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Early View

Original research article

Emergence of bedaquiline-resistance in a high-burden country of tuberculosis

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Emergence of bedaquiline-resistance in a high-burden country of tuberculosis

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Take home Message

Bedaquiline resistance emerged in >15% of *Mycobacterium tuberculosis* complex strains obtained from follow-up isolates of MDR-TB patients. Insufficient backbone regimens and cavitary disease were associated with treatment failure and death.

Author's contributions: JH, MM conceived the study. EC performed minimum inhibitory concentration determination. FPM and SA supported implementation of drug susceptibility testing in Moldova and provided reference diagnostics. SN, CU, IB performed whole genome sequencing and molecular drug resistance prediction. EC, MM analysed whole genome sequencing data. EC, MM, MR performed statistical analysis. EC, DC, JH, MM drafted the manuscript. All authors made substantial intellectual contribution and revised the manuscript and gave final approval.

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Key words: MDR-TB, treatment outcome, WHO, bedaquiline

Abstract

Rationale: Bedaquiline has been classified as a Group A drug for the treatment of multidrug-resistant tuberculosis (MDR-TB) by the World Health Organization, however globally emerging resistance threatens the effectivity of novel MDR-TB treatment regimens.

Objectives: We analyzed pre-existing and emerging bedaquiline resistance in bedaquiline-based MDR-TB therapies, and risk factors associated with treatment failure and death.

Methods: In a cross-sectional cohort study, we employed patient data, whole genome sequencing (WGS) and phenotyping of *Mycobacterium tuberculosis* complex (MTBC) isolates. We could retrieve baseline isolates from 30.5% (62/203) of all MDR-TB patients who received bedaquiline between 2016 and 2018 in the Republic of Moldova. This includes 26 patients for whom we could also retrieve a follow-up isolate.

Measurements and Main Results: At baseline, all MTBC isolates were susceptible to bedaquiline. Among 26 patients with available baseline and follow-up isolates, 4/26 (15.3%) patients harbored strains which acquired bedaquiline resistance under therapy, while 1/26 (3.8%) patients was re-infected with a second bedaquiline resistant strain. Treatment failure and death were associated with cavitary disease (P=0.011), and any additional drug prescribed in the bedaquiline containing regimen with WGS-predicted resistance at baseline *(*P=0.012, OR 1.92 per unit increase, 95%CI 1.15-3.21).

Conclusions:

MDR-TB treatments based on bedaquiline require a functional background regimen to achieve high cure rates and to prevent the evolution of bedaquiline resistance. Novel MDR-TB therapies with bedaquiline require timely and comprehensive drug resistance monitoring.

Introduction

Tuberculosis (TB) is an airborne infectious disease caused by bacteria of the *Mycobacterium tuberculosis* complex (MTBC). TB remains one of the most challenging health issues worldwide with an estimated 1.4 million people that died from this disease in 2019 [1]. Particularly, multidrug-resistant (MDR)-TB, i.e. resistance against at least rifampicin and isoniazid, jeopardizes TB control with poor treatment outcomes despite long therapy durations of 9-18 months or more [2, 3].

Based on the result of a systematic review and a meta-analysis, the World Health Organization (WHO) revised the guidelines for the management of patients with MDR-TB by prioritizing the fluoroquinolones, bedaquiline and linezolid (all classified as group A agents) in 2019 [2, 4]. Especially the recently introduced novel anti-TB drug bedaquiline raised great expectations with the potential to reduce death rates [5], shorten MDR-TB treatment durations [6], decrease treatment failure rates [7–10] and thus has been administered to MDR-TB patients in more than 50 countries to date [11, 12]. Another important aspect is that MTBC isolates are considered naïve to bedaquiline as it was never administered under programmatic conditions, though recently a study indicated pre-existing bedaquiline resistance predating the introduction of the drug in Southern Africa [13].

Bedaquiline is an adenosine triphosphatase (ATP) synthase inhibitor specifically targeting the protein AtpE, a transmembrane subunit of the ATP synthase. Consequently, mutations in the *atpE* gene are biologically linked to bedaquiline resistance [14]. Furthermore, mutations in *Rv0678* encoding a transcriptional regulator of the MmpS5-MmpL5 efflux pump, and mutations in the putative proline aminopeptidase gene *pepQ* (*Rv3525c*) have been shown as secondary resistance mechanisms and, importantly, can lead to cross-resistance against the chemically unrelated WHO group B agent clofazimine [6, 15–18]. In clinical isolates, mutations in *Rv0678* seem to be the main resistance conferring mechanism associated with variable minimum inhibitory concentrations (MICs) and often detected at variable frequencies [19–26]. Of note, *Rv0678* mutations often occur in combination with isolates/clones lacking mutations in canonical bedaquiline and clofazimine resistance associated genes, i.e. hetero-resistance [19–22, 24, 27]. Pre-existing and emerging resistance against bedaquiline in failing treatment regimens have raised concerns to lose this new front-line drug against MDR-TB [4, 26, 28, 29].

Here, we sought to investigate events of bedaquiline resistance acquisition in MDR-TB patients receiving a bedaquiline based combination therapy and risk factors associated with treatment failure and

death. We employed a country-wide cross-sectional cohort study and performed bacterial whole genome sequencing (WGS), phenotyping and epidemiological analyses to investigate MTBC isolates and MDR-TB patients who received bedaquiline in the Republic of Moldova between 2016 and 2018, a country with one of the highest MDR-TB burden globally [1].

Material and Methods

Selection of patients receiving bedaquiline between 2016 and 2018

Using the national TB electronic database (SIMETB - *Sistemul informațional de monitorizare și evaluare al tuberculozei*) in the Republic of Moldova, we retrospectively identified all MDR-TB patients who started a bedaquiline containing treatment regimen between January 1st 2016 and December 31st 2018, and who had at least one MTBC isolate (prior to or after initiation of this treatment episode) stored in the biobank of the National Tuberculosis Reference Laboratory in Chisinau, Republic of Moldova. Patient isolates from three other laboratories in the country (Balti, Vorniceni, and Bender) are not routinely stored, and were not available for inclusion in this study. Routine phenotypic drug susceptibility test (DST) results for TB and MDR-TB antibiotics, demographic and clinical data including treatment regimens and outcomes were extracted from SIMETB.

Phenotypic antimicrobial susceptibility testing

For all isolates, we determined growth at 0,5 mg/L, 1,0 mg/L (corresponding to the WHO critical concentration), and 2,0 mg/L of each bedaquiline, clofazimine and linezolid using the BACTEC MGIT960 system (Becton Dickinson, USA). Routine antimicrobial susceptibility testing for other antibiotics were performed in MGIT960 using WHO recommended critical concentrations and according to manufactures instruction (Becton Dickinson, USA) and as instructed in the WHO guidelines [30]. Handling details can be found in the **Supplementary Methods**.

Whole genome sequencing

Extracted DNA (see **Supplementary Methods**) of 97 *M. tuberculosis* isolates obtained from 71 MDR-TB patients receiving bedaquiline containing regimens was subjected to whole genome sequencing (WGS) at the Research Center Borstel, Germany with a minimum average genome coverage of 50x, using paired-end DNA libraries and Illumina technology (Nextera-XT and NextSeq500) according to the manufacturer's instructions (Illumina, USA). Fastq files (raw sequencing data) were submitted to the European Nucleotide Archive (Accession numbers provided in **Table S1**) and mapped to the *M. tuberculosis* H37Rv reference genome (GenBank ID: NC_000962.3) using the MTBseq pipeline [31]. Briefly, we considered mutations (single nucleotide polymorphisms (SNPs), insertions and deletion) in 92 genes implicated in drug resistance (see [32]) and covered by a minimum of one read in both forward and reverse orientation, and one read calling the allele with at least a phred score of 20. Genotypic resistance prediction was performed on the basis of a curated mutation catalogue employed at the SRL, Research Center Borstel, Germany, based on information available on July, 3rd, 2020. Based on WGS results we classified MTBC isolates as extremely drug resistant (XDR, i.e. MDR plus additional resistance against any fluoroquinolone and at least one injectable drug) according to the WHO classification until 12/2020, and pre-XDR (i.e. MDR plus additional resistance against any fluoroquinolone or at least one injectable drug).

Statistics

Predictors for negative treatment outcomes and odds ratios were analyzed with univariate logistic regression. Odds ratios for contingency tables with zero cell count were corrected with the Haldane-Anscombe method adding 0.5 to each cell. Means of patient age (non-normal distribution) were compared with Mann-Whitney U tests, other variables in Table S2 were compared with a Fisher Exact test.

Ethics

No physical interventions took place with the patients and all of the information collected was anonymized at the source. The study protocol of the study was approved by the Institutional Review Board of the Institute of Phthisiopneumology "Chiril Draganiuc", Chisinau, Republic of Moldova (#1/07.2019).

Results

Study population

Between January 1st 2016 and December 31st 2018, 2,967 patients initiated MDR-TB treatment in the Republic of Moldova (1,413 new and 1,554 re-treatment cases). In total, 203 (6.8%) of all MDR-TB patients received bedaquiline as part of their anti-TB treatment regimen (**Figure 1**). For this study, we could retrieve MTBC cultures at the National Reference Laboratory for Mycobacteriology in Moldova from 82/203 (40.4%) patients; cultures from the remaining 121 patients were not available after routine diagnostics (**Figure 1, see methods**). Furthermore, MTBC cultures from eleven patients failed to grow or were contaminated, and for nine patients we could only receive a follow-up culture, resulting in 62/203 (30.5%) patients with a baseline MTBC isolate, prior to the start of the bedaquiline-containing MDR-TB regimen (**Figure 1**).

This cohort comprised 18 new and 44 retreatment cases, the median age was 39 years (interquartile range (IQR) 34-45 years). The majority of the patients were HIV-seronegative (54/62, 87.1%), were diagnosed with cavitary disease (45/62, 72.6%), and were male (50/62, 80.6%).

No differences were observed for characteristics of patients not included in the subsequent analysis (due to lack of MTBC culture, or only follow-up culture available) with regard to residence, gender, age, microscopy result, case definition, HIV status, and treatment outcome ($P > 0.09$, **Table S2**).

Around half of the patients were infected with a MTBC lineage 2 isolate (35/62, 56.5%) while the other patients were infected with a MTBC lineage 4 isolate (27/62, 43.5%). Isolates of other MTBC lineages were not identified in our MDR-TB cohort (**Table S1**).

Based on WGS results, 20/62 (32.3%) patients were classified as pre-XDR*, and 31/62 (50.0%) were classified as XDR* prior to the start of the bedaquiline-containing therapy regimen (*WHO classification until 12/2020, **Table S1**). Resistance proportions to individual drugs, as predicted by

WGS, were as follows: 62/62 (100%) streptomycin, 41/62 (66.1%) ethambutol, 44/62 (71.0%) pyrazinamide, 37/62 (59.7%) fluoroquinolones, 45/62 (72.6%) kanamycin, 15/62 (24.2%) amikacin, 14/62 (22.6%) capreomycin, 47/62 (75.8%) ethionamide, 16/62 (25.9%) para-aminosalicylic acid, 8/62 (12.9%) cycloserine (**Table S1**). Within a personalized therapy regimen of at least five antibiotics, patients received a median of one drug (IQR 0.75-2.0) with WGS predicted drug resistance at baseline (**Table S1**).

At the time of analysis, 10/62 (16.1%) patients were either still on treatment or lost to follow up. Among the remaining 52 patients, 37/52 (71.2%) patients were considered as cured (i.e. no clinical or microbiological signs of disease relapse, up to 6 months after treatment completion), 3/52 (5.8%) patients died, and 12/52 (23.1%) patients experienced signs of treatment failure, i.e. no negative culture within 8 months of treatment (**Table S1**). The proportions of treatment failure (27.0%) and death (8.2%) were comparable among the patient who were excluded from the analysis (P>0.71, **Table S2**).

In the following, we first describe (1) bedaquiline resistance associated mutations and their resulting phenotype. We then (2) investigate in detail events of emerging bedaquiline resistance among 26 patients with baseline and follow-up isolates, and eventually (3) analyze factors associated with negative treatment outcomes.

Phenotypic and genotypic resistance against bedaquiline

We identified nine MTBC isolates with mutations in the genes *atpE* and/or *Rv0678* out of which one isolate had mutations in *atpE* only, six isolates had mutations in *Rv0678* only, and two isolates had mutations in both genes (**Table 1**). Eight MTBC isolates had a bedaquiline MIC of 2.0 mg/L or higher and thus tested resistant in MGIT960, one isolate (CAR-84) with two mutations in *Rv0678* tested susceptible against bedaquiline (MIC 1.0 mg/L) (**Figure S1, Table 1**). Notably, we found in seven isolates more than one mutation in *atpE* and/or *Rv0678* at different frequencies indicating the existence of different sub-populations in these patients. All bedaquiline resistant isolates were follow-up isolates from patients who were exposed to bedaquiline containing MDR-TB regimens for 77-451 days (**Table 1**).

Emerging bedaquiline resistance

Among 26 patients with available MTBC isolates prior and after administration of bedaquiline, baseline and follow-up isolate differed by a maximum of 4 SNPs, while four (15.4%) patients were likely re-infected with a second isolate with 26-1,126 SNPs difference compared to the respective baseline isolate (**Table S1**).

In total, 4/26 (15.4%) patient isolates acquired bedaquiline resistance following 90, 159, 348, and 451, days of bedaquiline administration, respectively (**Table 1**). One follow-up isolate (patient 29) with the mutation *atpE* p.I66M (97% frequency) was phenotypically bedaquiline-resistant but clofazimine susceptible (**Table 1**). A second follow-up isolate (patient 12) carried three mutations in the gene *Rv0678* with variable frequencies (p.D5fs (57%), p.G24D (19.8%), and p.S64fs (13%)). Another two follow-up isolates acquired the mutations *atpE* p.A63P (25%) in combination with *Rv0678* p.S64fs (2%) (patient 2), and the combination *atpE* p.E61D (28%), *atpE* p.I66M (3%), *Rv0678* p.S63fs (5%) and p.S64fs (44%) (patient 57, **Table 1**).

No additional drug resistances emerged under bedaquiline containing treatment regimens, except patient 56 who had a follow-up isolate, which acquired the mutation *rrs* g.1484 g/t in the 16S rRNA gene mediating cross-resistance against the second-line injectable drugs kanaymycin, capreomycin and amikacin (**Table S1**). However, we found one isolate that virtually lost phenotypic resistance against all second-line injectable drugs as well as one fluoroquinolone resistance mediating mutation (patient2, **Table S1**). The baseline isolate from patient 2 harbored the mutations *rrs* 1401 a/g (63%) and *gyrA* p.D94G (61%) in combination with *gyrA* p.S91P (44%). In the follow-up isolate that tested susceptible to all second-line injectable drugs, the mutations *rrs* g.1401 a/g and *gyrA* p.D94G were reduced to a frequency of 4% and 0.5%, respectively. The mutation *gyrA* p.S91P on the other hand increased to a frequency of 96% (**Table S1**).

Among the four patients re-infected with a different MTBC strain, patient 37 was re-infected with a bedaquiline-resistant strain carrying the mutation *Rv0678* p.T58P at a frequency of 100%. Although the second isolate had the same genotype (lineage 2.2.1/ Europe/Russian W148 Outbreak), a genetic distance of 26 SNPs compared to the baseline isolate clearly pointed towards a re-infection (**Table 1, Table S1**).

Risk factors for failure of bedaquiline-based MDR-TB therapies

To determine risk factors of bedaquiline-based therapies, we analyzed predictors for a negative outcome, i.e. death or treatment failure, for 52/62 (83.9%) patients with available treatment outcome data. In a univariate logistic regression analysis, we included the following factors: MTBC lineage, gender, case definition, XDR, presence of cavities in chest X-rays, HIV status, age, and number of drugs with predicted resistance (in the following also referred to as "inactive drugs") as part of the bedaquiline containing MDR-TB therapy regimen (**Table 2**). We found cavitary disease (P=0.011) associated with a negative treatment outcome. Furthermore, an increasing number of inactive drugs increased the odds of treatment failure (OR 1.92 per unit increase, 95% CI 1.15-3.21, P=0.012) (**Table 2, Figure 2**). Likewise, most regimens included antibiotics with WGS predicted resistance at baseline and patients with a negative outcome had more inactive drugs (on average 2.33) included in their bedaquiline-containing regimen compared to patients with positive treatment outcomes (on average 1.27 inactive drugs, P= 0.018, Mann-Whitney-U test).

Discussion

In this cross-sectional cohort study, we report bedaquiline resistance acquisition in >15% of all MDR-TB patients who received bedaquiline as part of their treatment regimen, and with available follow-up cultures. The odds for negative treatment outcomes increased with the presence of cavities and the number of ineffective drugs included in a regimen. Nevertheless, despite high numbers of re-treatment cases and extended drug resistance profiles, bedaquiline-based regimens achieved high cure rates (71%) among our patient cohort, which is also reflected by the overall low number of positive follow-up cultures.

Emerging resistance against bedaquiline has been described in patients previously [19–25, 28, 29]. In addition, high MICs among patient isolates who were never exposed to bedaquiline (and/or clofazimine) may potentially jeopardize the effectiveness of currently endorsed MDR-TB treatment regimens [13, 19–25, 28, 29]. New information from this study, in which all available baseline isolates were bedaquiline susceptible, indicates that the success of bedaquiline-containing therapies relies on a functional background regimen excluding underling resistances to the administered antibiotics [4]. Another important factor associated with treatment outcomes is the presence of pulmonary cavities, which further promote the emergence of drug resistance most likely due to higher bacterial loads [33–36]. Larger cavities also may hinder drugs in reaching the central lesion that contain the highest bacterial

load [36]. For example, clofazimine is unable to reach the necrotic centre of caseous lesions, and also bedaquiline accumulates rather in cellular regions of a granuloma, while linezolid and moxifloxacin effectively penetrate all lesions types [35, 37, 38]. Thus, cavities provide a micro-environment for the infecting MTBC strain with variable drug concentrations, and especially bedaquiline levels might temporarily fall below effective concentrations. This changing micro-environment may select different sub-populations of bedaquiline-resistant clones but also susceptible bacteria remain which lack any mutations in the canonical resistance genes (*Rv0678, atpE, pepQ*) as seen in our study and observed previously [19–22, 24, 27].

The complex pathology of granulomas, pharmacokinetics and pharmacodynamics can usually not be considered in routine clinical practice. However, rapid and comprehensive DST is key for a personalized MDR-TB treatment [39]. Resistance to pyrazinamide, for instance, is not routinely performed in many high-burden MDR-TB countries, and fluoroquinolones may be still given to patients despite proven resistance when no other antibiotics are available (personal communication with Dr. Aliona David, Chiril Draganiuc Phthisiopneumology Institute, Chisinau, Republic of Moldova). Nevertheless, we show the immediate risk of resistance development when bedaquiline is administered in partially ineffective background regimens. This is aggravated by the fact that the diagnostic work-up of rifampicin resistant TB and MDR-TB is currently hampered by a lack of rapid, i.e. sputum-based, genotypic tests to rule-out resistance to the WHO group A medicines bedaquiline and linezolid [18]. New approaches such as early targeted next generation sequencing (NGS), e.g. using the Deeplex ® assay [40], or even WGS of the MTBC genome directly from patient specimens [41] may complement confirmatory phenotypic DST to further improve management of MDR-TB patients in high burden countries such as the Republic of Moldova.

Universal drug susceptibility testing is an important but not the only measure to reduce the risk of drug resistance development under therapy. The current WHO recommendations for the management of MDR-TB give advice for situations with underlying drug-resistances or intolerance against certain anti-tuberculosis drugs, and provide recommendations for surgery as adjunctive therapy option [42]. In the Moldovian setting, the design of second-line treatment regimens is unfortunately driven by the availability of drugs. Surgery is performed in accordance with WHO recommendations and mostly on the basis of individual decisions, especially in patients with cavitary diseases. Furthermore, poor treatments adherence, and treatment interruption as well as patients refusing medication intake likely

also contribute to the selection of bedaquiline resistant strains. Thus, increasing patient awareness about the importance of medication adherence and regular drug supply is crucial to design effective MDR-TB therapies and reduce the risk of resistance evolution.

However, high costs of bedaquiline, lack of evidence on drug safety, limited experience with regard to side effects, and sometimes bureaucratic barriers are further complicating the programmatic implementation of bedaquiline in many high burden MDR-TB settings [43]. These factors were also the reasons why only 203 patients were actually treated with bedaquiline in the Republic of Moldova during the study period 2016-2018, as compared to all eligible MDR-TB patients in that timeframe. Following the WHO endorsement of bedaquiline as a group A MDR-TB drug in August 2018 [44], bedaquiline became available for the majority of all MDR-TB patients.

This cross-sectional cohort study has some limitations. We could only retrieve MTBC isolates from 35% of all patients who received bedaquiline between 2016 and 2018 in the Republic of Moldova. This emphasizes the immediate benefit of universal culture and DST for future studies, especially systematic bio banking of MDR MTBC strains will provide crucial information for drug resistance surveys. However, sampling of MTBC isolates in this study occurred prior to phenotypic and genotypic investigations and was not biased towards bedaquiline resistance. Due to overall rapid culture conversion times under bedaquiline treatment, and thus a lack of follow-up cultures for many patients, acquired bedaquiline resistance is mainly observed among patients with longer culture conversion times. Furthermore, cavitary disease is associated with negative treatment outcomes, but is likely also contributing to the emergence of antibiotic resistance during therapy, and needs to be considered as confounding factor for any association between resistance and treatment outcome.

In conclusion, we show that bedaquiline resistance emerged among >15% of MTBC strains from MDR-TB patients with available bacterial isolates prior and during bedaquiline therapy. MDR-TB therapy with an insufficient number of active drugs and cavitary disease were considered as risk factors for treatment failure and death in this cohort. Availability of adequate treatment regimens based on information provided by comprehensive and timely genotypic and phenotypic DSTs will be key to improve treatment outcomes for patients with MDR-TB and to avoid drug-resistance evolution in circulating MDR-MTBC strains.

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Tables and Figures

Table 1

Patients with whole genome sequencing predicted bedaquiline resistant *Mycobacterium tuberculosis* complex isolates in the Republic of Moldova between 2016 and 2018

Patient no., (isolate ID), sampling time	**Rv0678 (mutation frequency %)**	**atpE (mutation frequency %)**	**BDQ MIC MGIT960 (mg/mL)**	**CFZ MIC MGIT960 (mg/mL)**
Patient29, (CAR-13), prior bedaquiline	wild type	wild type	≤0,5 (S)	≤0,5 (S)
Patient29, (CAR-38), after bedaquiline, acquired resistance	wild type	I66M# (97%)	>2,0	≤0,5 (S)
Patient12, (CAR-52), prior bedaquiline	wild type	wild type	≤0,5 (S)	≤0,5 (S)
Patient12, (CAR-61) after bedaquiline, acquired resistance	16_del_g (57.4%); 193_del_g# (12.7%); G24D (19.8%)	wild type	2.0	1.0 (S)
Patient2, (CAR-78), prior bedaquiline	wild type	wild type	≤0,5 (S)	≤0,5 (S)
Patient2, (CAR-87), after bedaquiline, acquired resistance	192insG# (2%)	A63P# (25%)	>2,0 (R)	2.0 (R)
Patient37, (CAR-10), prior bedaquiline	wild type	wild type	≤0,5 (S)	≤0,5 (S)
Patient37, (CAR-18), after bedaquiline, re-infection	T58P (100%)	wild type	2.0 (R)	1.0 (S)
Patient57, (CAR-45), prior bedaquiline	wild type	wild type	≤0,5 (S)	≤0,5 (S)
Patient57, (CAR-55), after bedaquiline, acquired resistance	193_del_g# (44.4%); S63G# (5.5%)	E61D# (27,5); I66M# (2,6%)	>2,0 (R)	1.0 (S)
Patient32, (CAR-84), after bedaquiline	192_ins_g# (74.2%); 193_del_g# (5.7%)	wild type	1.0 (S)	1.0 (S)
Patient71, (CAR-40), after bedaquiline	192ins_g# (23.8%); L142P (64%)	wild type	>2,0 (R)	2.0 (R)
Patient61, (CAR-1), after bedaquiline	136_ins_g (7,1%); 141_ins_c# (69,0%); 195_ins_t# (5,8%); G66W (6.0%)	wild type	>2,0 (R)	2.0 (R)
Patient33, (CAR-43), after bedaquiline	436_ins_t (90.2%); R72W (28.5%)	wild type	>2,0 (R)	>2,0 (R)

BDQ=bedaquiline, CFZ=clofazimine, MIC=minimum inhibitory concentration, R=resistant, S=susceptible, #mutation reviewed in [45].

Table 2

Univariate analysis of factors associated with negative treatment outcomes of bedaquiline-based multidrug resistant tuberculosis therapies

	Negative outcome (n=15)	% or median (i.e. for inactive drugs, age)	Positive outcome (n=37)	% or median (i.e. for inactive drugs, age)	OR	95% lower	95% upper	P-value
Lineage								
L2	8	53.3	20	48.6	REF			
L4	7	46.7	17	51.4	1.03	0.31	3.43	1.0
Gender								
Female	4	26.7	6	19.4	REF			
Male	11	73.3	31	83.8	0.53	0.13	2.25	0.448
Case								
New case	4	26.7	13	32.4	REF			
Previously treated	11	73.3	24	67.6	1.49	0.39	5.63	0.747
Resistance category								
not XDR*	6	40.0	18	35.1	REF			
XDR*	9	53.3	19	45.9	1.42	0.42	4.80	0.760
Cavitary								
No	0#	0.0	13#	32.4	REF			
Yes	15#	100.0	24#	67.6	17.08	0.95	308.6	**0.011***
HIV status								
Negative	11	73.3	34	91.9	REF			
Positive	4	26.7	3	8.1	4.12	0.80	21.34	0.173
Inactive drugs (n)		2		1	1.92	1.15	3.21	**0.012***
Age		35		41	0.97	0.90	1.04	0.427

Haldane-Anscombe correction adding 0,5 to each cell to allow calculation of odds ratio

*XDR=extensively drug-resistant (WHO classification until 2020), i.e. resistance against one fluoroquinolone and one second-line injectable drug, OR=odds ratio, HIV=human immunodeficiency virus

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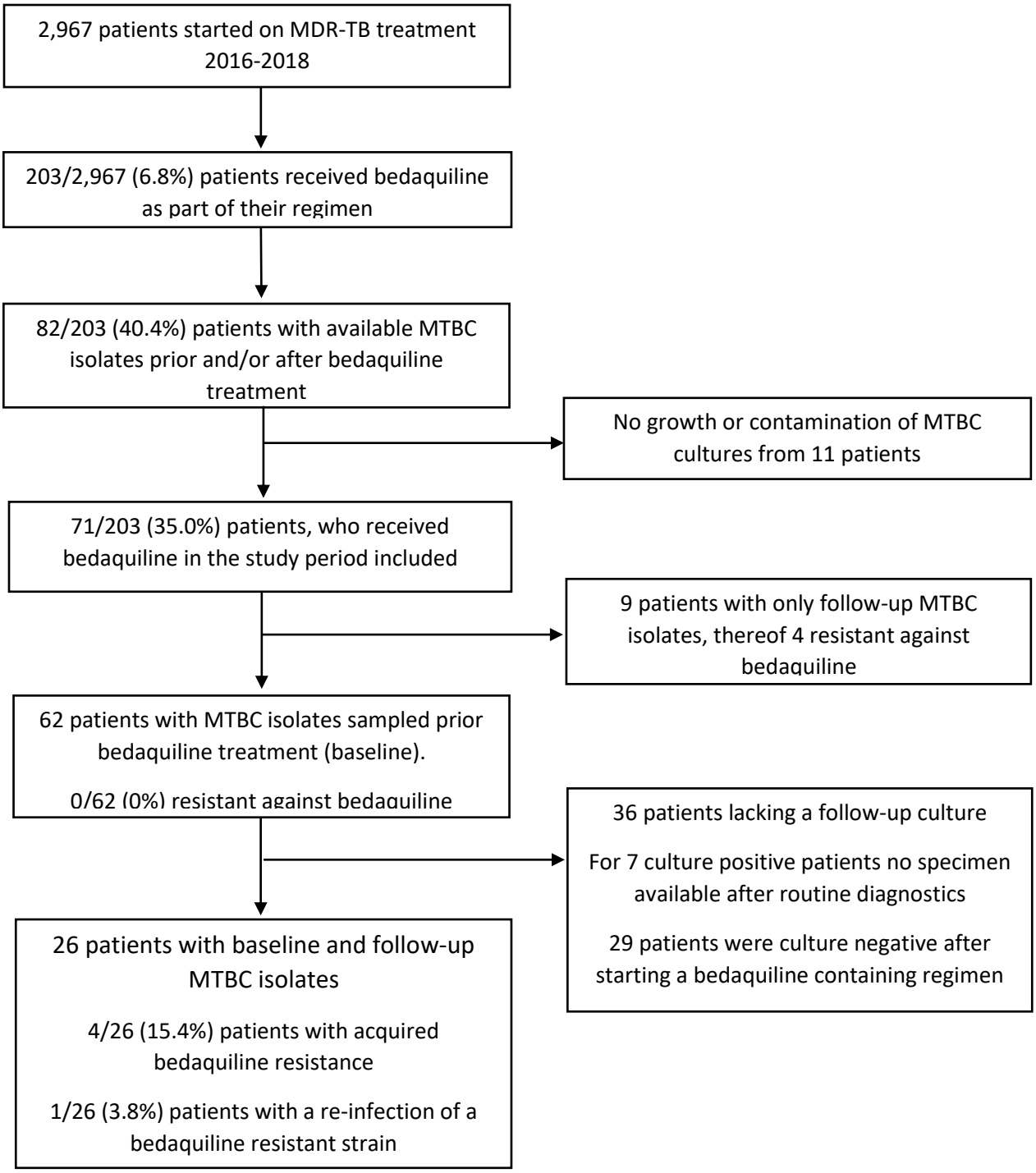
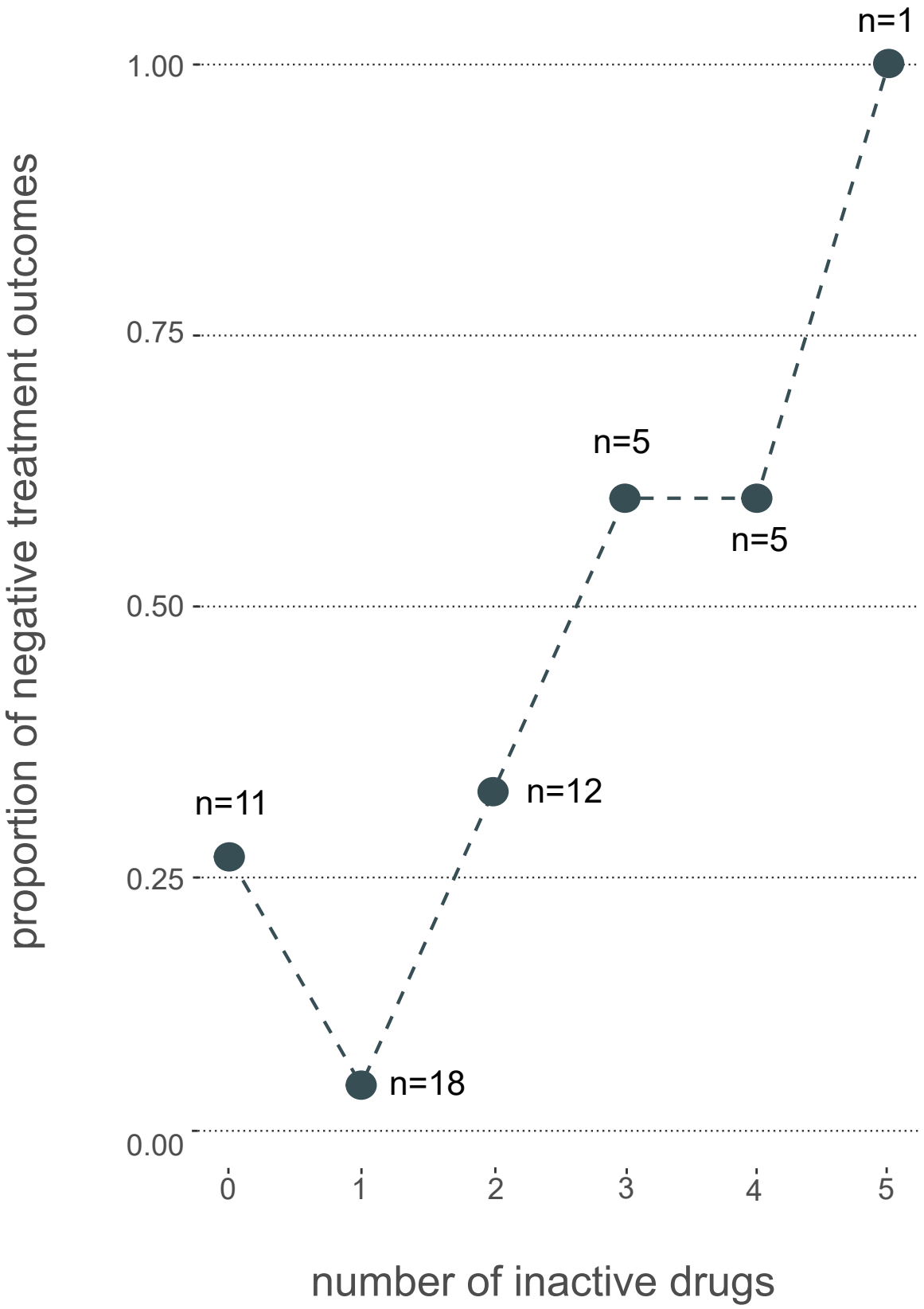
Figure 1



Study flow chart

MDR-TB=multidrug resistant tuberculosis, MTBC=*Mycobacterium tuberculosis* complex

Figure 2



Proportions of negative treatment outcomes, relative to the number of drugs used despite predicted resistance at baseline, for patients in the Republic of Moldova who received bedaquiline and at least four additional drugs as part of their multidrug resistant tuberculosis regimen (2016-2018). Numbers indicate patients per category.

Supplementary methods

Phenotypic antimicrobial susceptibility testing

Cultures from Lowenstein-Jensen medium, homogenized in 4.5 ml sterile water, and adjusted to McFarland standard 1.0 using optical density measurement, were transferred and grown in MGIT960 according to manufactured instructions (BD Microbiology systems, USA). The purity of the MGIT culture was checked by Ziehl–Neelsen stain, blood agar plate and MPT64 antigen rapid test (BD Microbiology systems, USA). A positive MGIT tube was used for DST up to and including the fifth day after incubation. 1.0 ml of the culture suspension was transferred to a container with 4.0 ml of sterile saline. 0.5 ml of 1:5 dilution of the test culture was used to inoculate in tubes containing the anti-TB agent 0.5-fold, 1-fold, and 2-fold of the current critical concentration of bedaquiline, clofazimine and linezolide, i.e. 1mg/L (WHO). The growth control in drug free medium was inoculated at 1:500. DST results were determined at the time the growth control tube displays >400 Growth Units (GU) between day 4 and day 13. The interpretation of the DST results was as follows: no growth in the drug vial "susceptible", 1-399 GU "intermediate", and >400 GU "resistant".

Isolation of genomic DNA

M. tuberculosis complex strains were inoculated on Löwenstein Jensen medium at 37 °C, until growth was clearly visible. Colonies were transferred to a microcentrifuge tube (2.0 ml) containing 400 µl TE buffer and heated for 20 min at 80°C to kill the bacteria. After 3 min centrifugation at 13,000 g we discarded the supernatant and added 400 µl TE-buffer, followed by vortexing to separate cells. We then added 50 µl lysozyme (10 mg/ml) vortexed briefly and incubated the solution overnight at 37 °C. The next day, we added 70 µl 10 % SDS, 5 µl proteinase K (10 mg/ml), vortexed softly and incubated the solution 10 min at 65 °C. Subsequently, we added 100 µl 5M NaCl, 100 µl CTAB/NaCl (pre-warmed at 65 °C), followed by vortexing and incubation for 10 min at 65° C. we then added 750 µl Chloroform/Isoamyalcohol mix (24:1?), inverted the tube few times and centrifuged at room temp for 15 min at 13,000 g. The aqueous supernatant was carefully transferred to a new microcentrifuge tube, and 0.6 volume isopropanol was added to precipitate the nucleic acids for 30 min at -20 °C (or longer). We then centrifuged for 10 min at room temperature at 13,000 g, discarded the supernatant, and washed the DNA in 0.5 ml of cold 75 % Ethanol while inverting the tube few times, followed by 5 min centrifugation at room temperature and discarding the supernatant cautiously. The DNA-pellet was dried at 60 °C for about 10 min, and DNA was eventually dissolved in 100 µl TE-buffer at 37 °C for 30 min or at room temperature until DNA was completely dissolved.

Rifampicin resistant tuberculosis treatment guidelines in the Republic of Moldova (2016-2018)

During the study, the treatment for MDR-TB patients in the Republic of Moldova was provided according to the National TB Treatment Protocol in accordance with the MDR-TB treatment guidelines of the WHO [1,2]. All patients initially started with a standardized regimen of five second-line TB drugs including a fluroquinolone (levofloxacin or moxifloxacin), a second-line injectable (capreomycin or amikacin), ethionamide, cycloserine and pyrazinamide). The standardized regimen was then adjusted, when necessary, once results of phenotypic drug susceptibility testing (DST) became available. The treatment duration was guided by the time of sputum culture conversion and consisted of an initial 6-8 months intensive phase followed by a continuation phase with a duration of 12-16 months.

Statistics

Patients with available baseline isolates and treatment outcomes were divided into two groups: positive treatment outcome (considered as cure, i.e. no signs of disease relapse (clinical or microbiological) up to 6 months after treatment completion) and negative treatment outcome (including death caused by TB or other causes, and treatment failure, i.e. no negative culture within 8 months of treatment). The following predictors for negative treatment outcome were analyzed: MTBC lineage, gender, case classification (new case, and previously treated), XDR (i.e. MDR with additional resistance against a fluoroquinolone and a second-line injectable drug; WHO classification until 12/2020), presence of cavities, HIV status, age, and number of drugs with predicted resistance at baseline that were included in the bedaquiline-based regimen, i.e. inactive drugs. Pairwise Fisher Exact tests were employed to compare differences between predictors with categorical variables and odds ratios were calculated for 2x2 contingency tables. For contingency tables with zero cell counts we used the Haldane-Anscombe correction by adding 0.5 to each cell. To compare predictors with continuous variables, i.e. age and number of inactive drugs, we employed logistic regression analysis. The difference between number of inactive drugs between patients with positive and negative treatment outcomes as well as patient age were compared with a Mann-Whitney-U test, as we did not assume a normal distribution ($P<0.001$, Shapiro-Wilk normality test). Pairwise comparisons of patients characteristics (included vs excluded patients) were performed with Fisher Exact tests.

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Pat.No	cohort	Days_BDQ	dataset	OrgID	BorstelID	Accession number	coll_lineag	neage_nam	eijing_linea	Gender	case	outcome	outcome simple	Cavitary	HIV	Age	*preXDR/XDR*	SNP_distance_follow-up	inactive_drugs	Bdq:100	Lzd:600	H:300	E:400	Z:400	Lfx:250/Mf	Km:1000	Cm:1000	Eto:250	PAS:4000	Cs:250	Clf:100	Imp_Amx/(	S:1000	Am:1000	Dlm:50
1	prior_BDQ	-83	table 2	6579	CAR-28	ERR4872280	4.2.1	Ural	not_Bejing	M	PTC-relaps	cured	POSITIVE	no	neg	41	XDR	NA	1	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
2	prior_after_BDQ	-16	table 2	5996	CAR-78	ERR4872337	2.2.1	Beijing	issian W14	M	PTC-failure	failure	NEGATIVE	yes	neg	34	XDR	3	2	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	Ps:4000	Cs:250	NA	NA	NA	NA	NA
2	prior_after_BDQ	348	follow-up	6282	CAR-87	ERR4872347	2.2.1	Beijing	issian W14	M	PTC-failure	failure	NEGATIVE	yes	neg	35	pre-XDR	3	2	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	Ps:4000	Cs:250	NA	NA	NA	NA	NA
3	prior_BDQ	-15	table 2	17691	CAR-77	ERR4872336	2.2.1	Beijing	Central Asi	F	new_case	cured	POSITIVE	yes	neg	38	MDR+	NA	2	Bdq:100	NA	H:300	E:400	Z:400	Lfx:250	NA	NA	Pto:250	NA	NA	NA	NA	NA	NA	NA
4	prior_after_BDQ	-11	table 2	13699	CAR-29	ERR4872283	4.2.1	Ural	not_Bejing	M	PTC-defaul	cured	POSITIVE	yes	neg	36	XDR	0	2	Bdq:100	Lzd:600	NA	E:400	NA	NA	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
4	prior_after_BDQ	78	follow-up	18104	CAR-44	ERR4872300	4.2.1	Ural	not_Bejing	M	PTC-defaul	cured	POSITIVE	yes	neg	36	XDR	0	2	Bdq:100	Lzd:600	NA	E:400	NA	NA	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
5	prior_BDQ	-147	table 2	10511	CAR-23	ERR4872275	4.2.1	Ural	not_Bejing	M	PTC-failure	failure	NEGATIVE	yes	neg	42	XDR	NA	2	Bdq:100	Lzd:600	H:300	NA	NA	NA	NA	Cm:1000	NA	Ps:4000	Cs:250	NA	Imp:500 A	NA	NA	NA
6	prior_BDQ	-21	table 2	C-5545	CAR-86	ERR4872346	2.2.1	Beijing	issian W14	M	new_case	cured	POSITIVE	no	neg	53	pre-XDR	NA	3	Bdq:100	NA	H:300	NA	Z:400	Lfx:250	Km:1000	NA	NA	NA	NA	NA	NA	NA	NA	NA
7	prior_BDQ	-40	table 2	11858	CAR-6	ERR4872328	2.2.1	Beijing	Central Asi	M	PTC-failure	failure	NEGATIVE	yes	neg	35	pre-XDR	NA	2	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	Ps:4000	Cs:250	NA	NA	NA	NA	NA
8	prior_BDQ	-63	table 2	8840	CAR-59	ERR4872316	4.2.1	Ural	not_Bejing	F	new_case	cured	POSITIVE	no	neg	36	XDR	NA	2	Bdq:100	Lzd:600	NA	E:400	Z:400	Lfx:250	NA	Cm:1000	Eto:250	NA	Cs:250	NA	NA	NA	NA	NA
9	prior_after_BDQ	-7	table 2	15261	CAR-20	ERR4872272	4.2.1	Ural	not_Bejing	M	PTC-failure	cured	POSITIVE	no	neg	25	XDR	0	4	Bdq:100	Lzd:600	NA	NA	Z:400	Mfx:400	NA	Cm:1000	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
9	prior_after_BDQ	21	follow-up	16933	CAR-42	ERR4872298	4.2.1	Ural	not_Bejing	M	PTC-failure	cured	POSITIVE	no	neg	25	XDR	0	4	Bdq:100	Lzd:600	NA	NA	Z:400	Mfx:400	NA	Cm:1000	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
10	prior_after_BDQ	-6	table 2	5650	CAR-72	ERR4872331	2.2.1	Beijing	Central Asi	M	PTC-failure	cured	POSITIVE	yes	neg	54	XDR	1118	0	Bdq:100	Lzd:600	NA	NA	Z:400	Lfx:250	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
10	prior_after_BDQ	38	follow-up	9191	CAR-34	ERR4872289	4.2.1	Ural	not_Bejing	M	PTC-failure	cured	POSITIVE	yes	neg	54	pre-XDR	1118	0	Bdq:100	Lzd:600	NA	NA	Z:400	Lfx:250	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
11	prior_BDQ	-212	table 2	4877	CAR-30	ERR4872285	4.2.1	Ural	not_Bejing	M	new_case	cured	POSITIVE	no	neg	45	pre-XDR	NA	0	Bdq:100	Lzd:600	NA	E:400	NA	Lfx:250	NA	NA	NA	NA	Cs:250	NA	NA	NA	NA	NA
12	prior_after_BDQ	-10	table 2	11299	CAR-52	ERR4872309	2.2.1	Beijing	issian W14	M	PTC-defaul	failure	NEGATIVE	yes	neg	35	pre-XDR	1	2	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
12	prior_after_BDQ	451	follow-up	14591	CAR-61	ERR4872319	2.2.1	Beijing	issian W14	M	PTC-defaul	failure	NEGATIVE	yes	neg	36	pre-XDR	1	2	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
13	prior_BDQ	-15	table 2	20592	CAR-46	ERR4872302	4.2.1	Ural	not_Bejing	F	new_case	cured	POSITIVE	yes	neg	29	pre-XDR	NA	2	Bdq:100	NA	H:300	E:400	Z:400	Lfx:250	NA	NA	Pto:250	NA	NA	NA	NA	NA	NA	NA
14	prior_after_BDQ	-55	table 2	6159	CAR-5	ERR4872317	2.2.1	Beijing	Central Asi	M	PTC-defaul	cured	POSITIVE	yes	neg	41	XDR	193	2	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	Ps:4000	Cs:250	NA	NA	NA	NA	NA
14	prior_after_BDQ	34	follow-up	1267	CAR-73	ERR4872332	2.2.1	Beijing	issian W14	M	PTC-defaul	cured	POSITIVE	yes	neg	41	XDR	193	2	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	Ps:4000	Cs:250	NA	NA	NA	NA	NA
15	prior_BDQ	-68	outcome_missing	10244	CAR-82	ERR4872342	2.2.1	Beijing	Central Asi	M	PTC-relaps	lost	NA	yes	neg	48	MDR+	NA	2	Bdq:100	NA	NA	NA	Z:400	NA	NA	NA	NA	Ps:4000	Cs:250	NA	NA	NA	NA	NA
16	prior_after_BDQ	-17	outcome_missing	14538	CAR-70	ERR4872329	4.2.1	Ural	not_Bejing	F	PTC-failure	lost	NA	yes	neg	35	XDR	0	0	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
16	prior_after_BDQ	9	follow-up	15530	CAR-54	ERR4872311	4.2.1	Ural	not_Bejing	F	PTC-failure	lost	NA	yes	neg	35	XDR	0	0	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
17	after_BDQ	53	only_follow-up	1658	CAR-76	ERR4872335	2.2.1	Beijing	Central Asi	M	PTC-failure	failure	NEGATIVE	no	neg	43	pre-XDR	NA	1	Bdq:100	NA	NA	NA	Z:400	Mfx:400	NA	NA	NA	NA	Cs:250	NA	Imp:500 A	NA	Am:1000	NA
18	prior_BDQ	-12	table 2	18762	CAR-47	ERR4872303	2.2.1	Beijing	issian W14	F	PTC-failure	failure	NEGATIVE	yes	neg	30	XDR	NA	4	Bdq:100	Lzd:600	NA	E:400	Z:400	NA	NA	NA	NA	Ps:4000	Cs:250	NA	Imp:500 A	NA	NA	NA
19	prior_BDQ	-42	table 2	1311	CAR-94	ERR4872355	2.2.1	Beijing	issian W14	M	new_case	cured	POSITIVE	no	neg	54	pre-XDR	NA	1	Bdq:100	Lzd:600	NA	NA	Z:400	Lfx:250	NA	NA	NA	NA	Cs:250	NA	NA	NA	NA	NA
20	after_BDQ	356	only_follow-up	B-74	CAR-71	ERR4872330	4.2.1	Ural	not_Bejing	M	PTC-failure	failure	NEGATIVE	yes	neg	35	pre-XDR	NA	1	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	NA	Eto:250	NA	NA	NA	Imp:500 A	NA	NA	NA
21	prior_after_BDQ	-15	table 2	13626	CAR-9	ERR4872357	2.2.1	Beijing	ral Asia out	M	new_case	cured	POSITIVE	yes	neg	41	MDR+	2	1	Bdq:100	NA	H:200	NA	Z:400	Lfx:250	Km:1000	NA	NA	NA	NA	Clf:100	NA	NA	NA	NA
21	prior_after_BDQ	12	follow-up	14764	CAR-68	ERR4872326	2.2.1	Beijing	ral Asia out	M	new_case	cured	POSITIVE	yes	neg	41	MDR+	2	1	Bdq:100	NA	H:200	NA	Z:400	Lfx:250	Km:1000	NA	NA	NA	NA	Clf:100	NA	NA	NA	NA
22	prior_BDQ	-74	table 2	11055	CAR-39	ERR4872294	4.2.1	Ural	not_Bejing	M	new_case	cured	POSITIVE	no	neg	50	XDR	NA	1	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	Eto:250	NA	Cs:250	NA	NA	NA	NA	NA
23	prior_BDQ	-8	table 2	22164	CAR-48	ERR4872304	2.2.1	Beijing	Central Asi	M	new_case	cured	POSITIVE	yes	neg	34	MDR+	NA	1	Bdq:100	NA	H:300	NA	Z:500	Lfx:250	Km:1000	NA	NA	NA	NA	NA	NA	NA	NA	NA
24	prior_after_BDQ	-262	table 2	9345	CAR-58	ERR4872315	2.2.1	Beijing	Central Asi	M	PTC-failure	cured	POSITIVE	no	neg	25	pre-XDR	1	1	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
24	prior_after_BDQ	54	follow-up	6419	CAR-93	ERR4872354	2.2.1	Beijing	Central Asi	M	PTC-failure	cured	POSITIVE	no	neg	25	pre-XDR	1	1	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
25	prior_BDQ	-90	outcome_missing	6714	CAR-19	ERR4872270	2.2.1	Beijing	ral Asia out	M	new_case	lost	NA	yes	neg	35	MDR+	NA	0	Bdq:100	Lzd:600	NA	NA	NA	Lfx:250	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
26	prior_after_BDQ	-10	table 2	13880	CAR-81	ERR4872341	4.2.1	Ural	not_Bejing	M	PTC-relaps	cured	POSITIVE	yes	neg	47	pre-XDR	0	0	Bdq:100	NA	NA	NA	Z:400	Lfx:250	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
26	prior_after_BDQ	46	follow-up	16612	CAR-14	ERR4872265	4.2.1	Ural	not_Bejing	M	PTC-relaps	cured	POSITIVE	yes	neg	47	pre-XDR	0	0	Bdq:100	NA	NA	NA	Z:400	Lfx:250	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
27	prior_after_BDQ	-48	table 2	60	CAR-291	ERR4872281	2.2.1	Beijing	Central Asi	M	PTC-defaul	cured	POSITIVE	yes	neg	32	pre-XDR	0	1	Bdq:100	Lzd:600	NA	NA	Z:400	Lfx:250	NA	NA	NA	Ps:4000	Cs:250	NA	Imp:500 A	NA	NA	NA
27	prior_after_BDQ	23	follow-up	1805	CAR-15	ERR4872266	2.2.1	Beijing	Central Asi	M	PTC-defaul	cured	POSITIVE	yes	neg	32	pre-XDR	0	1	Bdq:100	Lzd:600	NA	NA	Z:400	Lfx:250	NA	NA	NA	Ps:4000	Cs:250	NA	Imp:500 A	NA	NA	NA
28	prior_BDQ	-36	table 2	15173	CAR-21	ERR4872273	4.2.1	Ural	not_Bejing	M	PTC-failure	cured	POSITIVE	yes	neg	45	MDR+	NA	4	Bdq:100	NA	H:300	E:400	Z:500	Lfx:250	NA	NA	Pto:250	NA	NA	Clf:100	NA	NA	NA	NA
29	prior_after_BDQ	-2	table 2	22369	CAR-13	ERR4872264	2.2.1	Beijing	ral Asia out	M	PTC-failure	ath_due_to	NEGATIVE	yes	pos	31	XDR	1	5	Bdq:100	Lzd:600	NA	NA	Z:400	Mfx:400	NA	NA	NA	Ps:4000	Cs:250	NA	NA	NA	NA	NA
29	prior_after_BDQ	159	follow-up	9296	CAR-38	ERR4872293	2.2.1	Beijing	ral Asia out	M	PTC-failure	ath_due_to	NEGATIVE	yes	pos	31	XDR	1	5	Bdq:100	Lzd:600	NA	NA	Z:400	Mfx:400	NA	NA	NA	Ps:4000	Cs:250	NA	NA	NA	NA	NA
30	after_BDQ	22	only_follow-up	17981	CAR-4	ERR4872306	4.2.1	Ural	not_Bejing	F	PTC-relaps	lost	NA	yes	neg	31	XDR	NA	0	Bdq:100	Lzd:600	NA	NA	NA	NA	NA	NA	NA	Ps:4000	Cs:250	NA	Imp:500 A	NA	NA	NA
31	prior_BDQ	-107	table 2	19365	CAR-31	ERR4872286	4.2.1	Ural	not_Bejing	M	PTC-relaps	failure	NEGATIVE	yes	neg	55	XDR	NA	0	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	Ps:4000	Cs:250	NA	Imp:500 A	NA	NA	NA
32	after_BDQ	287	only_follow-up	B-423	CAR-84	ERR4872344	2.2.1	Beijing	ral Asia out	F	PTC-failure	cured	POSITIVE	yes	neg	27	XDR	NA	3	Bdq:100	Lzd:600	NA	NA	Z:400	Lfx:250	NA	NA	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
33	after_BDQ	236	only_follow-up	345	CAR-43	ERR4872299	4.2.1	Ural	not_Bejing	M	PTC-failure	failure	NEGATIVE	yes	neg	37	XDR	NA	4	Bdq:100	Lzd:600	NA	NA	Z:400	Mfx:400	NA	NA	NA	Ps:4000	Cs:250	Clf:100	Imp:500 A	NA	NA	NA
34	prior_after_BDQ	-340	table 2	22388	CAR-79	ERR4872338	2.2.1	Beijing	issian W14	M	new_case	cured	POSITIVE	yes	neg	48	XDR	1126	0	Bdq:100	Lzd:600	NA	NA	Z:400	Mfx:400	NA	NA	NA	NA	Cs:250	NA	NA	NA	NA	NA
34	prior_after_BDQ	29	follow-up	19304	CAR-32	ERR4872287	4.9	H37Rv-like	not_Bejing	M	new_case	cured	POSITIVE	yes	neg	49	MDR+	1126	0	Bdq:100	Lzd:600	NA	NA	Z:400	Mfx:400	NA	NA	NA	NA	Cs:250	NA	NA	NA	NA	NA
35	prior_after_BDQ	-127	table 2	8738	CAR-89	ERR4872349	2.2.1	Beijing	issian W14	M	PTC-failure	cured	POSITIVE	yes	neg	37	XDR	2	1	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
35	prior_after_BDQ	61	follow-up	21776	CAR-22	ERR4872274	2.2.1	Beijing	issian W14	M	PTC-failure	cured	POSITIVE	yes	neg	38	XDR	2	1	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
36	prior_BDQ	-135	table 2	10418	CAR-26	ERR4872278	4.2.1	Ural	not_Bejing	M	PTC-relaps	cured	POSITIVE	no	neg	44	XDR	NA	0	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
37	prior_after_BDQ	-223	table 2	B-1898	CAR-10	ERR4872261	2.2.1	Beijing	issian W14	M	PTC-failure	failure	NEGATIVE	yes	pos	31	XDR	26	4	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	NA	Eto:250	Ps:4000	Cs:250	NA	NA	NA	NA	NA
37	prior_after_BDQ	459	follow-up	B-1687	CAR-18	ERR4872269	2.2.1	Beijing	issian W14	M	PTC-failure	failure	NEGATIVE	yes	pos	33	XDR	26	4	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	NA	Eto:250	Ps:4000	Cs:250	NA	NA	NA	NA	NA
38	prior_after_BDQ	-71	table 2	B-3929	CAR-49	ERR4872305	2.2.1	Beijing	Central Asi	M	PTC-failure	cured	POSITIVE	yes	pos	40	XDR	3	1	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	NA	NA	NA	Cs:250	NA	NA	NA	NA	NA
38	prior_after_BDQ	97	follow-up	B-437	CAR-75	ERR4872334	2.2.1	Beijing	Central Asi	M	PTC-failure	cured	POSITIVE	yes	pos	40	XDR	3	1	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	NA	NA	NA	Cs:250	NA	NA	NA	NA	NA
39	prior_BDQ	-275	outcome_missing	7687	CAR-41	ERR4872297	4.3.3	LAM	not_Bejing	M	PTC-failure	lost	NA	no	pos	39	XDR	NA	1	Bdq:100	Lzd:600	NA	NA	NA	NA	NA	NA	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
40	prior_after_BDQ	-28	table 2	1891	CAR-88	ERR4872348	2.2.1	Beijing	unknown	F	PTC-failure	cured	POSITIVE	yes	neg	29	pre-XDR	1	1	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
40	prior_after_BDQ	124	follow-up	11674	CAR-95	ERR4872356	2.2.1	Beijing	unknown	F	PTC-failure	cured	POSITIVE	yes	neg	30	pre-XDR	1	1	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
41	prior_after_BDQ	-96	table 2	3480	CAR-25	ERR4872277	2.2.1	Beijing	Central Asi	F	new_case	failure	NEGATIVE	yes	neg	41	XDR	0	3	Bdq:100	Lzd:600	NA	NA	Z:400	Lfx:250	Km:1000	NA	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
41	prior_after_BDQ	398	follow-up	6326	CAR-62	ERR4872320	2.2.1	Beijing	Central Asi	F	new_case	failure	NEGATIVE	yes	neg	42	XDR	0	3	Bdq:100	Lzd:600	NA	NA	Z:400	Lfx:250	Km:1000	NA	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
42	prior_BDQ	-90	table 2	18729	CAR-7	ERR4872339	4.2.1	Ural	not_Bejing	F	PTC-failure	failure	NEGATIVE	yes	pos	33	XDR	NA	4	Bdq:100	Lzd:600	H:300	NA	Z:400	NA	NA	Cm:1000	NA	Ps:4000	Cs:250	NA	Imp:500 A	NA	Am:500	NA
43	prior_after_BDQ	-328	table 2	22225	CAR-12	ERR4872263	4.2.1	Ural	not_Bejing	F	PTC-defaul	failure	NEGATIVE	yes	neg	48	XDR	2	3	Bdq:100	NA	NA	E:400	Z:400	Mfx:400	NA	Cm:1000	Eto:250	NA	NA	NA	Imp:500 A	NA	NA	NA
43	prior_after_BDQ	25	follow-up	18057	CAR-24	ERR4872276	4.2.1	Ural	not_Bejing	F	PTC-defaul	failure	NEGATIVE	yes	neg	49	XDR	2	3	Bdq:100	NA	NA	E:400	Z:400	Mfx:400	NA	Cm:1000	Eto:250	NA	NA	NA	Imp:500 A	NA	NA	NA
44	prior_BDQ	-231	table 2	4162	CAR-60	ERR4872318	4.2.1	Ural	not_Bejing	M	PTC-relaps	cured	POSITIVE	yes	neg	47	XDR	NA	0	Bdq:100	Lzd:600	NA	NA	NA	NA	NA	NA	NA	Ps:4000	Cs:250	NA	NA	NA	NA	Dlm:50
45	prior_BDQ	-81	table 2	11062	CAR-51	ERR4872308	4.2.1	Ural	not_Bejing	M	new_case	cured	POSITIVE	yes	neg	58	pre-XDR	NA	1	Bdq:100	Lzd:600	NA	E:400	Z:400	Lfx:250	NA	Cm:1000	Eto:250	NA	Cs:250	NA	NA	NA	NA	NA
46	prior_BDQ	-310	table 2	6576	CAR-65	ERR4872323	4.3.3	LAM	not_Bejing	M	PTC-failure	cured	POSITIVE	yes	neg	55	XDR	NA	3	Bdq:100	Lzd:600	NA	NA	Z:400	Mfx:400	NA	NA	NA	Ps:4000	Cs:250	NA	Imp:500 A	NA	NA	NA
47	prior_BDQ	-38	table 2	17598	CAR-57	ERR4872314	2.2.1	Beijing	issian W14	M	PTC-relaps	cured	POSITIVE	no	neg	40	XDR	NA	2	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	Ps:4000	NA	NA	NA	NA	NA	Dlm:50
48	prior_after_BDQ	-248	table 2	6967	CAR-53	ERR4872310	4.2.1	Ural	not_Bejing	F	PTC-failure	cured	POSITIVE	yes	neg	52	pre-XDR	0	0	Bdq:100	Lzd:600	NA	NA	NA	Lfx:250	NA	Cm:1000	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
48	prior_after_BDQ	10	follow-up	23440	CAR-33	ERR4872288	4.2.1	Ural	not_Bejing	F	PTC-failure	cured	POSITIVE	yes	neg	53	pre-XDR	0	0	Bdq:100	Lzd:600	NA	NA	NA	Lfx:250	NA	Cm:1000	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
49	prior_BDQ	-119	outcome_missing	4978	CAR-63	ERR4872321	4.2.1	Ural	not_Bejing	M	PTC-defaul	_on_treatm	NA	no	neg	44	pre-XDR	NA	1	Bdq:100	Lzd:600	NA	NA	Z:400	Lfx:250	NA	Cm:1000	Eto:250	Ps:4000	Cs:250	NA	NA	NA	NA	NA
50	prior_BDQ	-104	table 2	19390	CAR-50	ERR4872307	4.2.1	Ural	not_Bejing	M	new_case	cured	POSITIVE	yes	neg	39	pre-XDR	NA	0	Bdq:100	Lzd:600	NA	NA	NA	Mfx:400	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
51	prior_after_BDQ	-123	table 2	B-4450	CAR-35	ERR4872290	2.2.1	Beijing	issian W14	M	PTC-failure	cured	POSITIVE	no	neg	38	MDR+	1	1	Bdq:100	Lzd:600	NA	NA	Z:400	Lfx:250	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
51	prior_after_BDQ	51	follow-up	B-1127	CAR-2	ERR4872284	2.2.1	Beijing	issian W14	M	PTC-failure	cured	POSITIVE	yes	neg	38	MDR+	1	1	Bdq:100	Lzd:600	NA	NA	Z:400	Lfx:250	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
52	after_BDQ	300	only_follow-up	14146	CAR-67	ERR4872325	2.2.1	Beijing	Central Asi	F	PTC-failure	ath_due_to	NEGATIVE	yes	neg	28	pre-XDR	NA	4	Bdq:100	Lzd:600	H:300	NA	Z:500	Mfx:400	NA	Cm:1000	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
53	prior_BDQ	-71	table 2	20807	CAR-80	ERR4872340	4.2.1	Ural	not_Bejing	M	new_case	failure	NEGATIVE	yes	neg	50	pre-XDR	NA	0	Bdq:100	Lzd:600	NA	E:400	NA	Lfx:250	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
54	prior_after_BDQ	-25	outcome_missing	13077	CAR-83	ERR4872343	2.2.1	Beijing	ral Asia out	M	PTC-defaul	lost	NA	no	neg	38	pre-XDR	0	3	Bdq:100	Lzd:600	NA	E:400	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
54	prior_after_BDQ	4	follow-up	14454	CAR-56	ERR4872313	2.2.1	Beijing	ral Asia out	M	PTC-defaul	lost	NA	no	neg	38	pre-XDR	0	3	Bdq:100	Lzd:600	NA	E:400	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
55	prior_BDQ	-171	table 2	12473	CAR-16	ERR4872267	4.2.1	Ural	not_Bejing	M	new_case	_to_the_ot	NEGATIVE	yes	neg	40	pre-XDR	NA	0	Bdq:100	Lzd:600	NA	NA	Z:400	Lfx:250	NA	Cm:1000	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
56	prior_after_BDQ	-449	table 2	B-1713	CAR-8	ERR4872350	2.2.1	Beijing	issian W14	M	PTC-failure	cured	POSITIVE	yes	neg	39	XDR	1	2	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
56	prior_after_BDQ	103	follow-up	B-5545	CAR-64	ERR4872322	2.2.1	Beijing	issian W14	M	PTC-failure	cured	POSITIVE	yes	neg	41	XDR	1	2	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
57	prior_after_BDQ	-92	table 2	6116	CAR-45	ERR4872301	2.2.1	Beijing	Central Asi	M	PTC-defaul	failure	NEGATIVE	yes	pos	29	pre-XDR	0	3	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	NA	Eto:250	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
57	prior_after_BDQ	90	follow-up	3024	CAR-55	ERR4872312	2.2.1	Beijing	Central Asi	M	PTC-defaul	failure	NEGATIVE	yes	pos	30	MDR+	0	3	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	NA	Eto:250	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
58	prior_BDQ	-131	outcome_missing	2880	CAR-37	ERR4872292	2.2.1	Beijing	Central Asi	F	PTC-failure	lost	NA	yes	neg	29	MDR+	NA	2	Bdq:100	Lzd:600	H:300	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
59	prior_BDQ	-181	table 2	14046	CAR-92	ERR4872353	2.2.1	Beijing	Central Asi	F	PTC-failure	cured	POSITIVE	yes	neg	39	XDR	NA	1	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	Ps:4000	Cs:250	NA	Imp:500 A	NA	NA	NA
60	after_BDQ	14	only_follow-up	20166	CAR-3	ERR4872295	2.2.1	Beijing	issian W14	F	PTC-failure	failure	NEGATIVE	yes	neg	34	XDR	NA	5	Bdq:100	Lzd:600	H:300	NA	Z:400	Mfx:400	NA	NA	NA	Ps:4000	Cs:250	NA	Imp:500 A	NA	NA	NA
61	after_BDQ	77	only_follow-up	18795	CAR-1	ERR4872271	2.2.1	Beijing	Central Asi	M	PTC-failure	lost	NA	yes	pos	34	pre-XDR	NA	3	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	Ps:4000	Cs:250	NA	NA	NA	NA	NA
62	prior_BDQ	-11	table 2	24091	CAR-69	ERR4872327	4.2.1	Ural	not_Bejing	M	PTC-failure	cured	POSITIVE	no	pos	42	XDR	NA	1	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
63	prior_BDQ	-41	table 2	13442	CAR-91	ERR4872352	4.2.1	Ural	not_Bejing	M	PTC-failure	cured	POSITIVE	yes	pos	37	XDR	NA	1	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
64	prior_BDQ	-6	table 2	16610	CAR-27	ERR4872279	2.2.1	Beijing	ral Asia out	M	PTC-defaul	cured	POSITIVE	yes	neg	34	pre-XDR	NA	1	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	Cm:1000	NA	NA	Cs:250	NA	Imp:500 A	NA	NA	NA
65	prior_BDQ	-84	outcome_missing	20104	CAR-66	ERR4872324	2.2.1	Beijing	Central Asi	M	new_case	_on_treatm	NA	no	neg	33	XDR	NA	1	Bdq:100	Lzd:600	NA	NA	NA	NA	NA	NA	NA	Ps:4000	Cs:250	NA	Imp:500 A	NA	NA	NA
66	prior_BDQ	-72	outcome_missing	20107	CAR-74	ERR4872333	2.2.1	Beijing	Central Asi	M	PTC-defaul	_on_treatm	NA	yes	neg	31	MDR+	NA	0	Bdq:100	Lzd:600	NA	NA	Z:400	Lfx:250	NA	Cm:1000	Eto:250	NA	Cs:250	NA	NA	NA	NA	NA
67	prior_BDQ	-147	table 2	22930	CAR-85	ERR4872345	2.2.1	Beijing	issian W14	M	PTC-relaps	cured	POSITIVE	yes	neg	45	MDR+	NA	1	Bdq:100	Lzd:600	NA	NA	Z:400	Lfx:250	NA	Cm:1000	NA	Ps:4000	Cs:250	NA	NA	NA	NA	NA
68	prior_after_BDQ	-9	outcome_missing	20035	CAR-17	ERR4872268	2.2.1	Beijing	Central Asi	M	PTC-defaul	_on_treatm	NA	yes	neg	37	MDR+	2	0	Bdq:100	Lzd:600	NA	NA	NA	Lfx:250	NA	Cm:1000	NA	NA	Cs:250	Clf:100	Imp:500 A	NA	NA	NA
68	prior_after_BDQ	26	follow-up	505	CAR-295	ERR4872282	2.2.1	Beijing	Central Asi	M	PTC-defaul	_on_treatm	NA	yes	neg	37	MDR+	2	0	Bdq:100	Lzd:600	NA	NA	NA	Lfx:250	NA	Cm:1000	NA	NA	Cs:250	Clf:100	Imp:500 A	NA	NA	NA
69	prior_after_BDQ	-149	table 2	8380	CAR-90	ERR4872351	2.2.1	Beijing	Central Asi	M	PTC-failure	cured	POSITIVE	no	neg	42	XDR	4	2	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	NA	NA	NA	Cs:250	NA	NA	NA	NA	NA
69	prior_after_BDQ	19	follow-up	19981	CAR-11	ERR4872262	2.2.1	Beijing	Central Asi	M	PTC-failure	cured	POSITIVE	no	neg	43	XDR	4	2	Bdq:100	Lzd:600	NA	NA	Z:400	NA	NA	NA	NA	NA	Cs:250	NA	NA	NA	NA	NA
70	prior_BDQ	-74	table 2	11482	CAR-36	ERR4872291	4.2.1	Ural	not_Bejing	M	new_case	ath_due_to	NEGATIVE	yes	neg	56	pre-XDR	NA	1	Bdq:100	NA	NA	NA	Z:400	Lfx:250	NA	Cm:1000	NA	NA	Cs:250	NA	NA	NA	NA	NA
71	after_BDQ	132	only_follow-up	7995	CAR-40	ERR4872296	2.2.1	Beijing	ral Asia out	M	PTC-failure	failure	NEGATIVE	yes	neg	47	pre-XDR	NA	4	Bdq:100	Lzd:600	NA	NA	Z:400	Lfx:250	NA	NA	Eto:250	NA	Cs:250	NA	Imp:500 A	NA	NA	NA

R:300	BDQ_pheno_0.5	BDQ_pheno_1.0	BDQ_pheno_2.0	CFZ_pheno_0.5	CFZ_pheno_1.0	CFZ_pheno_2.0	BDQ_geno	CFZ_geno	Rv0678 (%) mmpR	Rv0678 protein	mmpL5 (%)	mmpL5 protein	mmpS5 (%)	mmpS5 protein	atpE (%)	atpE protein	pepQ (%)	LZD_pheno_0.5	LZD_pheno_1.0	LZD_pheno_2.0	LZD geno	rplC (%)	rplC protein	rrl (%) Rvnr02	H_pheno_0.1	H_geno	katG	fabG1	inhA	R_pheno_1.0	R_geno	rpoB_complete	S_pheno_5.0 LI	S_geno	rrs	rpsL	E_pheno_5.0	E_geno	embB	embA
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I88R (aag/a	S	S	97A (tcg/G	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	1401a>g	I3R (aag/a	R	R	196H (aat/C	-16c>t
NA	R	R	R	R	S	R	R	R	92ins_g (29	S64fs	WT	WT	WT	WT	.87g>c (259	53P (gca/Cc	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	R	R	196H (aat/C	-16c>t
NA	S	S	S	S	S	S	S	S	WT	WT	I35a>g (83	35ST (atg/a	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	L430P (ctg/cCg	R	R	WT	I8R (aag/a	S	R	306I (atg/a	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	cg/tTg); H835R	NA	R	WT	I8R (aag/a	R	R	197R (cag/c	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	cg/tTg); H835R	NA	R	WT	I8R (aag/a	R	R	197R (cag/c	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	R	R	R	R	i60T>C (739	154R (tgt/C	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I8R (aag/a	R	R	97A (tcg/G	-16c>t
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I8R (aag/a	R	R	306V (atg/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	34T>C (100	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I3R (aag/a	R	R	06D (ggc/g	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I8R (aag/a	S	S	97A (tcg/G	WT
NA	S	S	S	R	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	46G>A (54	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I8R (aag/a	R	R	97A (tcg/G	-8c>g
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	R	R	R	R	WT	WT	46G>A (99	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I8R (aag/a	NA	R	97A (tcg/G	-8c>g
NA	S	S	S	S	S	S	S	S	WT	WT	100%) 326	523F (ctc/TT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I8R (aag/a	S	S	97A (tcg/G	WT
NA	R	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	R	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I8R (aag/a	S	S	97A (tcg/G	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	S	S	54A (gac/g	WT
NA	R	R	S	R	S	S	S	R	3_del_g (1	4fs, G24D (	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	R	R	54A (gac/g	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	cg/tTg); H835R	NA	R	WT	I8R (aag/a	S	S	WT	WT
NA	S	S	S	S	S	S	S	S	WT	WT	!397t>g (5	67D (gaa/g	WT	WT	WT	WT	WT	R	R	R	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	R	R	306V (atg/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	R	R	R	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	1401a>g	I3R (aag/a	R	R	306I (atg/a	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	cg/tTg); I488V	NA	R	WT	I3R (aag/a	S	R	306I (atg/a	-12c>t
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I8R (aag/a	R	S	97A (tcg/G	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I8R (aag/a	R	S	97A (tcg/G	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	41g>c (100	27S (acc/ac	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a | WT | WT | R | R | cg/tTg); I488V (	NA	R	WT	I3R (aag/a	NA	R	306I (atg/a	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	R	R	R	R	WT	WT	14G>T (100	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	NA	R	1401a>g	I3R (aag/a	S	R	54A (gac/g	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	1401a>g	I3R (aag/a	R	R	306V (atg/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	031g>a (42	23F (ctc/TT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I8R (aag/a	R	S	97A (tcg/G	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I8R (aag/a	S	R	WT	-8c>a
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	S	R	WT	-8c>a
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I8R (aag/a	S	R	97A (tcg/G	-16c>t
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	34T>C (100	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	S	S	WT	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	cg/tTg); I488V (	NA	R	WT	I3R (aag/a	NA	R	306I (atg/a	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	cg/tTg); I488V (	R	R	WT	I3R (aag/a	R	R	306I (atg/a	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I3R (aag/a	R	R	306V (atg/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I8R (aag/a	S	S	97A (tcg/G	WT
NA	R	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	R	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I8R (aag/a	R	S	97A (tcg/G	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	94T (atc/aC	R	R	H445D (cac/Gac	R	R	514a>c	WT	R	S	176V (ttc/G	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	WT	-15c>t	94T (atc/aC	R	R	H445D (cac/Gac	R	R	517c>t	WT	R	S	76V (ttc/GT	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	!03L (ctg/ct	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I8R (aag/a	R	R	gCc); D102	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	R	R	R	R	WT	WT	100%); 281	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	1401a>g	I3R (aag/a	R	R	06A (ggc/g	-8c>a
NA	R	R	S	S	S	S	R	S	WT	WT	WT	WT	WT	WT	.98c>g (97	6M (atc/at	WT	R	R	R	R	WT	WT	98%); 281	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	NA	R	1401a>g	I3R (aag/a	R	R	06A (ggc/g	-8c>a
NA	R	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I8R (aag/a	S	R	97A (tcg/G	-12c>t
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	R	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I8R (aag/a	R	R	97A (tcg/G	-16c>t
NA	R	S	S	R	S	S	R	R	4.2%); 193	S64fs	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	H445Y (cac/Tac	R	R	1401a>g	I3R (aag/a	R	R	197R (cag/c	WT
NA	R	R	R	R	R	R	R	R	5%); 436	irf2W (cgg/Tg	WT	WT	WT	WT	WT	WT	WT	R	R	R	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I8R (aag/a	S	S	icg) F176V	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	1401a>g	I3R (aag/a	R	R	306V (atg/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	R	S	S	S	WT	WT	WT	R	S	WT	WT	WT	R	S	WT	NA	S	WT	WT	R	S	WT	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	S	S	319S (tat/tC	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	S	S	319S (tat/tC	WT
NA	R	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I8R (aag/a	S	R	97A (tcg/G	-16c>t
NA	R	R	S	R	S	S	S	R	72a>c (100	58P (acg/Cc	WT	WT	WT	WT	WT	WT	WT	R	R	R	R	50T>C (100	154R (tgt/C	WT	R	R	15T (agc/a	WT	WT	R	R	;/aTc); G1041G	R	R	1401a>g	I3R (aag/a	R	S	196H (aat/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	1401a>g	I3R (aag/a	R	R	306V (atg/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	(92%); 148	I3R (aag/a	R	R	306V (atg/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	R	R	R	R	50T>C (100	154R (tgt/C	WT	R	R	15T (agc/a	-15c>t	WT	R	R	D435V (gac/gTc	NA	R	1a>c; 1401a	WT	S	R	306I (atg/a	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	S	R	306V (atg/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	NA	R	306V (atg/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	1401a>g	I3R (aag/a	R	R	306V (atg/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	1401a>g	I3R (aag/a	R	R	306V (atg/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I8R (aag/a	S	R	97A (tcg/G	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I8R (aag/a	S	R	97A (tcg/G	-16c>t
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I8R (aag/a	S	S	97A (tcg/G	-16c>t
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I8R (aag/a	S	S	97A (tcg/G	WT
NA	R	S	S	S	S	S	S	R	WT	WT	WT	WT	WT	WT	WT	WT	WT	R	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I8R (aag/a	S	S	97A (tcg/G	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	R	S	196H (aat/C	WT
NA	R	S	S	S	S	S	S	R	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	R	S	196H (aat/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	R	R	R	R	50T>C (100	154R (tgt/C	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I8R (aag/a	R	R	34H (tac/C	-12c>t
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I8R (aag/a	S	S	97A (tcg/G	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I3R (aag/a	R	R	06A (ggc/g	-8c>a
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I3R (aag/a	NA	R	06A (ggc/g	-8c>a
NA	S	S	S	R	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I8R (aag/a	S	S	97A (tcg/G	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	R	R	196H (aat/C	-12c>t
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	tg/tTa); H445N	R	R	484g>t (58	I3R (aag/a	R	R	196H (aat/C	-12c>t
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	R	R	R	R	i60T>C (929	154R (tgt/C	WT	R	R	WT	-15c>t	94T (atc/aC	R	R	H445D (cac/Gac	R	R	; 1401a>g;	WT	R	S	WT	WT
NA	R	R	R	R	S	S	R	R	44.4%); 18	563G (agc	WT	WT	WT	WT	7,5%); 198	/gaC); I66A	WT	R	R	R	R	i60T>C (949	154R (tgt/C	WT	R	R	WT	-15c>t	94T (atc/aC	R	R	H445D (cac/Gac	R	R	4a>c; 1401	WT	R	S	WT	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	R	R	R	R	I60t>c (26%	154R (tgt/C	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	R	R	306V (atg/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	!03L (ctg/ct	WT	R	R	D435V (gac/gTc	NA	R	517c>t	WT	R	R	306V (atg/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	R	R	R	R	i60T>C (969	154R (tgt/C	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	R	R	306V (atg/C	-11c>t
NA	R	R	S	R	R	S	R	R	(69.0%); 19,	G65fs, G6I	WT	WT	WT	WT	WT	WT	WT	R	R	S	S	WT	WT	00%); 2691	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	R	R	197R (cag/c	WT
NA	R	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	R	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	R	R	WT	I8R (aag/a	S	R	97A (tcg/G	-8c>a
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I8R (aag/a	S	S	97A (tcg/G	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	S	R	WT	I3R (aag/a	R	R	319S (tat/tC	-8c>a
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	1401a>g	I3R (aag/a	R	S	l99T (aac/a	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	cg/tTg); I488V (	NA	R	WT	I3R (aag/a	S	R	306I (atg/a	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	S	S	196H (aat/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	cg/tTg); I488V (	NA	R	WT	I3R (aag/a	R	R	306I (atg/a	WT
NA	R	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	34T>C (100	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	R	R	306V (atg/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	34T>C (100	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	R	R	306V (atg/C	WT
NA	S	S	S	S	S	S	S	S	WT	WT	WT	WT	WT	WT	WT	WT	WT	S	S	S	S	WT	WT	WT	R	R	15T (agc/a	-15c>t	WT	R	R	S450L (tcg/tTg)	NA	R	WT	I8R (aag/a	S	R	306V (atg/C	-12c>t
NA	R	R	R	R	R	S	R	R	23.8%); 42	L142P (ctg	WT	WT	WT	WT	WT	WT	WT	R	R	R	S	WT	WT	WT	R	R	15T (agc/a	WT	WT	R	R	S450L (tcg/tTg)	R	R	WT	I3R (aag/a	R	R	197K (cag/A	WT

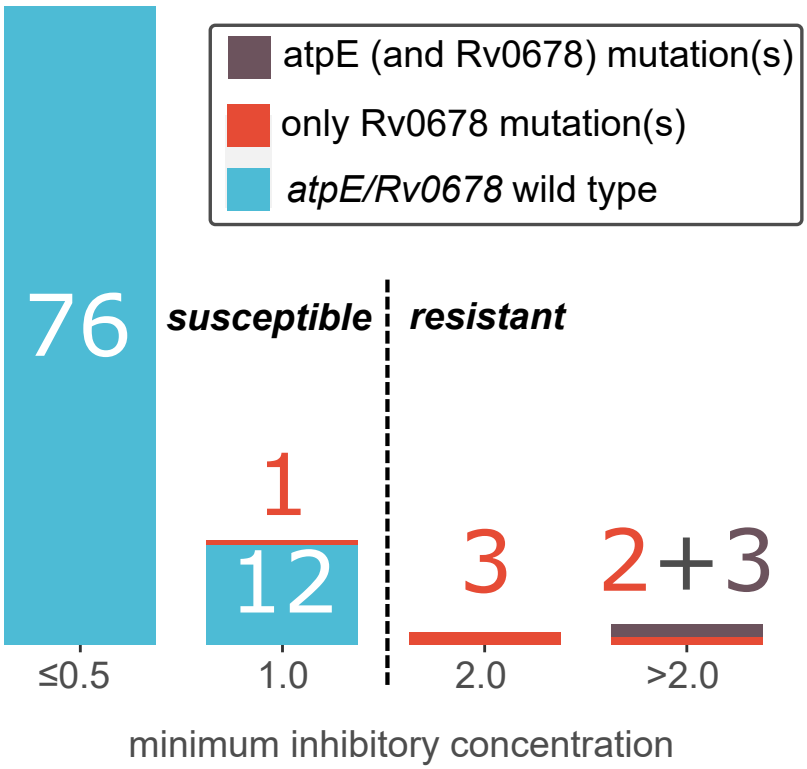
Z_pheno_100	Z_geno	pncA	rpsA	Lfx_pheno_1.0	LFX_geno	gyrB	gyrA	KM_pheno_2.5	KM_geno	rrs	eis	AM_pheno_1.0	AM_geno	rrs	eis	CM_pheno_2.5	CM_geno	rrs	tlyA	Eto_pheno_5.0	Ethioamides_geno	ethA	fabG1	inhA	PAS_pheno_1.0 LJ	PAS_geno	thyA	folC	Rv2670c	Cs_pheno_30.0 LJ	Cs_geno	alr	ald
NA	R	392_ins_gg	WT	R	R	WT	34N (gac/A	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	S	R	81P (cac/c	-15 C/T	WT	NA	S	WT	WT	WT	NA	S	WT	WT
NA	R	G105V (ggc/gTc)	WT	R	R	WT	44%); D94(	NA	R	401a>g (63	WT	R	R	401a>g (63	WT	R	R	1401a>g (63%)	WT	S	R	del_ga (99.(	WT	WT	S	S	WT	WT	WT	S	S	WT	WT
R	R	G105V (ggc/gTc)	WT	R	R	WT	591P (96%	S	S	WT (99.5%	WT	S	S	WT (99.5%	WT	S	S	WT (99.5%)	WT	S	R	del_ga (98.:	WT	WT	S	S	WT	WT	WT	S	S	WT	WT
S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	S	WT	WT	WT	S	S	WT	WT	WT	S	S	WT	WT
R	R	L45 (ttg/tCg)	WT	S	R	WT	34G (gac/g	R	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	NA	R	22L (tcg/tT	WT
R	R	L45 (ttg/tCg)	WT	S	R	WT	34G (gac/g	R	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	R	R	22L (tcg/tT	WT
R	R	W68_ (tgg/tAg)	WT	R	R	WT	34H (gac/C	R	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	S	S	WT	WT
NA	R	471_ins_a	WT	S	S	WT	WT	NA	R	WT	-10g>a	S	S	WT	-10g>a	S	S	WT	WT	R	R	-73 A/C	WT	WT	S	S	WT	WT	NA	S	WT	WT	WT
R	R	C14R (tgc/Cgc)	WT	R	R	WT	34G (gac/g	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	S	79D (aac/G	WT	WT	S	R	R222G	WT	WT	NA	S	WT	WT
S	S	WT	WT	R	R	WT	34G (gac/g	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	NA	S	WT	WT	WT	NA	S	WT	WT
NA	R	K96E (aag/Gag)	WT	R	R	WT	30V (gcg/g	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	NA	R	WT	791_ins_g
NA	R	K96E (aag/Gag)	WT	R	R	WT	30V (gcg/g	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	S	R	WT	791_ins_g
NA	R	-12a>c	WT	S	R	WT	34G (gac/g	NA	R	WT	-10g>a	S	S	WT	-10g>a	S	S	WT	WT	R	S	79D (aac/G	WT	WT	S	R	R222G	WT	WT	NA	R	WT	526_ins_c
NA	S	WT	1,5%); E40(	S	S	WT	WT	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	NA	S	WT	WT
NA	R	G162A (ggt/gCt)	WT	S	S	WT	WT	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	NA	S	WT	WT
R	R	D63A (gac/gCc)	WT	R	R	WT	30V (gcg/g	NA	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	R	largeDEL	WT	WT	S	S	WT	WT	WT	S	S	WT	WT
R	R	D63A (gac/gCc)	WT	S	R	WT	30V (gcg/g	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	R	largeDEL	WT	WT	S	S	WT	WT	WT	NA	S	WT	WT
S	S	WT	WT	S	S	WT	WT	R	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	NA	S	WT	WT	WT	NA	S	WT	WT
R	R	-12a>c	WT	R	R	WT	34G (gac/g	R	R	WT	-10g>a	S	S	WT	-10g>a	S	S	WT	WT	S	S	79D (aac/G	WT	WT	S	R	R222G	WT	WT	R	S	WT	WT
R	R	G105V (ggc/gTc)	WT	R	R	WT	34A (gac/g	R	R	1401a>g	-10g>a	R	R	1401a>g	-10g>a	S	R	1401a>g	WT	NA	R	del_a (93.9	WT	WT	S	S	WT	WT	WT	R	S	WT	WT
R	R	-7 A/G	WT	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	S	79D (aac/G	WT	WT	NA	R	R222G	WT	WT	NA	S	WT	WT
NA	R	392_ins_gg	WT	R	R	WT	34N (gac/A	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	NA	S	WT	WT
NA	R	largeDEL	WT	R	R	WT	34N (gac/A	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	S	S	WT	WT
R	R	largeDEL	WT	R	R	WT	30V (gcg/g	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	S	79D (aac/G	WT	WT	S	R	R222G	WT	WT	NA	S	WT	WT
NA	R	D63A (gac/gCc)	WT	R	R	WT	34G (gac/g	NA	R	1401a>g	WT	R	R	1401a>g	WT	R	R	1401a>g	WT	R	R	largeDEL	WT	WT	S	S	WT	WT	WT	S	R	WT	34delG (96%)
NA	R	I6T (atc/aCc)	WT	S	S	WT	WT	NA	R	1401a>g	WT	R	R	1401a>g	WT	R	R	1401a>g	WT	R	R	4_del_ga (9	WT	WT	R	S	WT	WT	WT	NA	S	WT	WT
R	S	WT	WT	R	S	WT	WT	NA	R	WT	-12c>t	R	S	WT	-12c>t	R	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	R	S	WT	WT
S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	R	.47_ (tac/ta	WT	WT	NA	S	WT	WT	WT	S	S	WT	WT
S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	R	.47_ (tac/ta	WT	WT	S	S	WT	WT	WT	S	S	WT	WT
S	S	H137R (cat/cGt)	WT	R	R	WT	94Y (gac/Ta	R	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	S	R	81P (cac/c	-15 C/T	WT	NA	S	WT	WT	WT	NA	S	WT	WT
NA	S	WT	WT	S	S	WT	WT	NA	S	WT	WT	S	S	WT	WT	S	S	WT	WT	S	R	79D (aac/G	WT	WT	R	R	R222G	WT	WT	S	S	WT	WT
R	R	T160P (aca/Cca)	WT	R	R	WT	34G (gac/g	NA	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	R	79D (aac/G	WT	WT	S	R	R222G	WT	WT	NA	S	WT	WT
NA	R	T160P (aca/Cca)	WT	R	R	WT	34G (gac/g	NA	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	S	79D (aac/G	WT	WT	S	R	R222G	WT	WT	NA	S	WT	WT
R	R	P69L (cca/cTa)	WT	S	S	WT	WT	NA	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	R	114I (acc/a	WT	WT	NA	S	WT	WT	WT	NA	S	WT	WT
S	S	WT	WT	S	S	WT	WT	R	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	NA	S	WT	WT	WT	NA	S	WT	WT
NA	S	WT	WT	S	S	WT	WT	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	NA	S	WT	WT	WT	S	S	WT	WT
NA	S	WT	WT	R	R	318T (gct/A	30V (gcg/g	NA	S	514a>c	WT	R	S	514a>c	WT	R	S	514a>c	W242_ (tgg/tAg)	NA	R	WT	-15 C/T	94T (atc/aC	S	S	242_ (tgg/t	WT	WT	S	S	-243 C/T	WT
NA	S	WT	WT	R	R	318T (gct/A	30V (gcg/g	NA	S	514a>c	WT	R	S	514a>c	WT	R	S	514a>c	W242_ (tgg/tAg)	R	R	WT	-15 C/T	94T (atc/aC	S	S	242_ (tgg/t	WT	WT	S	S	-243 C/T	WT
R	R	Q10P (cag/cCg)	WT	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	R	WT	203L (ctg/ct	WT	S	R	WT	WT	.5V (gca/gT	NA	S	WT	WT
NA	R	D8E (gac/gaA)	WT	S	R	WT	30V (gcg/g	NA	R	1401a>g	WT	R	R	1401a>g	WT	S	R	1401a>g	WT	R	R	.47_ (tac/ta	WT	WT	NA	S	WT	WT	WT	NA	R	44N (gac/A	WT
NA	R	D8E (gac/gaA)	WT	R	R	WT	30V (gcg/g	NA	R	1401a>g	WT	R	R	1401a>g	WT	R	R	1401a>g	WT	R	R	.47_ (tac/ta	WT	WT	S	S	WT	WT	WT	R	R	44N (gac/A	WT
R	R	55_del_c (100%)	WT	R	R	WT	30V (gcg/g	R	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	R18_ (cga/Tga)	R	R	81P (cac/c	-15 C/T	WT	NA	S	18_ (cga/Tg	WT	WT	NA	S	WT	WT
NA	S	H137R (cat/cGt)	WT	R	R	WT	94Y (gac/Ta	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	S	S	WT	WT
NA	R	G24D (ggc/gAc)	WT	R	R	WT	34H (gac/C	NA	R	1401a>g	WT	R	R	1401a>g	WT	R	R	1401a>g	WT	NA	R	del_ga (99.(	WT	WT	S	S	WT	WT	WT	NA	S	WT	WT
R	R	F58S (ttc/tCc)	WT	R	R	/Cac); A50(	WT	S	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	NA	S	F4L (ttc/ttG	WT
NA	R	I6T (atc/aCc)	WT	R	R	WT	30V (gcg/g	NA	R	1401a>g	WT	S	R	1401a>g	WT	R	R	1401a>g	WT	R	R	del_ga (98.(	WT	WT	R	S	WT	WT	WT	S	S	WT	WT
NA	S	WT	WT	NA	S	WT	WT	NA	S	WT	WT	R	S	WT	WT	R	S	WT	WT	R	S	WT	WT	WT	S	S	WT	WT	WT	R	S	WT	WT
NA	R	I31S (atc/aGc)	WT	R	R	WT	A90V; D94(	NA	R	WT	-10g>a	S	S	WT	-10g>a	NA	S	WT	WT	R	R	del_gt (99.(	WT	WT	NA	S	WT	WT	WT	NA	S	WT	WT
NA	R	I31S (atc/aGc)	WT	R	R	WT	34G (gac/g	NA	R	WT	-10g>a	S	S	WT	-10g>a	R	S	WT	WT	R	R	del_gt (99.(	WT	WT	S	S	WT	WT	WT	NA	S	WT	WT
NA	S	H137R (cat/cGt)	WT	R	R	WT	94Y (gac/Ta	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	NA	S	WT	WT
NA	R	G105V (ggc/gTc)	WT	R	R	WT	34A (gac/g	NA	R	1401a>g	WT	S	R	1401a>g	WT	R	R	1401a>g	WT	S	R	del_ga (99.(	WT	WT	S	S	WT	WT	WT	NA	S	WT	WT
NA	R	G105V (ggc/gTc)	WT	R	R	WT	34A (gac/a(	NA	R	1401a>g	WT	R	R	1401a>g	WT	R	R	1401a>g	WT	NA	R	) del_a (10	WT	WT	R	S	WT	WT	WT	S	S	WT	WT
NA	R	-11a>g	WT	R	R	WT	34G (gac/g	NA	R	1401a>g	WT	R	R	1401a>g	WT	R	R	1401a>g	WT	R	S	79D (aac/G	WT	WT	R	R	R222G	WT	WT	S	S	WT	WT
NA	R	-11a>g	'Q (aag/Cag	R	R	WT	34G (gac/a(	NA	R	(92%); 148	WT	R	R	(92%); 148	WT	R	R	01a>g (92%); 1484g>t (7	WT	NA	S	79D (aac/G	WT	WT	R	R	R222G	WT	WT	NA	S	WT	WT
R	R	-11a>g	WT	R	R	WT	30V (gcg/g	R	R	01a>g; 514	WT	R	R	01a>g; 514	WT	R	R	1401a>g; 514 a>c	WT	R	R	11H (tac/C	-15 C/T	WT	R	R	WT	WT	.5V (gca/gT	NA	S	WT	WT
NA	R	I133T (att/aCt)	WT	S	S	WT	WT	NA	R	WT	-10g>a	S	S	WT	-10g>a	S	S	WT	WT	R	S	37R (tgc/C	WT	WT	S	S	WT	84G (gggt/g	WT	NA	S	WT	WT
NA	R	I133T (att/aCt)	WT	S	S	WT	WT	NA	R	WT	-10g>a	S	S	WT	-10g>a	S	S	WT	WT	R	S	37R (tgc/C	WT	WT	S	S	WT	84G (ggg/g	WT	NA	S	WT	WT
NA	R	H57D (cac/Gac)	WT	R	R	WT	34G (gac/g	NA	R	1401a>g	WT	R	R	1401a>g	WT	NA	R	1401a>g	WT	R	S	79D (aac/G	WT	WT	R	R	R222G	WT	WT	NA	S	WT	WT
NA	R	H57D (cac/Gac)	WT	R	R	WT	34G (gac/g	NA	R	1401a>g	WT	R	R	1401a>g	WT	R	R	1401a>g	WT	R	S	79D (aac/G	WT	WT	R	R	R222G	WT	WT	R	S	WT	WT
NA	R	-11a>g	WT	R	R	WT	34A (gac/g	NA	R	1484g>t (7%	WT	R	R	1484g>t (7%	-12c>t	R	R	1484g>t (7%)	S159_ (tcg/tAg)	R	R	81P (cac/c	-15 C/T	WT	S	S	59_ (tcg/tA	WT	WT	R	S	WT	WT
R	R	C14Y (tgc/tAc)	WT	R	R	WT	30V (gcg/g	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	S	R	44N (gac/A	WT
R	R	C14Y (tgc/tAc)	WT	R	R	WT	30V (gcg/g	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	NA	R	44N (gac/A	WT
S	R	-11a>g	1,5%) L140	R	R	:/Cac); A61(	WT	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	NA	S	WT	WT	WT	NA	S	WT	WT
NA	S	WT	WT	S	S	WT	WT	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	NA	S	WT	WT
NA	R	E107_ (gaa/Taa)	WT	R	R	WT	34G (gac/g	NA	R	01a>g; 514	WT	R	R	01a>g; 514	WT	R	R	1401a>g; 514 a>c	WT	R	R	50D (ggt/g	-15 C/T	WT	S	R	WT	WT	.5V (gca/gT	NA	S	WT	WT
NA	R	I6T (atc/aCc)	WT	R	R	WT	30V (gcg/g	NA	R	1401a>g	WT	R	R	1401a>g	WT	R	R	1401a>g	WT	R	R	del_ga (98.(	WT	WT	S	S	WT	WT	WT	R	S	WT	WT
NA	S	WT	WT	S	S	WT	WT	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	NA	S	WT	WT
NA	S	WT	WT	S	S	WT	WT	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	NA	S	WT	WT
NA	S	WT	WT	S	S	WT	WT	NA	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	NA	S	WT	WT	WT	NA	S	WT	WT
S	S	WT	WT	R	S	WT	WT	S	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	NA	S	WT	WT	WT	NA	S	WT	WT
NA	R	G105V (ggc/gTc)	WT	S	S	WT	WT	NA	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	R	del_ga (98.(	WT	WT	S	S	WT	WT	WT	S	S	WT	WT
NA	R	G105V (ggc/gTc)	WT	S	S	WT	WT	NA	S	WT	WT	S	S	WT	WT	S	S	WT	WT	NA	R	del_ga (97.(	WT	WT	S	S	WT	WT	WT	S	S	WT	WT
NA	R	D136V (gat/gTt)	WT	S	R	WT	34G (gac/g	NA	S	WT	WT	S	S	WT	WT	S	S	WT	WT	S	R	WT	-15 C/T	WT	S	S	WT	WT	WT	NA	S	WT	WT
S	S	WT	WT	S	S	WT	WT	R	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	NA	S	WT	WT	WT	NA	S	WT	WT
R	R	D8E (gac/gaA)	WT	R	R	WT	30V (gcg/g	NA	S	WT	WT	S	S	WT	WT	S	S	WT	WT	NA	R	.47_ (tac/ta	WT	WT	S	S	WT	WT	WT	NA	R	WT	400_ins_gc
NA	R	D8E (gac/gaA)	WT	R	R	WT	30V (gcg/g	NA	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	R	.47_ (tac/ta	WT	WT	S	S	WT	WT	WT	NA	R	WT	400_ins_cg
NA	S	WT	WT	S	S	WT	WT	R	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	NA	S	WT	WT
NA	R	G105V (ggc/gTc)	WT	R	R	WT	91P (tcg/Cc	NA	R	WT	-10g>c	S	S	WT	-10g>c	S	S	WT	WT	S	R	del_a (99.1(	WT	WT	S	S	WT	WT	WT	NA	S	WT	WT
NA	R	G105V (ggc/gTc)	WT	R	R	WT	91P (tcg/Cc	NA	R	484g>t (58	-10g>c	S	R	484g>t (58	-10g>c	S	R	1484g>t (58%)	WT	S	R	del_ga (93.(	WT	WT	S	S	WT	WT	WT	S	S	WT	WT
NA	S	WT	WT	R	S	WT	WT	NA	R	01a>g;1402	WT	R	R	01a>g;1402	WT	R	R	1401a>g;1402c>t	WT	S	R	WT	-15 C/T	94T (atc/aC	S	S	WT	WT	WT	S	S	-243 C/T	WT
NA	S	WT	WT	S	S	WT	WT	NA	R	01a>g; 514	WT	R	R	01a>g; 514	WT	R	R	1401a>g; 514 a>c	WT	NA	R	WT	-15 C/T	94T (atc/aC	S	S	WT	WT	WT	R	S	-243 C/T	WT
S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	S	79D (aac/G	WT	WT	S	R	R222G	WT	WT	NA	S	WT	WT
R	R	V163G (gtg/gGg)	WT	R	R	WT	34G (gac/g	NA	R	517c>t	-14c>t	S	R	517c>t	-14c>t	R	S	517c>t	WT	R	R	del_gg (99.2	03L (ctg/ct	WT	S	S	WT	WT	WT	NA	S	WT	WT
NA	R	H71Y (cat/Tat)	WT	R	R	04T (gcg/A	34A (gac/g	NA	R	WT	-12c>t	S	S	WT	-12c>t	R	S	WT	Q21_ (caa/Taa)	R	S	78L (ccc/c	WT	WT	S	R	21_ (caa/Ta	43T (atc/aC	WT	R	S	6_ (gag/Ta	WT
NA	R	C14G (tgc/GgcI; -12a>c	WT	R	R	WT	34G (gac/g	NA	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	S	79D (aac/G	WT	WT	S	R	R222G	WT	WT	S	S	WT	WT
NA	R	G97S (ggt/Agt)	WT	R	R	WT	34N (gac/A	S	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	S	S	WT	WT
R	R	167_ins_g	WT	R	R	WT	34N (gac/A	R	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	NA	S	WT	WT	WT	NA	S	WT	WT
S	R	W119R (tgg/Cgg)	WT	R	R	WT	34N (gac/A	NA	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	R	.47_ (tac/ta	WT	WT	S	S	WT	WT	WT	S	S	WT	WT
R	R	P62L (ccg/cTg)	WT	R	R	23A (gca/g	34G (gac/g	R	R	1401a>g	WT	R	R	1401a>g	WT	R	R	1401a>g	WT	R	S	79D (aac/G	WT	WT	S	R	R222G	WT	WT	S	S	WT	WT
R	R	largeDEL	WT	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	S	79D (aac/G	WT	WT	NA	R	R222G	WT	WT	NA	S	WT	WT
NA	R	G105V (ggc/gTc)	WT	S	S	WT	WT	NA	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	R	del_ga (98.(	WT	WT	NA	S	WT	WT	WT	NA	S	WT	WT
NA	R	largeDEL	WT	S	S	WT	'Cag); G668	NA	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	S	79D (aac/G	WT	WT	S	R	R222G	WT	WT	S	S	WT	WT
NA	R	largeDEL	WT	S	S	WT	'Cag); G668	NA	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	S	79D (aac/G	WT	WT	S	R	R222G	WT	WT	S	S	WT	WT
NA	R	295_del_t	WT	R	R	WT	94A (gac/g	NA	R	WT	-10g>a	S	S	WT	-10g>a	S	S	WT	WT	R	S	79D (aac/G	WT	WT	R	R	R222G	WT	WT	R	R	WT	ins_g; 896_ins_g
NA	R	295_del_t	WT	R	R	WT	94A (gac/g	NA	R	WT	-10g>a	S	S	WT	-10g>a	S	S	WT	WT	R	S	79D (aac/G	WT	WT	R	R	R222G	WT	WT	R	R	WT	ins_g; 896_ins_g
R	R	T167I (acc/aTc)	WT	S	S	WT	WT	R	R	WT	-12c>t	S	S	WT	-12c>t	S	S	WT	WT	R	R	81P (cac/c	-15 C/T	WT	S	S	WT	WT	WT	NA	S	WT	WT
R	R	K96N (aag/aaC)	WT	S	R	WT	94A (gac/g	S	S	WT	WT	S	S	WT	WT	S	S	WT	WT	R	R	1M (acg/a	WT	WT	S	S	WT	WT	WT	NA	S	WT	WT

Supplementary Table S2

Characteristics of all patients receiving a bedaquiline (BDQ) containing treatment regimen against multidrug resistant tuberculosis in the Republic of Moldova (2016-2018). IQR= interquartile range, PTC=previously treated case

Patient characteristics	All patients receiving BDQ 2016-2018 % (n)	Patients included % (n)	Patients excluded % (n)	*P*-value
Urban	48.8 (99/203)	41.9 (26/62)	51.8 (73/141)	0.2240
Male	75.9 (154/203)	80.6 (50/62)	73.8 (104/141)	0.3736
Age, median (IQR)	37 (31-45)	39 (34-45)	36 (30-45)	0.0938
Microscopy +	72.4 (147/203)	74.2 (46/62)	71.6 (101/141)	0.7367
Case definition				
New case	25.1 (51/203)	29.0 (18/62)	23.4 (33/141)	0.4824
PTC-relapse	14.8 (30/203)	12.9 (8/62)	15.6 (22/141)	0.6741
PTC-default	13.8 (28/203)	17.7 (11/62)	12.1 (17/141)	0.2784
PTC-failure	46.3 (94/203)	40.3 (25/62)	48.9 (69/141)	0.2868
Treatment outcome				
still on treatment	6.9 (14/203)	6.5 (4/62)	7.1 (10/141)	1.0000
lost to follow-up	7.4 (15/203)	9.7 (6/62)	6.4 (9/141)	0.3975
cured	66.7 (116/174)	71.2 (37/52)	64.8 (79/122)	0.4838
failure	25.9 (45/174)	23.1 (12/52)	27.0 (33/122)	0.7059
died	7.5 (13/174)	5.8 (3/52)	8.2 (10/122)	0.7571
HIV status				
HIV +	12.7 (25/197)	12.9 (8/62)	12.6 (17/135)	1.0000
HIV status unknown	3.0 (6/203)	0.00 (0/62)	4.3 (6/141)	0.1804

Figure S1



Bedaquiline minimum inhibitory concentrations (MICs) of *Mycobacterium tuberculosis* complex (MTBC) isolates from patients receiving a bedaquiline containing multidrug resistant tuberculosis regimen between 2016 and 2018 in the Republic of Moldova. The WHO-endorsed critical concentration for bedaquiline is 1 mg/L for the MGIT960 system, MTBC isolates with bedaquiline MICs >1 mg/L are considered bedaquiline resistant.