (*katG*)	INH	4/7 (57%)
c.-8T>C (*fabG1*)	ETH INH	14/14 (100%)
c.-8T>C (*fabG1*); p.Ser315Thr (*katG*)	INH ETH	8/14 (57%)
c.102_102del (*gid*)	SM	5/7 (71%)
c.1054_1054del (*ethA*)	ETH	1/1 (100%)
c.115_115del (*gid*)	SM	6/7 (86%)
c.1247_1248insT (*katG*); c.-81C>T (*ahpC*)	INH	0/1 (0%)
c.1282_1290del (*rpoB*)	RIF	1/1 (100%)
c.1292_1293del (*ethA*)	ETH	1/1 (100%)
c.139_139del (*pncA*)	PZA	1/1 (100%)
c.140_140del (*ethA*)	ETH	2/2 (100%)
c.171_172insAC (*pncA*)	PZA	1/1 (100%)
c.210_210del (*ethA*)	ETH	1/1 (100%)
c.341_341del (*ethA*)	ETH	2/2 (100%)
c.351_351del (*gid*)	SM	2/2 (100%)
c.389_389del (*pncA*)	PZA	2/2 (100%)
c.391_392insG (*pncA*)	PZA	1/1 (100%)
c.407_408insA (*pncA*)	PZA	1/1 (100%)
c.433_434insGC (*ald*)	CS	1/1 (100%)
c.459_466del (*pncA*)	PZA	1/1 (100%)
c.517_518insG (*pncA*)	PZA	7/7 (100%)
c.597_597del (*ethA*)	ETH	1/1 (100%)
c.626_627del (*ethA*)	ETH	2/2 (100%)
c.639_640del (*ethA*)	ETH	3/3 (100%)
Chromosome:g.2288682_2289080del (*pncA*)	PZA	1/1 (100%)
Chromosome:g.4407912_4408042del (*gid*)	SM	2/2 (100%)
p.Ala146Glu (*pncA*)	PZA	1/1 (100%)
p.Ala146Thr (*pncA*)	PZA	4/4 (100%)
p.Ala28Asp (*pncA*)	PZA	1/1 (100%)
p.Ala381Pro (*ethA*)	ETH	1/1 (100%)
p.Ala90Val (*gyrA*)	CIP LFX MFX OFX	6/6 (100%)
p.Ala95Thr (*ethR*)	ETH	2/2 (100%)
p.Asn138His (*katG*)	INH	0/1 (0%)
p.Asp12Ala (*pncA*)	PZA	3/4 (75%)
p.Asp136Gly (*pncA*)	PZA	1/1 (100%)

p.Asp354Ala (*embB*)	EMB	1/1 (100%)
p.Asp435Phe (*rpoB*)	RIF	0/3 (0%)
p.Asp435Tyr (*rpoB*)	RIF	0/2 (0%)
p.Asp435Tyr (*rpoB*); p.Pro454His (*rpoB*)	RIF	0/1 (0%)
p.Asp435Val (*rpoB*)	RIF	0/42 (0%)
p.Asp494Ala (*gyrB*)	CIP LFX MFX OFX	1/1 (100%)
p.Asp8Ala (*pncA*)	PZA	1/1 (100%)
p.Asp8Asn (*pncA*)	PZA	2/2 (100%)
p.Asp8Gly (pncA)	PZA	1/1 (100%)
p.Asp94Ala (*gyrA*)	CIP LFX MFX OFX	4/5 (80%)
p.Asp94Gly (*gyrA*)	CIP LFX MFX OFX	8/12 (67%)
p.Cys14Arg (*pncA*)	PZA	2/2 (100%)
p.Cys14Gly (*pncA*)	PZA	1/1 (100%)
p.Cys14Trp (*pncA*)	PZA	1/1 (100%)
p.Cys72Arg (*pncA*)	PZA	1/1 (100%)
p.Gln10Arg (*pncA*)	PZA	5/5 (100%)
p.Gln165Pro (*ethA*)	ETH	3/3 (100%)
p.Gln429His (*rpoB*); p.Asp435Phe (*rpoB*)	RIF	0/1 (0%)
p.Gln429His (*rpoB*); p.Asp435Tyr (*rpoB*)	RIF	0/2 (0%)
p.Gln432Leu (*rpoB*)	RIF	0/1 (0%)
p.Gln432Lys (rpoB)	RIF	0/1 (0%)
p.Gln497Arg (*embB*)	EMB	7/8 (88%)
p.Gln497Lys (*embB*)	EMB	2/2 (100%)
p.Gln497Lys (*embB*); p.Asp1024Asn (*embB*)	EMB	1/1 (100%)
p.Glu405Asp (*embB*)	EMB	1/1 (100%)
p.Gly234Glu (*katG*); c.-74G>A (*ahpC*)	INH	0/1 (0%)
p.Gly240Arg (*embR*)	EMB	1/1 (100%)
p.Gly297Val (*katG*)	INH	1/1 (100%)
p.Gly406Ala (*embB*)	EMB	2/2 (100%)
p.Gly406Asp (*embB*)	EMB	3/3 (100%)
p.Gly406Asp (*embB*); p.Asp1024Asn (*embB*)	EMB	1/1 (100%)
p.Gly406Cys (*embB*)	EMB	1/1 (100%)
p.Gly406Ser (*embB*)	EMB	2/2 (100%)
p.Gly406Ser (*embB*); p.His1002Arg (*embB*)	EMB	1/1 (100%)
p.Gly78Asp (*pncA*)	PZA	1/1 (100%)
p.Gly97Cys (*pncA*)	PZA	1/1 (100%)
p.His1002Arg (*embB*)	EMB	1/1 (100%)
p.His445Asn (*rpoB*)	RIF	0/1 (0%)
p.His445Asp (*rpoB*)	RIF	0/16 (0%)
p.His445Gln (*rpoB*)	RIF	0/1 (0%)
p.His445Leu (*rpoB*)	RIF	1/7 (14%)
p.His445Ser (*rpoB*)	RIF	0/2 (0%)
p.His445Ser (*rpoB*); p.Lys446Gln (*rpoB*)	RIF	0/2 (0%)
p.His445Thr (*rpoB*); p.Lys446Gln (*rpoB*)	RIF	0/1 (0%)
p.His445Tyr (*rpoB*)	RIF	0/9 (0%)
p.His51Arg (*pncA*)	PZA	8/8 (100%)
p.His57Tyr (*pncA*)	PZA	2/2 (100%)
p.His71Arg (*pncA*)	PZA	1/1 (100%)
p.His82Arg (*pncA*)	PZA	1/1 (100%)
p.Ile43Thr (*folC*)	PAS	1/1 (100%)
p.Ile491Phe (*rpoB*)	RIF	0/1 (0%)
p.Ile5Ser (*pncA*)	PZA	1/1 (100%)
p.Ile90Ser (*pncA*)	PZA	1/1 (100%)
p.Leu113Arg (*alr*)	CS	3/3 (100%)
p.Leu120Pro (*pncA*)	PZA	2/2 (100%)
p.Leu159Arg (*pncA*)	PZA	1/1 (100%)
p.Leu172Pro (*pncA*)	PZA	1/1 (100%)
p.Leu272Pro (*ethA*)	ETH	1/1 (100%)
p.Leu27Pro (*pncA*)	PZA	1/1 (100%)
p.Leu430Pro (*rpoB*)	RIF	0/7 (0%)
p.Leu430Pro (*rpoB*); p.Asp435Gly (*rpoB*)	RIF	0/1 (0%)
p.Leu430Pro (*rpoB*); p.Ser431Thr (*rpoB*)	RIF	0/1 (0%)
p.Leu452Pro (*rpoB*)	RIF	0/6 (0%)
p.Leu4Ser (*pncA*)	PZA	1/1 (100%)
p.Lys43Arg (*rpsL*)	SM	22/35 (63%)
p.Lys48Thr (*pncA*)	PZA	2/2 (100%)
p.Lys88Arg (*rpsL*)	SM	3/6 (50%)
p.Lys88Gln (*rpsL*)	SM	1/1 (100%)
p.Lys88Thr (*rpsL*)	SM	1/1 (100%)
p.Met1000Arg (*embB*)	EMB	1/1 (100%)
p.Met306Ile (*embB*)	EMB	28/34 (82%)
p.Met306Ile (*embB*); p.Asp328Gly (*embB*)	EMB	1/1 (100%)
p.Met306Ile (*embB*); p.Asp354Ala (*embB*)	EMB	0/1 (0%)
p.Met306Ile (*embB*); p.Gly406Ala (*embB*)	EMB	1/1 (100%)
p.Met306Leu (*embB*)	EMB	2/2 (100%)

p.Met306Val (*embB*)	EMB	27/39 (69%)
p.Phe110Leu (*ethR*)	ETH	2/2 (100%)
p.Phe94Leu (*pncA*)	PZA	1/1 (100%)
p.Pro54Leu (*pncA*)	PZA	1/1 (100%)
p.Ser315Asn (*katG*)	INH	0/2 (0%)
p.Ser315Thr (*katG*)	INH	19/111 (17%)
p.Ser315Thr (*katG*); p.Asp73His (*ahpC*)	INH	0/1 (0%)
p.Ser441Gln (*rpoB*)	RIF	0/1 (0%)
p.Ser447Phe (*gyrB*); p.Asp94Gly (*gyrA*)	CIP LFX MFX OFX	1/1 (100%)
p.Ser450Leu (*rpoB*)	RIF	2/79 (3%)
p.Ser450Leu (*rpoB*); p.Leu527Val (*rpoC*)	RIF	0/2 (0%)
p.Ser450Leu (*rpoB*); p.Phe452Ser (*rpoC*)	RIF	0/1 (0%)
p.Ser450Trp (*rpoB*)	RIF	0/1 (0%)
p.Ser67Pro (*pncA*)	PZA	1/1 (100%)
p.Ser94Ala (*inhA*)	ETH INH	2/2 (100%)
p.Thr168Asn (*pncA*)	PZA	1/1 (100%)
p.Thr400Ala (*rpoB*); p.Ser450Leu (*rpoB*)	RIF	0/1 (0%)
p.Thr76Pro (*pncA*)	PZA	1/1 (100%)
p.Tyr103* (*pncA*)	PZA	1/1 (100%)
p.Tyr319Ser (*embB*)	EMB	5/5 (100%)
p.Val139Ala (*pncA*)	PZA	1/1 (100%)
p.Val170Phe (*rpoB*)	RIF	0/2 (0%)
p.Val170Phe (*rpoB*); p.His445Tyr (*rpoB*)	RIF	0/1 (0%)
p.Val1Ala (*katG*)	INH	1/1 (100%)
r.1401a>g (*rrs*)	AMK CAP KM	9/10 (90%)
r.513c>t (*rrs*)	SM	1/1 (100%)
r.514a>c (*rrs*)	SM	10/11 (91%)
r.517c>t (*rrs*)	SM	2/2 (100%)
r.905c>g (*rrs*)	SM	2/2 (100%)
r.906a>g (*rrs*)	SM	1/3 (33%)
r.907a>t (*rrs*)	SM	1/1 (100%)

Footnote: The mutation with the corresponding gene is according to the Human Genome Variation Society (HGVS) nomenclature. The c. stand for coding DNA reference sequence, p. for protein reference sequence, r. for RNA reference sequence, and the * in the mutation stands for translation termination (stop) codon.

Abbreviations: SM, streptomycin; PAS, para-aminosalicylic-acid; INH, isoniazid; PZA, pyrazinamide; CS, cycloserine; KM, kanamycin; ETH, ethionamide; EMB, ethambutol; RIF, rifampicin; OFX, ofloxacin; CIP, ciprofloxacin; MFX moxifloxacin; LFX, levofloxacin, LZD, linezolid; BDQ, bedaquiline; CFZ, clofazimine; DLM, delamanid; CLR, clarithromycin; AMX, amoxicillin; CM, capreomycin; AM, Amikacin

Supplementary Table 4. Classification of treatment regimens by drug resistance profile.

Drug resistance according to WGS	Total	Treatment compatible with WHO guidelines	Total	Under-treatment	Total	Over-treatment
Pan-susceptible	320	320 INH PZA EMB RIF	0		19	1 INH PZA EMB OFX
						2 INH PZA KM EMB MFX CFZ
						1 PZA CS KM EMB LFX
						4 PZA CS KM LFX
						9 PZA KM ETH EMB MFX
						1 SM INH PZA EMB OFX
						1 SM INH PZA EMB RIF
Monoresistance	27		8		0	
INH	1	1 PZA CS KM LFX	7	7 INH PZA EMB RIF	0	
PZA	2	2 INH PZA EMB RIF	0		0	
EMB	1	1 INH PZA EMB RIF	0		0	
RIF	23	2 INH PZA KM EMB MFX CFZ	1	1 INH PZA EMB RIF	0	
		2 PZA CS AMK LFX				
		4 PZA CS KM LFX				
		14 PZA KM ETH EMB MFX				
		1 SM INH PZA EMB RIF				
MDR	110	51 INH PZA KM EMB MFX CFZ	30	1 CS KM ETH EMB LFX	0	
		2 PAS INH PZA KM ETH EMB MFX LZD BDQ CFZ DLM		15 INH PZA EMB RIF		
		2 PAS PZA CS KM ETH EMB		1 INH PZA KM EMB LFX		
		1 PAS PZA CS KM ETH LFX		1 PZA CS KM ETH EMB LFX		
		1 PAS PZA KM ETH EMB LFX		1 PZA EMB RIF LFX		
		1 PAS PZA KM ETH MFX LZD CFZ		11 PZA KM ETH EMB MFX		
		3 PZA CS AMK LFX				
		1 PZA CS ETH EMB AMK LFX				
		3 PZA CS KM EMB LFX				
		1 PZA CS KM ETH EMB				
		7 PZA CS KM ETH EMB LFX				
		21 PZA CS KM LFX				
		14 PZA KM ETH EMB MFX				
		2 SM INH PZA EMB RIF				
Pre-XDR/XDR	12	3 INH PZA KM EMB MFX CFZ	12	1 INH PZA EMB RIF	0	
		2 PAS INH PZA KM ETH EMB MFX LZD BDQ CFZ DLM		7 INH PZA KM EMB MFX CFZ		
		1 PAS PZA CS KM ETH EMB		1 PZA CS KM EMB OFX		
		2 PAS PZA KM ETH MFX LFX LZD BDQ		3 PZA CS KM LFX		
		3 PAS PZA KM ETH MFX LZD CFZ				
		1 PZA CS KM LFX				
Other:	21		17		0	
5 ETH		5 INH PZA EMB RIF				
1 CS		1 INH PZA EMB RIF				
9 SM		9 INH PZA EMB RIF				
1 EMB SM		1 INH PZA EMB RIF				

1 EMB RIF LFX MFX OFX CIP SM	1 PZA CS KM LFX	
1 RIF PZA ETH SM	1 PZA KM ETH EMB MFX	
1 INH PZA	1 PZA KM ETH EMB MFX	
1 EMB INH SM	1 PZA KM ETH EMB MFX	
1 EMB RIF	1 PZA CS AMK LFX	
14 INH ETH		14 INH PZA EMB RIF
1 INH LFX MFX OFX PAS CIP		1 INH PZA EMB RIF
1 INH SM		1 INH PZA EMB RIF
1 INH ETH SM		1 INH PZA EMB RIF

Abbreviations: vs, versus; WGS, whole-genome sequencing; WHO, World Health Organization; MDR, multidrug resistance; Pre-XDR/XDR, pre-/ extensively drug resistance; SM, streptomycin; PAS, para-aminosalicylic-acid; INH, isoniazid; PZA, pyrazinamide; CS, cycloserine; KM, kanamycin; ETH, ethionamide; EMB, ethambutol; RIF, rifampicin; OFX, ofloxacin; CIP, ciprofloxacin; MFX moxifloxacin; LFX, levofloxacin, LZD, linezolid; BDQ, bedaquiline; CFZ, clofazimine; DLM, delamanid.

Supplementary Table 5. Results from univariable logistic regression model on the probability of death during tuberculosis treatment.

Category	Number of patients (n=530)	Number of deaths (n=63)	OR (95% CI)
Gender			
Men	323	44	1.56 (0.9-2.81)
Women	207	19	1
Age			
At diagnosis [IQR]	34 (27-43)	37 (30-47)	1.03 (1-1.05)
HIV status			
HIV-positive	218	24	1.15 (0.68-2.01)
HIV-negative	312	39	1
History of tuberculosis			
Yes	200	29	1.48 (0.86-2.51)
No	330	34	1
Sputum			
Positive	427	53	0.76 (0.35-1.49)
Negative	103	10	1

Abbreviations: IQR, interquartile range; OR, odds ratio; CI: Confidence Interval.

Supplementary Table 6. Available and routinely performed drug resistance testing during the study period and in 2020. Newer drugs are indicated in bold.

Country	Study period		2020	
	DST tests reported as available	**Drug resistances that were tested among study participants**	**DST tests reported as available**	**Drug resistances which are routinely tested**
Ivory Coast	Culture	INH, RIF	Xpert, LPA (HAIN MTBDRplus), Culture	INH, RIF, EMB, PZA, SM
DRC	Xpert, Culture	INH, RIF, PZA, EMB, SM, AMK, MFX	Xpert, Culture	RIF, INH, EMB, PZA, SM, MFX, OFX, LFX
Kenya	Xpert	INH, RIF	Xpert, LPA (HAIN MTBDRsl), Culture	RIF
Nigeria	Xpert, LPA (HAIN MTBDRplus), Culture	INH, RIF	Xpert, LPA (HAIN MTBDRplus and HAIN MTBDRsl), Culture	INH, RIF, AMK, KM, MFX, OFX, LFX, ETH, PAS, CS, CM, CS, VIOMYCIN
South Africa	Xpert, LPA (HAIN MTBDRplus), Culture	INH, RIF, INJ, FQ	Xpert, LPA (HAIN MTBDRplus and HAIN MTBDRsl), Culture	RIF, INH, FQ
Peru	Culture	INH, RIF	Xpert, LPA (HAIN MTBDRplus), Culture	RIF, INH, EMB
Thailand	Culture	INH, RIF, SM	Xpert, LPA (HAIN MTBDRplus and HAIN MTBDRsl), Culture	INH, RIF, EMB, SM, AMK, MFX, OFX, LFX, ETH, PAS, CS, CFZ, AMX, CIP, CLR, IPM, KAN, **LZD**, MPM, PTO

Abbreviations: SM, streptomycin; PAS, para-aminosalicylic-acid; INH, isoniazid; PZA, pyrazinamide; CS, cycloserine; KM, kanamycin; ETH, ethionamide; EMB, ethambutol; RIF, rifampicin; OFX, ofloxacin; CIP, ciprofloxacin; MFX moxifloxacin; LFX, levofloxacin, LZD, linezolid; BDQ, bedaquiline; CFZ, clofazimine; DLM, delamanid; CLR, clarithromycin; AMX, amoxicillin; CM, capreomycin; IPM, imipenem; AMK, amikacin; MPM, meropenem**.**

Supplementary Table 7. Sequence reference number and accession number for the 582 *Mycobacterium tuberculosis* strains analysed.

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Supplementary Table 8. List of collaborators

First Name	Surname
Alash’le	Abimiku
Anchalee	Avihingsanon
Marie	Ballif
Guido	Bloemberg
Erik C.	Boettger
Sonia	Borrell
E. Jane	Carter
Jimena	Collantes
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Lameck	Diero
Matthias	Egger
Nicholas	Ezati
Lukas	Fenner
Sebastien	Gagneux
Joachim	Gnokoro
Eduardo	Gotuzzo
Rico	Hömke
Robin	Huebner
Feldmann	Julia
Naruporn	Kasipong
Kamon	Kawkitinarong
Peter	Keller
Olivier	Marcy
Eugène	Messou
Kouassi	N'Guessan
Tor	Petersen
Martina	Reichmuth
Miriam	Reinhard
Neesha	Rockwood
Annette	Sohn
Elizabeth	Streicher
Martine	Tabala
Robin	Warren
Landry	Wenzi
Robert J.	Wilkinson
Marcel	Yotebieng
Carlos	Zamudio
Kathrin	Zürcher