Incorporating PZA into Treatment Based on Susceptibility Testing

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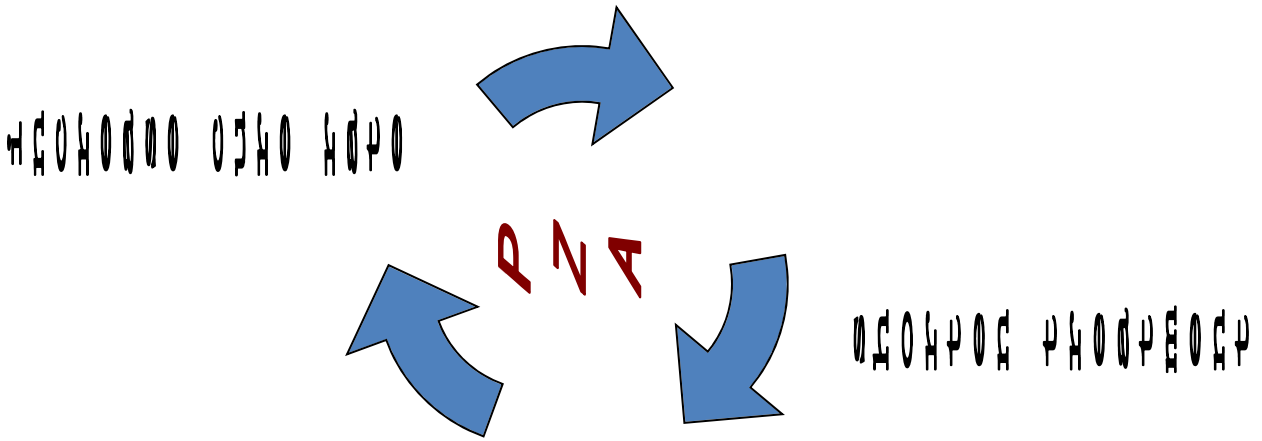
PZA improves the outcome of tuberculosis

- PZA has treatment-shortening effect in regimens containing isoniazid (INH) with or without rifampin
- PZA is likely to improve drug-resistant as well as susceptible TB



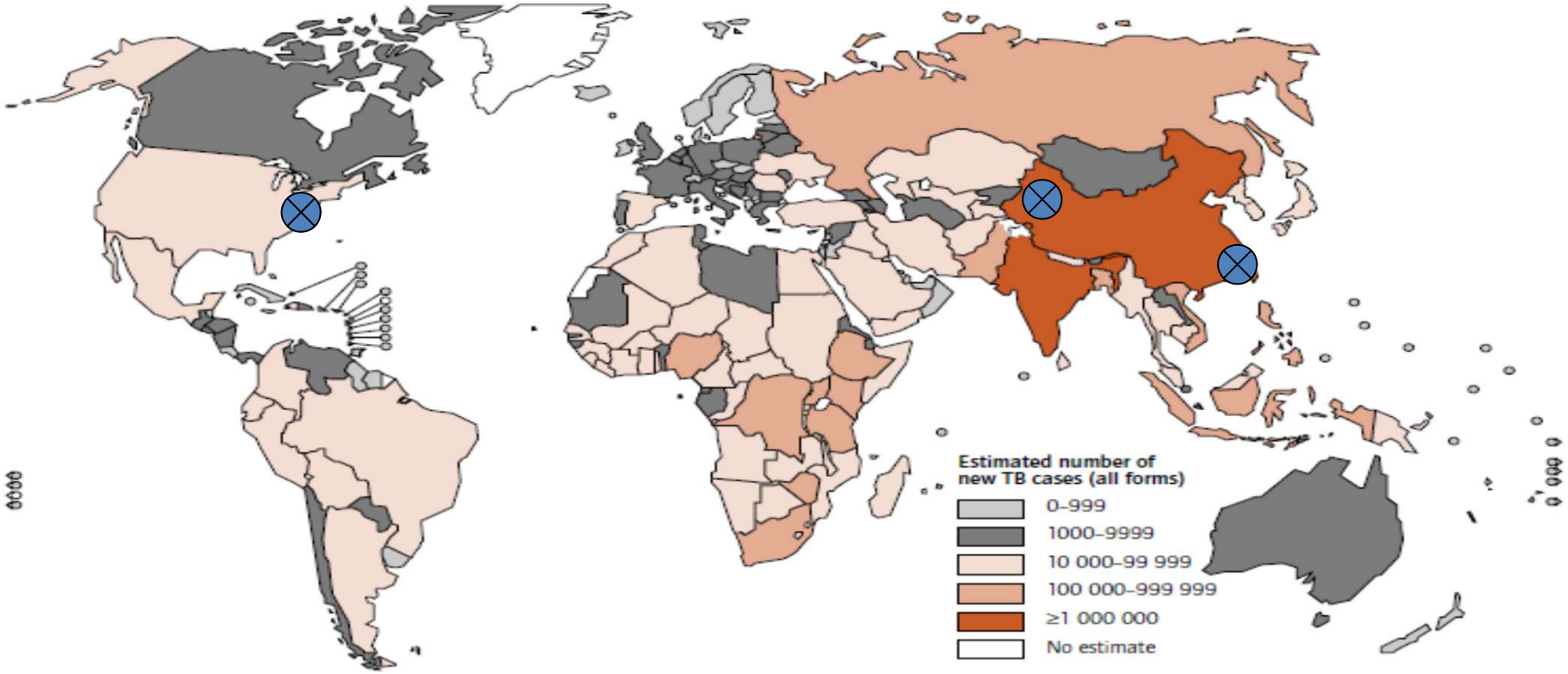
Fox W, Ellard GA, Mitchison DA. Int J Tuberc Lung Dis 1999; 3:S231–79.

Unresonveld problems for use of PZA in drug-resistant TB

- High incidence of PZA resistance among drug-resistant tuberculosis strains
- Challenges in performing drug susceptibility testing
- Poor understanding of clinical implications of PZA resistance

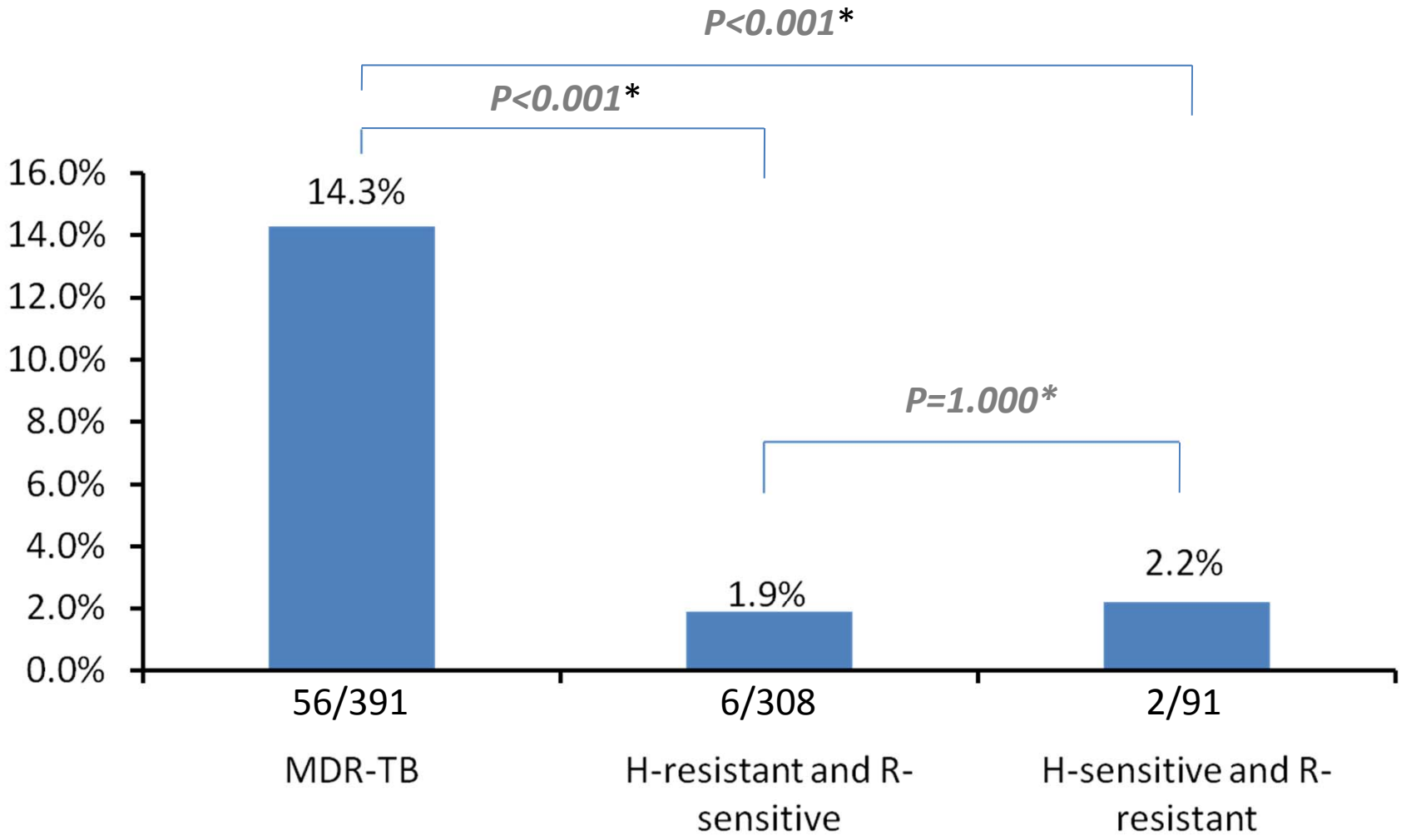
Mphahlele M, et al.J Clin Microbiol 2008; 46:3459–64

Estimated number of new TB cases, by country



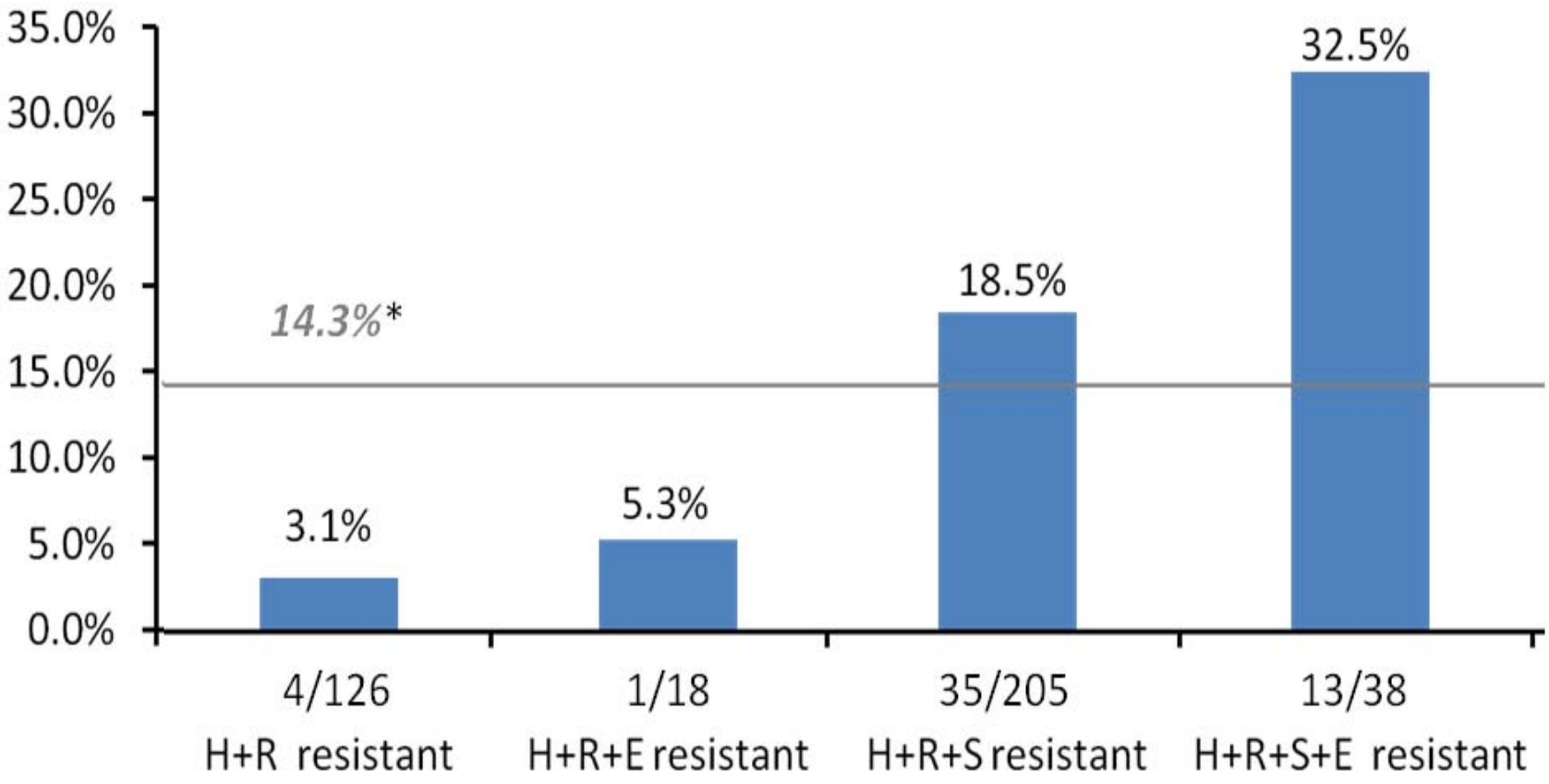
Global Tuberculosis Control 2009, WHO

Phenotypic PZA-resistance among drug resistant TB: Western region of China data



*Fisher exact test

Distribution of phenotypic PZA-resistance in MDR-TB



*The total PZA-resistant rate in MDR-TB

Priority Ranking of Drugs for Additional Research on Optimization for Drug-Resistant Tuberculosis Treatment

Priority Ranking	Drug	Reasons for Continued Research on Use in Regimens for Drug-Resistant Tuberculosis	Barriers to Optimization for Drug-Resistant Tuberculosis Treatment
High	Pyrazinamide	Sterilizing activity in first-line regimens, so may shorten drug-resistant tuberculosis treatment duration Synergistic effects with new drugs in clinical development	Resistance may be common in multidrug-resistant tuberculosis strains Phenotypic resistance testing problematic Multiple different mutations can confer resistance, impeding development of rapid genotypic resistance test
	Isoniazid	Cheap, well tolerated, and widely available Low-level resistance may be overcome with higher doses Rapid genotypic resistance test may predict which patients with drug-resistant tuberculosis may benefit from higher doses	MIC distribution among resistant strains unknown Correlation between genotypic resistance test result and MIC not established Interpatient variability in PK and acetylation complicates dose selection
	Amikacin, kanamycin, capreomycin	Susceptibility to injectables confers better outcomes in drug-resistant tuberculosis Relative efficacy of injectable drugs is unknown Optimal treatment duration of injectable use is unknown	Amikacin not widely available and expensive Poor early bactericidal activity prevents using this method to compare efficacy Large sample sizes needed to study comparative efficacy and treatment duration
Medium	Ethionamide and prothionamide	Only second-line oral drug with potential bactericidal activity Relationship between drug exposure and GI tolerability unknown	Use of isoniazid in initial tuberculosis treatment may select for isoniazid and ethionamide cross-resistance Ability of rapid genotypic tests to predict susceptibility requires further study
	Ethambutol	Better tolerated than many second-line drugs Relationship between drug exposure and ocular toxicity unknown Animal models suggest that neuroprotective agents may prevent optic neuritis, allowing for higher ethambutol dosing	Resistance may be common in drug-resistant tuberculosis strains given the use of ethambutol in first-line tuberculosis treatment Concerns over ocular toxicity may limit use doses that optimize efficacy
Low	Para-aminosalicylic	Minimum drug exposure necessary for	Poor GI tolerability and risk of hypersensitivity

PZA for drug-resistant tuberculosis is complicated

- High incidence of PZA resistance among drug-resistant tuberculosis strains
- Challenges in performing drug susceptibility testing
- Poor understanding of clinical implications of PZA resistance

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pncA sequencing: a practical choice to identify PZA-susceptibility?

Concordance of *pncA* gene analysis and PZA susceptibility testing by the BACTEC MGIT 960 method

	pncA gene mutation		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PZA susceptibility	Yes					
Overall, n = 66			80.6	96.7	96.7	80.6
Resistance	29	7				
Susceptible	1	29				
Beijing strain, n = 37			76.2	93.8	94.1	75
Resistance	16	5				
Susceptible	1	15				
Non-Beijing strain, n = 29			86.7	100	100	87.5
Resistance	13	2				
Susceptible	0	14				

PZA, pyrazinamide; PPV, positive predictive value; NPV, negative predictive value.

Chiu et al. BMC Infectious Diseases 2011, 11:240

Research Questions to Inform Optimization of Drug-Resistant Tuberculosis Treatment Regimens

Research Questions by Theme	Suggested Studies	Relevant Drugs
Translation of Preclinical Findings to Clinical Settings		
What are human equivalent doses for studies in animal models?	PK/PD studies in animals to define the PD parameter most closely correlated with activity	AMK, KM, CM, ETA, PAS
Use of PK/PD Relationships to Optimize Dosing		
Which PK/PD targets correlate best with efficacy and prevention of resistance?	PK/PD studies in *in vitro* and animal models	PZA, EMB, INH, RBT, ETA, PAS, CS/TZ
Can target attainment be further optimized?	Dose-ranging human efficacy trials with PK/PD component	
Can toxicity be reduced through changes in dosing, while preserving efficacy?	Animal and human PK/PD and toxicodynamic studies	PZA, EMB, PAS, CS/TZ, ETA
	Human efficacy and tolerability studies using toxicodynamically optimized doses	
Can toxicity be reduced through changes in formulation and/or delivery?	Animal and human PK/PD and toxicity/tolerability studies of new formulations, studies of novel delivery systems for existing drugs	AMK, KM, CM, ETA, PAS, CS/TZ
Enhanced Use of Genotypic and Phenotypic Testing to Inform Drug Choices		
Can rapid resistance tests identify patients with drug-resistant tuberculosis who are likely to benefit from a drug that ordinarily would not be used?	Correlation of rapid genotypic resistance test results with minimum inhibitory concentrations	INH, RBT, ETA
	Human genotyping to identify mutations likely to affect drug absorption or clearance in human PK and efficacy trials	
What is the correlation between phenotypic resistance and clinical treatment outcomes? Can this be further refined with genotypic testing?	Randomized trial of drug in question in patients whose isolates have documented phenotypic resistance, or collection of phenotypic and genotypic data of the drug in question among patients enrolled in trials of other compounds	PZA, CS/TZ
Designing an Optimized Background Regimen of Existing Drugs		
What is the activity of this drug in humans?	Extended (14-d) EBA study alone and with	CM

PZA for drug-resistant tuberculosis is complicated

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Hongkong Study: Pyrazinamide may improve treatment of multidrug-resistant tuberculosis

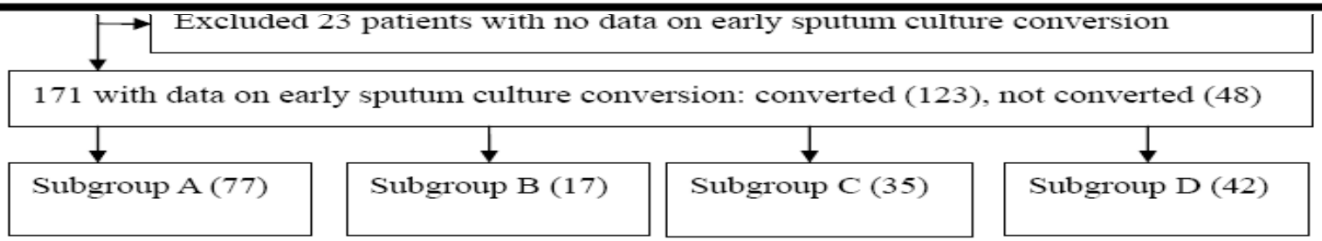
Chang et al., AAC Accepts, published online ahead of print on 6 August 2012

Subgroup A: 83 Z users with Z^S MDR-TB

Subgroup B: 24 Z users with Z^R MDR-TB

Subgroup C: 40 Z non-users with Z^S MDR-TB

Subgroup D: 47 Z non-users with Z^R MDR-TB



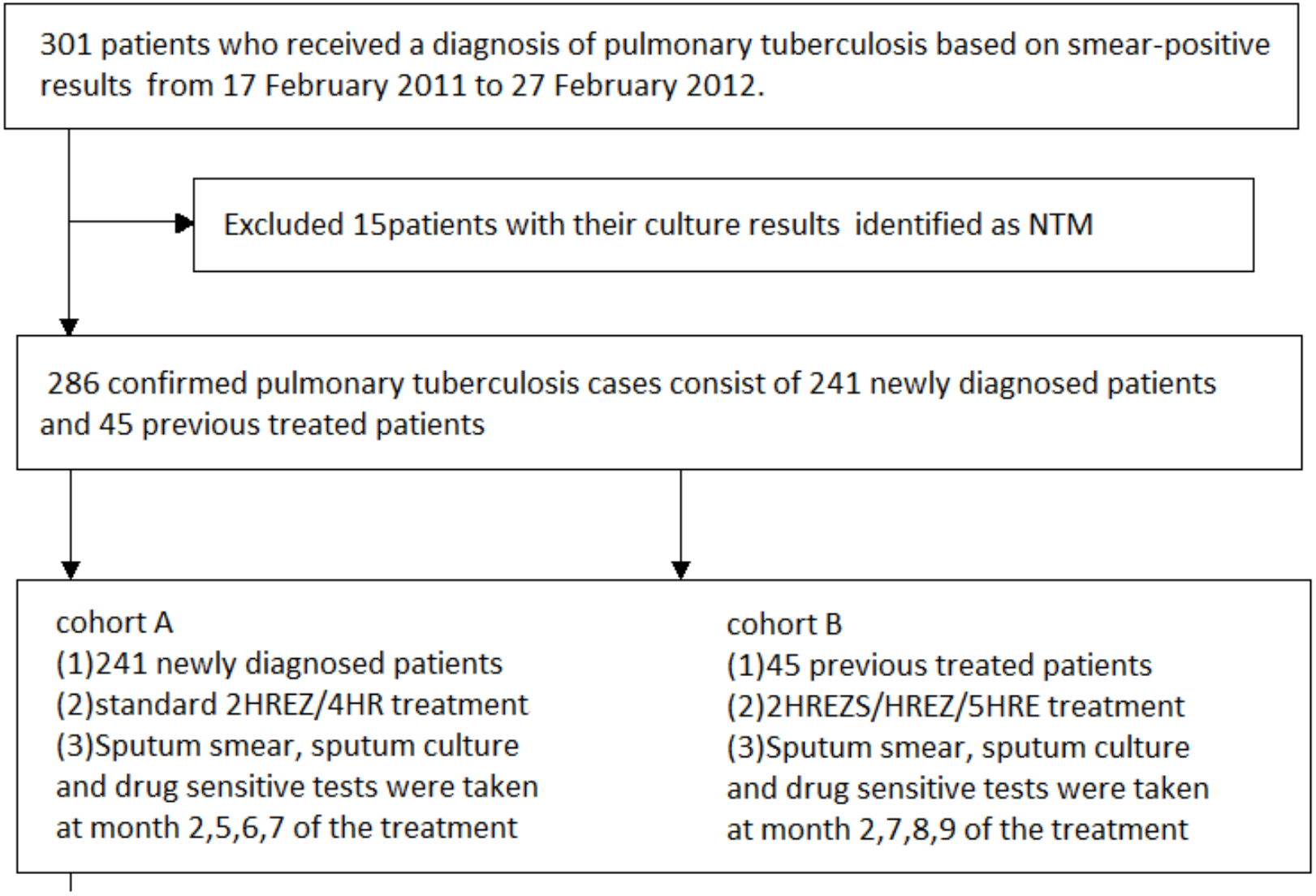
Pyrazinamide users showed increased proportion of early culture conversion

Procedures and results of robust Poisson regression analysis of the association between treatment success and pyrazinamide use with susceptibility [a]

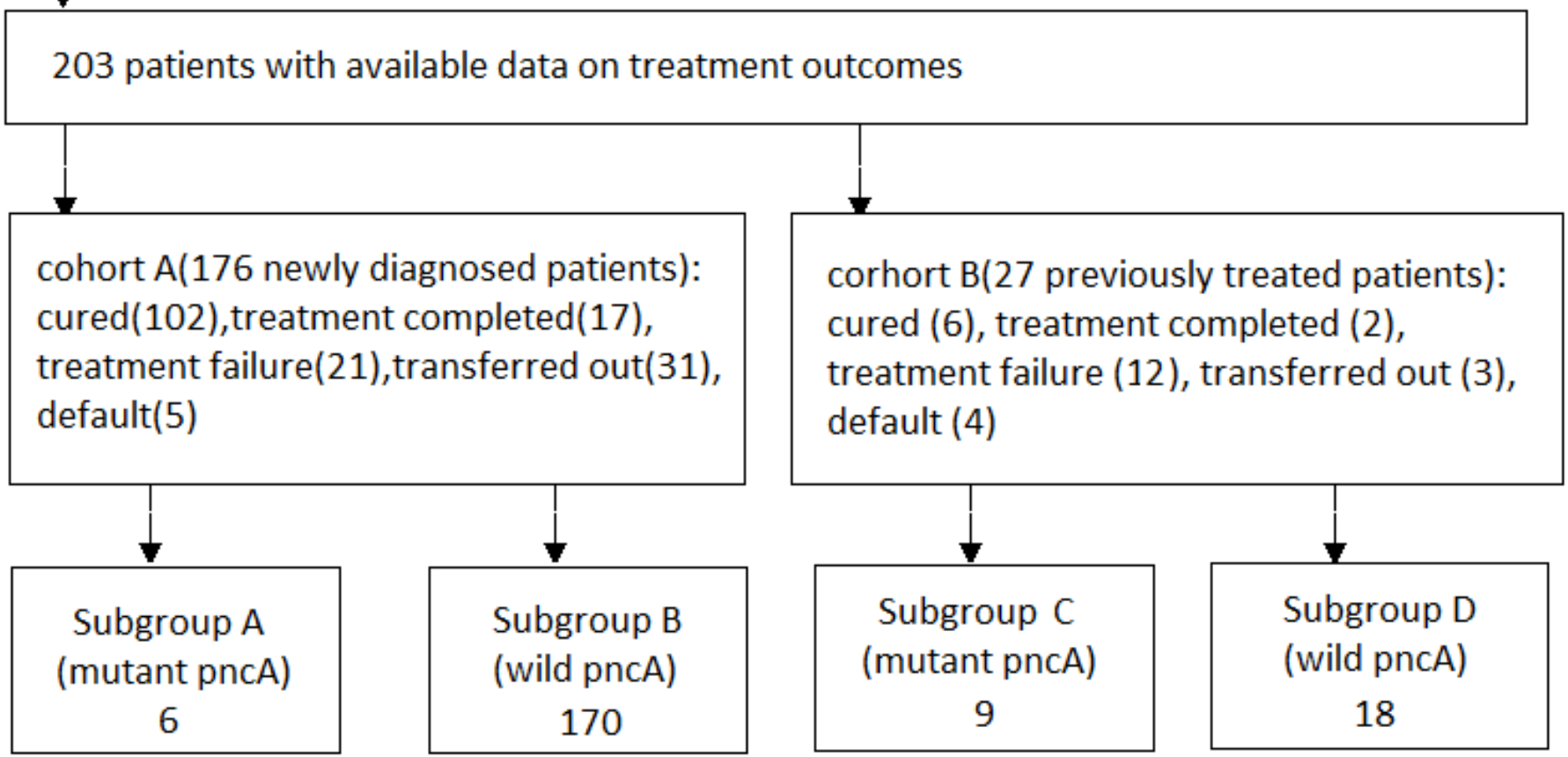
Factors	Change in coefficient of Z use with susceptibility (%)	Reason for exclusion from multivariable analysis	Adjusted risk ratio (95% CI)
Adverse social factor [b]	-10.0	-	0.81 (0.64-1.03)
Use of linezolid	6.7	< 10% change in coefficient	-
Total no. of drugs used with activity *in vitro* < 4 [b]	-65.0	-	0.68 (0.51-0.91)
Susceptible to ofloxacin	-31.7	multicollinearity	-
Susceptible to cycloserine	3.3	< 10% change in coefficient	-
Z use with susceptibility [b, c]	-	-	Subgroup A as reference
Z use with resistance (Subgroup B)	-	-	0.723 (0.460-1.135) [d]
Z non-use with susceptibility (Subgroup C)	-	-	1.006 (0.792-1.278) [e]
Z non-use with resistance (Subgroup D)	-	-	1.062 (0.832-1.355) [f]

Chang et al. AAC Accepts, published online ahead of print on 6 August 2012

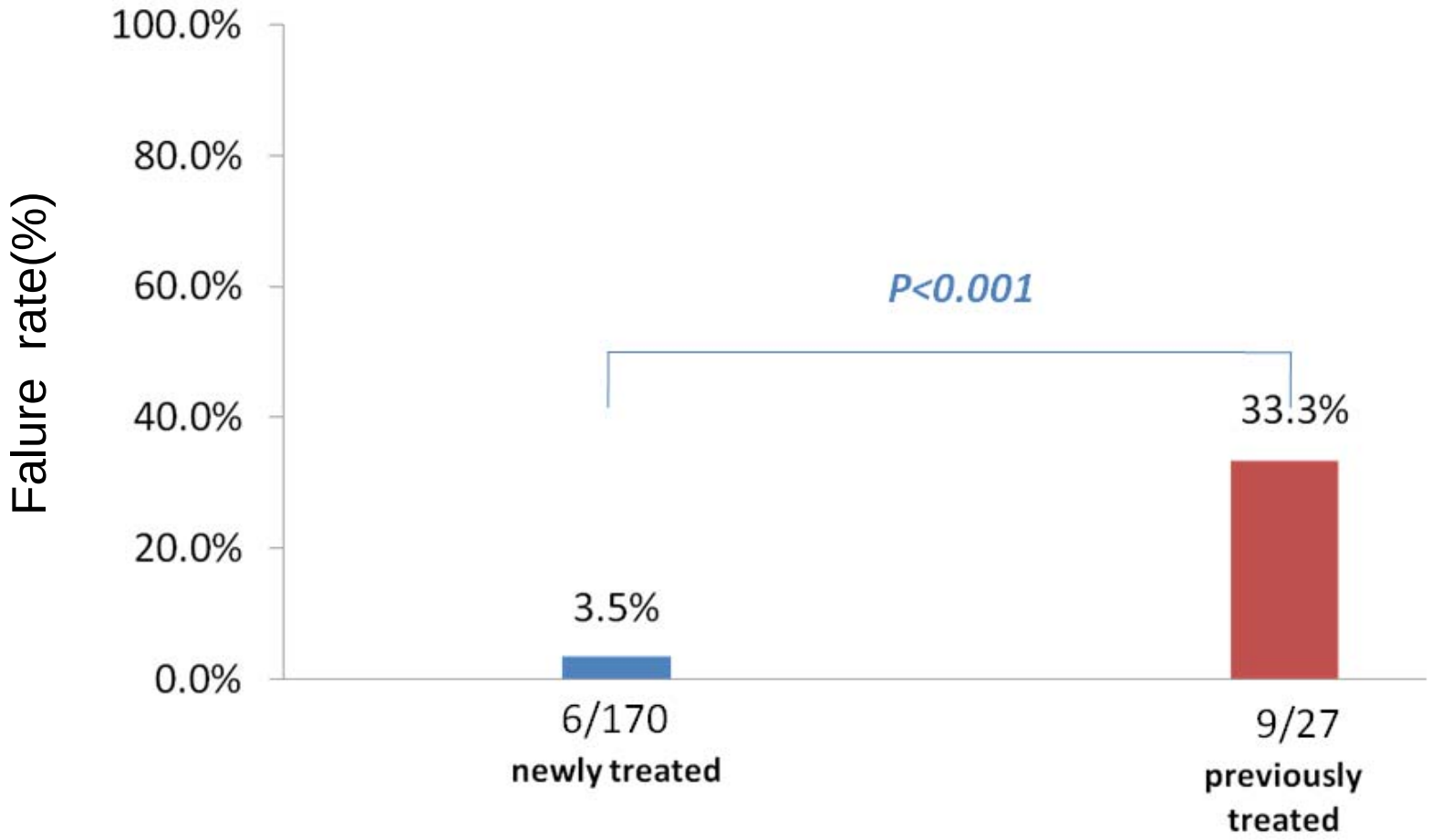
Real-life Cohort Study: Pyrazinamide improves treatment of previously treated TB cases



Zhang et al. AAC submitted.


203 patients with available data on treatment outcomes
cohort A(176 newly diagnosed patients): cured(102),treatment completed(17), treatment failure(21),transferred out(31), default(5)
corhort B(27 previously treated patients): cured (6), treatment completed (2), treatment failure (12), transferred out (3), default (4)
Subgroup A (mutant pncA) 6
Subgroup B (wild pncA) 170
Subgroup C (mutant pncA) 9
Subgroup D (wild pncA) 18

Distribution of patients with mutant *pncA* (N=197)



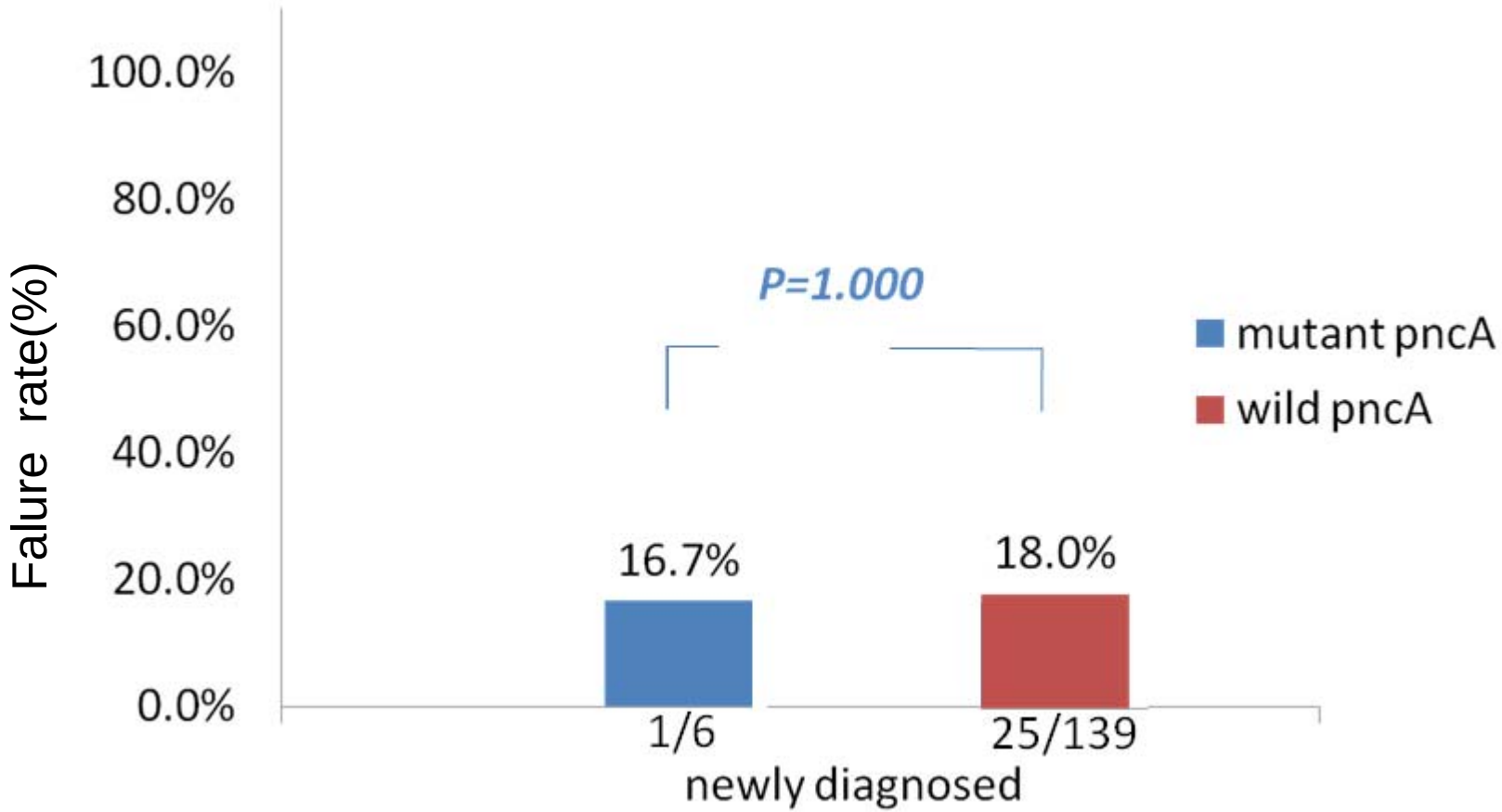
Zhang et al. AAC submitted.

Univariate analysis of factors associated with

Treatment outcomes in initially treated TB cases

	Success (N=167)	Failure /death (N=31)	P value	OR (95% CI)
Age(yrs, mean(SD))	44(21)	59(18.5)	<0.001	1.03(1.01-1.05)
Male sex, n(%)	105(62.9)	26(83.9)	0.029	3.07(1.12-8.40)
Complication, n(%)	14(8.4)	12(67.7)	<0.001	6.90(2.79-17.09)
Adverse reactions, n(%)	10(6.0)	8(25.8)	0.001	5.46(1.95-15.26)
Cavitary TB, n(%)	78(46.7)	21(67.7)	0.035	2.40(1.06-5.40)
Baseline TB bacteria load ≥3+, n(%)	65(38.9)	14(45.2)	0.515	1.29(0.60-2.80)
substandard treatment , n(%)	9(5.4)	9(29.0)	<0.001	7.18(2.57-20.04)
Smear-positive at 2 month, n(%)	32(22.2,N=144)	21(72.4,N=29)	<0.001	9.19(2.74-19.20)
Beijing genotype, n(N,%)	100(82.0, N=122)	19(70.4, N=27)	0.172	0.52(0.20-1.33)
Mutant pncA gene, n(N,%)	5(4.2,N=119)	1(3.8,N=26)	0.934	0.91(0.10-8.15)
Baseline MDR-TB, n(N,%)	2(1.5, N=131)	2(6.9,N=29)	0.116	5.00(0.67-37.12)

Treatment failure rate stratified by *pncA* mutation in initially treated patients(N=145)



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Variate analysis of factors associated with

Treatment outcomes in initially treated TB cases

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P value
Age	1.03(1.01-1.05)	1.02(0.99-1.04)	0.267
Male sex	3.07(1.12-8.40)	1.73(0.50-6.00)	0.385
Complication	6.90(2.79-17.09)	5.68(1.68-19.19)	0.005
Adverse reactions	5.46(1.95-15.26)	3.23(0.77-13.54)	0.108
Cavitary TB	2.40(1.06-5.40)	1.93(0.67-5.55)	0.223
substandard treatment	7.18(2.57-20.04)	6.24(1.57-24.79)	0.009
Smear-positive at 2 month	9.19(2.74-19.20)	5.81(1.94-17.44)	0.002

Factors associated with treatment outcomes in previously treated pulmonary TB patients

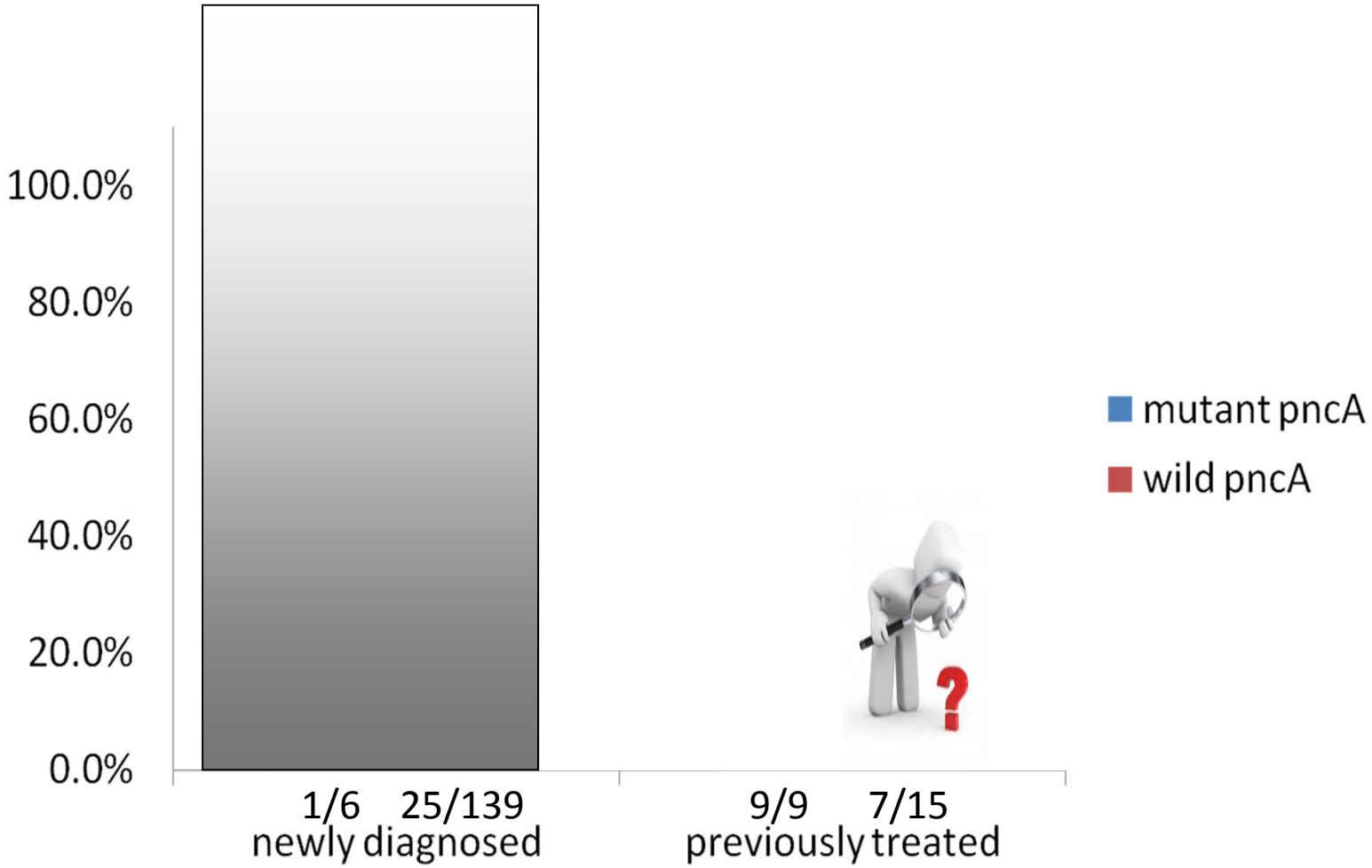
	Success (N=17)	Failure /death (N=18)	P* value	OR(95%CI)
Age(yrs, mean(SD))	62(14)	57(16)	0.987	---
Male sex, n(%)	14(82.4)	15(83.3)	1.000	1.07(0.19-6.22)
Complication, n(%)	2(11.8)	10(55.6)	0.012	9.38(1.64-53.62)
Adverse reactions, n(%)	0(0)	2(11.1)	0.486	3.18(0.30-33.58)
Cavitary TB, n(%)	5(29.4)	14(77.8)	0.007	8.40(1.83-38.57)
Baseline TB bacteria load ≥3+, n(%)	1(5.9)	10(55.6)	0.003	20.00(2.16-184.87)
substandard treatment , n(%)	0(0)	3(16.7)	0.229	4.50(0.46-44.55)
Smear-positive at 2 month, n(%)	1(22.2,N=11)	10(76.9,N=13)	0.001	33.33(2.94-377.49)
Beijing genotype, n(N,%)	9(82.0, N=10)	12(75.0, N=16)	0.617	0.33(0.03-3.52)
Mutant pncA gene, n(N,%)	0(0.0,N=8)	9(56.3,N=16)	0.009	11.25(1.17-108.41)
Baseline MDR-TB n(N,%)	1(25.0, N=8)	8(47.1,N=17)	0.182	6.22(0.62-62.16)

** Fisher exact test*

Distribution of pncA gene mutations in previously treated pulmonary TB patients

	Wild pncA (N=18)	Mutant pncA (N=9)	P value	OR (95% CI)
Age> 60yrs(n, %)	5(27.8)	7(77.8)	0.037	9.10(1.39-59.62)
Male sex, n(%)	4(22.2)	1(11.1)	0.636	0.44(0.04-4.62)
Cavitary TB, n(%)	11(61.1)	8(88.9)	0.201	5.09(0.52-50.00)
Baseline TB bacteria load ≥3+, n(%)	9(50.0)	4(44.4)	1.000	0.80(0.16-3.99)
Beijing genotype, n(N,%)	15(83.3)	5(55.6)	0.175	0.25(0.04-1.52)
Baseline resistance to any kind of antitubercular agent (HREZSKm), n(N,%)	10(55.6)	8(88.9)	0.193	6.40(0.66-62.40)
MDR-TB	5(27.8)	6(66.7)	0.097	5.20(0.92-29.26)

Treatment failure rate stratified by *pncA* mutation in previously treated patients(N=169)



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Factors associated with treatment outcomes in previously treated patients with wild pncA gene(N=15)

	Success (N=8)	Failure /death (N=7)	P *value	OR (95% CI)
Age(yrs, mean(SD))	67(22)	69(7)	0.824	------
Male sex, n(%)	6(75.0)	5(71.4)	1.000	0.83(0.08-8.24)
Complication, n(%)	1(12.5)	2(28.6)	0.569	2.80(0.20-40.06)
Cavitary TB, n(%)	3(37.5)	6(85.7)	0.119	10.0(0.77-128.78)
Baseline TB bacteria load ≥3+, n(%)	1(12.5)	5(71.4)	0.041	17.5(1.22-250.36)
substandard treatment , n(%)	0(0)	2(28.6)	0.200	4.50(0.37-54.16)
Smear-positive at 2 month, n(N,%)	1(16.7.,N=6)	3(60.0,N=5)	0.242	7.50(0.46-122.70)
Beijing genotype, n(%)	7(87.5)	7(100)	1.000	2.00(0.15-26.73)
Baseline MDR-TB n(%)	1(12.5)	1(14.3)	1.000	1.17(0.06-22.94)
Baseline resistance to any kind of antitubercular agent (HREZSKm), n(N,%)	4(50.0)	4(57.1)	1.000	1.33(0.17-10.25)

**Fisher exact test*

Conclusions

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Thank you!


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