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Epidemiology of pyrazinamide-resistant tuberculosis in the United States, 1999-2009

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Abstract

Introduction—Pyrazinamide (PZA) is essential in tuberculosis (TB) treatment. We describe the prevalence, trends and predictors of PZA resistance in *Mycobacterium tuberculosis* complex (MTBC) in the U.S.

Methods—We analyzed culture-positive MTBC cases with reported drug susceptibility tests (DST) for PZA in 38 jurisdictions routinely testing for PZA susceptibility from 1999-2009. National TB Genotyping Service data for 2004-2009 were used to distinguish *Mycobacterium tuberculosis* from *Mycobacterium bovis* and determine phylogenetic lineage.

Results—Overall 2.7% (2,167/79,321) of MTBC cases had PZA resistance, increasing annually from 2.0% to 3.3% during 1999-2009 ($P < 0.001$), largely due to an increase in PZA monoresistance. PZA-monoresistant MTBC (versus drug-susceptible) was associated with age 0-24 years (adjusted prevalence ratio [aPR]=1.50, 95% CI 1.31-1.71), Hispanic ethnicity (aPR=3.52, 2.96-4.18), HIV infection (aPR=1.43, 1.15-1.77), extrapulmonary disease (aPR=3.02,

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent official views of the U.S. Centers for Disease Control and Prevention.

Author Contributions:

Ekaterina V. Kurbatova had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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2.60-3.52), and normal chest radiograph (aPR=1.88, 1.63-2.16), and inversely associated with Asian (aPR=0.59, 0.47-0.73) and Black (aPR=0.37, 0.29-0.49) race. Among multidrug-resistant (MDR) cases 38.0% were PZA-resistant; PZA resistance in MDR MTBC was associated with female sex (aPR=1.25, 1.08-1.46) and previous TB diagnosis (aPR=1.37, 1.16-1.62). Of 28,080 cases with genotyping data, 925 (3.3%) had PZA resistance; 465/925 (50.3%) were *M. bovis*. In non-MDR *M. tuberculosis* cases, PZA resistance was higher in the Indo-Oceanic than the East Asian lineage (2.2% versus 0.9%; respectively; aPR=2.26, 1.53-3.36), but in MDR cases it was lower in the Indo-Oceanic lineage (22.0% versus 43.4%, respectively; aPR=0.54, 0.32-0.90).

Conclusions—Specific human and mycobacterial characteristics were associated with pyrazinamide-resistant MTBC, reflecting both specific subgroups of the population and phylogenetic lineages of the mycobacteria.

Keywords

tuberculosis; drug resistance; epidemiology; pyrazinamide

Introduction

Pyrazinamide (PZA) is an important component of first-line and second-line regimens for treatment of drug-susceptible and multidrug-resistant (MDR) tuberculosis (TB) [1-3]. PZA has remarkable sterilizing effects, playing a unique role in killing semi-dormant TB bacilli not easily killed by other antibiotics[4, 5]. In drug-susceptible TB, adding PZA to rifampin and isoniazid allowed shortening the duration of treatment from 9 to 6 months in most patients[6, 7]. Recent murine and human early bactericidal activity studies of novel drug regimens, demonstrated PZA was essential to well-performing regimens[8-10].

Growth-based testing for PZA resistance is difficult because the drug is active only in an acidic microenvironment (pH 5.5), but such low pH itself inhibits the growth of *Mycobacterium tuberculosis* complex (MTBC). Further, even modest variations in inoculum size can alter the pH and lead to differing results[11, 12]. For these technical reasons, most countries and some mycobacteriology laboratories in the U.S. do not test for PZA susceptibility, and the global extent of PZA resistance is largely unknown. The Clinical and Laboratory Standards Institute recommended the BACTEC 460TB (BD, Sparks, MD, USA) as a reference method for PZA susceptibility testing[13]. However, in 2011 BD stopped producing reagents for the BACTEC 460TB system, so BACTEC Mycobacteria Growth Indicator Tube® (MGIT) 960 system (BD, Sparks, MD, USA) and VersaTREK® (TREK Diagnostic Systems, Inc., Cleveland, OH, USA) are currently the only Food and Drug Administration (FDA) cleared systems for PZA drug susceptibility testing (DST)[14]. These systems, however, may have a higher potential for false-resistant test results for PZA resistance than the BACTEC 460TB[12, 15].

Mycobacterium bovis, a member of MTBC, is intrinsically resistant to PZA, and PZA-monoresistance is characteristic of *M. bovis*[16, 17]. In the U.S., *M. bovis* is transmitted to humans primarily by ingestion of unpasteurized dairy products and more often involves extrapulmonary sites of disease[18, 19].

Because PZA will likely remain a central component in the treatment of tuberculosis for the foreseeable future, it is critically important to understand the epidemiology of PZA resistance. We describe the prevalence, trends, and risk factors for initial resistance to PZA among MTBC cases in the U.S.

Methods

Case reporting

The U.S. National TB Surveillance System (NTSS) at the U.S. Centers for Disease Control and Prevention (CDC) has collected nationwide TB incidence data since 1953[20]. We analyzed data on all verified, culture-positive tuberculosis cases reported by the 50 states and the District of Columbia through the Report of Verified Case of Tuberculosis (RVCT) form between 1 January 1999 and 31 December 2009. The RVCT form includes socio-demographic and clinical information as well as DST results based on the initial positive culture of sputum or other specimen[21]. We examined overall and annual proportions of culture-positive MTBC cases with reported initial DST results for PZA. For this analysis, we excluded TB cases without reported DST results for isoniazid (INH), rifampin (RMP), and ethambutol (EMB). We also excluded states where the overall proportion of culture-positive TB cases with reported initial DST results to PZA was <85% during the study period.

Since data about sub-species are not available to most clinicians who treat TB (as the majority of the US public health labs use Accuprobe™ tests for culture identification reported as MTBC, and the genotype data which identifies sub-species are not immediately available)[22], we first characterize the epidemiology and factors associated with PZA-resistance among cases of MTBC as a whole. Because *M. bovis* has intrinsic resistance to PZA, we distinguished MTB and *M. bovis* for a sub-set of MTBC cases by linking NTSS data to data in the National TB Genotyping Service (NTGS) database[23] from 2004, when the NTGS was launched, to 2009. Spacer oligonucleotide typing (spoligotyping) and mycobacterial interspersed repetitive unit variable number tandem repeats (MIRU-VNTR) techniques distinguished *M. tuberculosis* (*Mtb*) and *M. bovis* and identified phylogenetic lineages for *Mtb* as previously described[18, 24, 25].

Definitions

“Drug-susceptible” was defined as susceptibility to INH, RMP, EMB, and PZA. MDR was defined as resistance to at least INH and RMP. “PZA monoresistance” was defined as resistance to PZA, and susceptibility to INH, RMP and EMB. “PZA polyresistance” was defined as resistance to PZA with additional resistance to INH, RMP, or EMB, but not both INH and RMP.

“Acquired” resistance to an anti-TB drug was used to describe a case in which the DST of the initial isolate was recorded as “susceptible,” and that of the final isolate was recorded as “resistant” to the same drug.

Statistical analyses

Statistical analyses were performed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC). A P value of 0.05 was considered statistically significant. Risk factors associated with PZA resistance were determined among cases with MTBC, and among a subset of cases with infection with *Mtb* for 2004-2009 after matching with genotyping data. Prevalence ratios (PR) with 95% confidence intervals (CI) were calculated. Factors significant at a value of $P < 0.05$ and plausible epidemiological or biological associations with PZA resistance were included in a multivariable log-binomial regression model. We used backward selection starting with all candidate variables selected based on statistical criteria and plausible epidemiological or biological associations with PZA resistance and tested if the deletion of variables improved precision around point estimates in the model, repeating this process until no further improvement was possible.

For testing the significance of trends, we assessed the slope of the regression line using Poisson regression for event count data. Annual Percent Change (APC) in rates with confidence limits (CL) was calculated using Joinpoint Regression Program, Version 3.5.2. October 2011 (Statistical Research and Applications Branch, National Cancer Institute)[26].

Results

PZA resistance proportions, trends, and predictors in MTBC cases

During the 11-year study period, 125,778 culture positive MTBC cases were reported by the 50 U.S. states and the District of Columbia (**Figure 1**). In 36 states and 2 other public health jurisdictions, the proportion of culture-positive MTBC cases that had DST results reported to the NTSS for PZA was 85% (**Figure 2A**), amounting to 82,672 TB cases. Of these, 79,321 (95.9%) had DST result for all 4 first-line drugs and were included in the analysis (**Figure 1**). A total of 2,167 (2.7%) cases had initial PZA resistance: 1,441 (66.5%) were PZA-monoresistant, 312 (14.4%) were PZA-polyresistant and 414 (19.1%) were PZA-resistant MDR cases. Resistance to PZA was reported in 2.2% of non-MDR cases, and 38.0% of MDR cases. In the 14 states excluded from analysis, $<50\%$ of cases per year had a DST result for PZA during the study period, with the exception of 2009 (**Figure 2B**).

The proportion of any resistance to PZA increased significantly from 2.0% in 1999 to 3.3% in 2009 ($P < 0.001$) (**Figure 2A**). Overall reported PZA resistance increased mainly because the proportion of PZA-monoresistance increased from 1.2% in 1999 to 2.5% in 2009 with the inflection point (“joinpoint”) for APC in 2002 (APC 1999-2002: 12.9, CL: 5.0, 19.7, $P = 0.005$; APC 2002-2009: 6.0, CL: 4.3, 7.6; $P < 0.001$), while the proportions were stable for PZA-polyresistance ($P = 0.40$) and PZA resistance among MDR cases ($P = 0.98$) (**Figure 3A**).

A total of 4,961 cases were alive at diagnosis, initially treated with PZA and had both initial and final DST result to PZA reported to the NTSS. Of 4,769 (96.1% of 4961) cases with an initial isolate reported as PZA-susceptible, 36 (0.8%) cases had a final DST reported as resistant (i.e., “acquired” resistance to PZA).

Results of descriptive analysis of predictors of monoresistance, polyresistance, and PZA resistance with MDR in MTBC cases are shown in **Table 1**. The results of multivariable

analysis are presented in **Table 2**. PZA-mono-resistance (versus drug-susceptible) was associated with age 0-24 years (adjusted prevalence ratio [aPR]=1.50, 95% CI 1.31-1.71), Hispanic ethnicity (aPR=3.52, 2.96-4.18), HIV infection (aPR=1.43, 1.15-1.77), extrapulmonary disease (aPR=3.02, 2.60-3.52), normal chest radiograph (aPR=1.88, 1.63-2.16), and inversely associated with Asian (aPR=0.59, 0.47-0.73) and Black (aPR=0.37, 0.29-0.49) race, substance use (aPR=0.80, 0.67-0.97), homelessness (aPR=0.43, 0.28-0.65), and residence in correctional facility (aPR=0.41, 0.23-0.73). PZA-poly-resistance (versus drug-susceptible) was associated with Hispanic ethnicity (aPR=2.49, 1.67-3.71), Asian (aPR=2.68, 1.82-3.96) race, previous TB diagnosis (aPR=1.78, 1.15-2.75), and normal chest x-ray (aPR=1.56, 1.17-2.08), and inversely associated with age \geq 45 years (aPR=0.72, 0.56-0.92). PZA resistance in MDR cases (versus PZA-susceptible MDR) was associated with female sex (aPR=1.25, 1.08-1.46) and previous TB diagnosis (aPR=1.37, 1.16-1.62).

PZA resistance proportions and trends in MTBC cases with available genotyping

The NTGS began in 2004 and by the end of 2009, genotyping results were available for 28,080 (69.9%) of 40,151 TB cases during that period that had DST to 4 first-line drugs. Among the genotyped isolates, 27,428 (97.7%) were *Mtb*, 500 (1.8%) were *M. bovis*, and 152 (0.5%) were *M. africanum*. Of 28,080 MTBC isolates, 925 (3.3%) had any PZA resistance, including 465 (50.3%) that were *M. bovis*. Among 27,428 *Mtb* isolates, 458 (1.7%) had any resistance to PZA: 196 (42.8%) were PZA-mono-resistant, 94 (20.5%) were PZA-poly-resistant, and 168 (36.7%) were PZA-resistant MDR.

M. bovis accounted for 427 (68.3%) of 625 MTBC isolates with PZA-mono-resistance, 37 (28.2%) of 131 with reported PZA-poly-resistance, and 1 (0.6%) of 169 with PZA-resistant MDR cases. Of 500 *M. bovis* isolates, 35 (7.0%) were reported as PZA-susceptible.

During 2004-2009, the annual proportion of *M. bovis* among MTBC isolates ranged between 1.6-2.0% and did not significantly change over time (APC=2.1, CL: -4.6, 9.2; P=0.45) (**Appendix. Figure 1A**). Among 28,080 MTBC isolates, the proportions of PZA-mono-resistance increased significantly (P=0.004) (**Figure 3B**). This trend remained significant when *M. bovis* was excluded (P=0.02), although proportions of mono-resistance to PZA were approximately three times lower in the sub-set of *Mtb* cases compared to MTBC (**Figure 3C**).

Predictors of PZA resistance in *M. tuberculosis* cases

Further analyses were limited to the subset of cases with *Mtb* only, excluding *M. bovis* and *M. africanum*, in order to understand factors associated with PZA resistance in *Mtb*. The prevalence of any PZA resistance differed by *Mtb* lineage: 2.9% of East Asian (110/3,857), 2.4% of Indo-Oceanic (121/5,037), 1.8% of East African Indian (25/1,367), and 1.2% of Euro-American (206/17,314). The proportion of *Mtb* cases with Indo-Oceanic lineage significantly increased from 2004-2009 (APC=4.7, CL: 1.6, 7.9; P=0.01) (**Appendix. Figure 1A**). Similarly, the proportion of PZA-mono-resistance significantly increased among *Mtb* cases infected with Indo-Oceanic (APC=14.2, CL: 7.0-21.8; P=0.005) and East African Indian (APC=38.6, CL: 1.0-90.3; P=0.05) isolates, but not among other lineages.

The results of multivariable analysis examining the associations between clinical and demographic characteristics and PZA resistance in *Mtb* cases are presented in **Table 3**. The patient characteristics associated with PZA resistance in the subset of cases with *Mtb* differed from those for all MTBC cases. Among cases with *Mtb*, PZA mono-resistance was associated with Asian race and extrapulmonary TB. When *Mtb* lineage was included in the multivariable model, PZA monoresistance was associated with Indo-Oceanic lineage and was no longer associated with race or site of disease (**Table 4**). MDR status significantly modified the association between PZA resistance and *Mtb* lineage ($P < 0.001$, Breslow-Day test). Among non-MDR cases, PZA resistance was significantly higher in the Indo-Oceanic (2.2%) versus East Asian (0.9%) lineage (aPR=2.26, 95% CI 1.53-3.36), while in MDR cases, PZA resistance was significantly lower in the Indo-Oceanic (22.0%) versus East Asian (43.4%) lineage (aPR=0.54, 0.32-0.90), controlling for age, race, foreign birth, HIV status, previous TB diagnosis and site of TB disease (**Table 4**).

Discussion

This large study of PZA resistance among MTBC cases in the U.S. demonstrates PZA resistance in 2.7% of tested MTBC cases in 38 public health jurisdictions routinely testing for PZA susceptibility: 2.2% of non-MDR and 38.0% of MDR cases. For comparison, Australia surveillance data for 2008-2009 reported PZA resistance in 1.0%-1.2% of all TB cases[27]. Four rounds of drug resistance surveys in South Korea conducted from 1999-2004 showed a significant increase of PZA resistance in new cases from 0.8% to 2.1% [28]. In re-treatment cases, PZA resistance varied from 3.5% to 15.9% with no clear trend[28]. A study from Thailand indicated PZA resistance in 6% of non-MDR and 49% MDR TB isolates[29]. The proportion of MDR TB cases with PZA resistance ranged from 36% to 85% in other reports[30-34].

Patient characteristics associated with PZA monoresistance among all cases with MTBC included Hispanic race, young age, and extrapulmonary disease. PZA monoresistance is typical of [0]*M. bovis*, and the patient characteristics we identified in this analysis are similar characteristics associated with TB due to *M. bovis*[18]. Indeed, two thirds of all PZA-monoresistant cases were among cases with *M. bovis*. In contrast, among MDR TB cases, PZA resistance was higher in females, in cases with previous TB, and almost exclusively in MTB species. Interestingly, the adjusted prevalence of PZA polyresistance, compared to drug-susceptible TB, included a mix of risk factors found for PZA monoresistance and PZA resistance in MDR, likely reflecting the broader mix of *M. bovis* and MTB species. Clinicians should be aware that patients with certain characteristics are more likely to have PZA-resistant TB. However, our findings confirm previous reports that PZA monoresistance is not a reliable marker of *M. bovis*[18, 35, 36]. Although not typically available for initial case management, species identification is important to better understand these findings.

Factors associated with PZA resistance among cases of *Mtb* are less well understood. In the analysis of only cases with *Mtb* we found that PZA monoresistance was associated with Asian race rather than Hispanic ethnicity, and with exclusively extrapulmonary disease. Because site of disease has been shown to be associated with *Mtb* lineage[24, 37], and these

lineages are differentially associated with human populations globally[38], we sought to determine whether the patient characteristics associated with *Mtb* PZA monoresistance reflected differences in *Mtb* lineage. In multivariable analysis including *Mtb* lineage, only Indo-Oceanic lineage remained significantly associated with PZA monoresistance, suggesting that bacterial lineage, rather than host characteristic, was the primary association. Globally, Indo-Oceanic lineage is primarily localized to South and Southeast Asia[38]. Our findings suggest two possible hypotheses for the association between PZA monoresistance and Indo-Oceanic lineage. First, this may reflect a biological difference by lineage in the propensity towards development of resistance to this drug. Second, these results would also be consistent with international differences in rates of PZA resistance (e.g. due to regional or national programmatic differences in TB treatment). Over half of all TB cases in the US are foreign-born[20].

In contrast to other first-line drugs (including any resistance and monoresistance to INH or rifampin as well as MDR)[20], the proportion of cases with reported resistance to PZA increased in the U.S. from 2.0% to 3.3%, 65% relative increase, largely due to an increase in PZA-monoresistance. Since PZA-monoresistance is characteristic of *M. bovis*, we assessed proportions of *M. bovis* in a sub-set of MTBC cases with genotyping results available for 2004-2009. *M. bovis* did not significantly increase, and the proportion of PZA-monoresistance increased irrespective of *M. bovis*. The prevalence of PZA resistance differed among different lineages of *Mtb* and the relative prevalence of these lineages among TB isolates was changing over time in our study population. Among MDR TB cases, PZA resistance was significantly higher in the East Asian lineage, while in non-MDR cases PZA resistance was significantly higher in the Indo-Oceanic lineage. Even though the proportion of PZA resistance among isolates from MDR TB cases is much higher than those among non-MDR cases, there were only 1,090 MDR TB cases in this analysis compared with 78,231 non-MDR TB cases. Both the proportion of TB cases with Indo-Oceanic lineage and the proportion of Indo-Oceanic cases with PZA resistance increased over time. Therefore, given that increasing PZA monoresistance in the U.S. does not appear to be related to *M. bovis*, it may be related to increases in the proportion of Indo-Oceanic strains. An increase in the proportion of Indo-Oceanic strains could be related to an increase in the proportion of cases in the U.S. among foreign-born persons from regions in which the Indo-Oceanic lineage is common.

On the other hand, because MGIT 960 has been shown to have higher rates of false-resistant results compared to the BACTEC 460 system [15, 39], we considered that increasing proportions of PZA monoresistance might reflect the progressive change from BACTEC 460TB to MGIT 960 after FDA clearance in 2002[40]. However, PZA resistance began increasing 3 years earlier, in 1999, and did not accelerate after 2002, suggesting the change in technology may not be the main reason behind the trend in PZA DST results.

Our analysis was subject to several important limitations. The main limitation is restriction of the analysis to 38 public health jurisdictions that routinely test for susceptibility to PZA. For the other 14 states the prevalence and trends may have been due to selection bias. Thus, the study findings may not generalize to the whole country. However, the overall proportion of cases with reported PZA resistance during 1999-2009 was similar in the jurisdictions

included in analysis (2.7%) and the 14 states excluded (2.9%); in both subsets, the proportions of resistance to PZA were significantly increasing. Second, the genotyping data was limited to 2004-2009. Genotyping in the U.S. is voluntary and coverage increased substantially from 51.2% to 88.2% during 2004-2010 [25]. Therefore selection bias cannot be excluded. Third, surveillance data have intrinsic limitations, and we could not exclude PZA susceptibility testing or reporting errors. For example, 7% of *M. bovis* cases were reported as PZA-susceptible, likely representing intrinsic variability of the PZA test itself and reporting errors[18]. PncA gene sequencing for PZA resistant strains is not routinely performed and surveillance data does not include this information, therefore we were not able to determine the correlation between phenotypic drug resistance result and PncA genotype.

PZA resistance in terms of absolute numbers represents a small fraction of U.S. TB cases, but the increasing trend in PZA resistance makes it an important public health problem because PZA is an essential part of treatment [1-3, 8-10]. Thus, DST for PZA is critical. The trend in PZA resistance calls attention to the limitations of growth-based DST for PZA, although meticulous attention to the size of the inoculum seems to improve its reproducibility[12]. Nonetheless, the development of faster, more reliable laboratory methods to detect PZA resistance is a priority[41, 42]. The phylogenetic diversity of *Mtb* may have important clinical consequences and implications for development of molecular assays for PZA resistance.

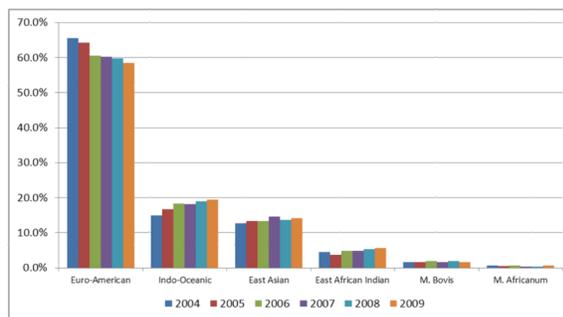
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Appendix

Figure 1A. Time trends in proportion of MTBC species and *M. tuberculosis* lineages (N=28,080)



Note. Percents are shown using total number of MTBC as a denominator.

Among 27,428 *M. tuberculosis* cases the phylogenetic lineages were assigned as following: Euro-American 17,208 (62.7%), Indo-Oceanic - 5,019 (18.3%), East Asian - 3,839 (14.0%),

East African Indian - 1,362 (5.0%). From 2004 to 2009, no significant changes in proportions of *M. bovis* (APC=2.1, CL: -4.6, 9.2; P=.45). The proportion of Indo-Oceanic lineage significantly increased (APC=4.7, CL: 1.6, 7.9; P=.01), and the proportion of Euro-American lineage significantly decreased (APC=-2.2, CL: -3.1, -1.3; P=.003). Proportions of East Asian (APC=2.1, CL: -0.6, 4.8; P=.10) and East African Indian (APC=5.6, CL: -0.6, 12.2; P=.07) lineages did not change significantly. No significant changes in *M. africanum* proportions (APC=-5.7, CL: -17.0, 7.1; P=.27).

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Key points

In U.S. jurisdictions routinely testing *Mycobacterium tuberculosis* complex for pyrazinamide susceptibility, pyrazinamide resistance increased from 2.0% to 3.3% per year during 1999-2009. Changing human and mycobacterial characteristics were associated with this increase in resistance, including phylogenetic lineage of *M. tuberculosis*.

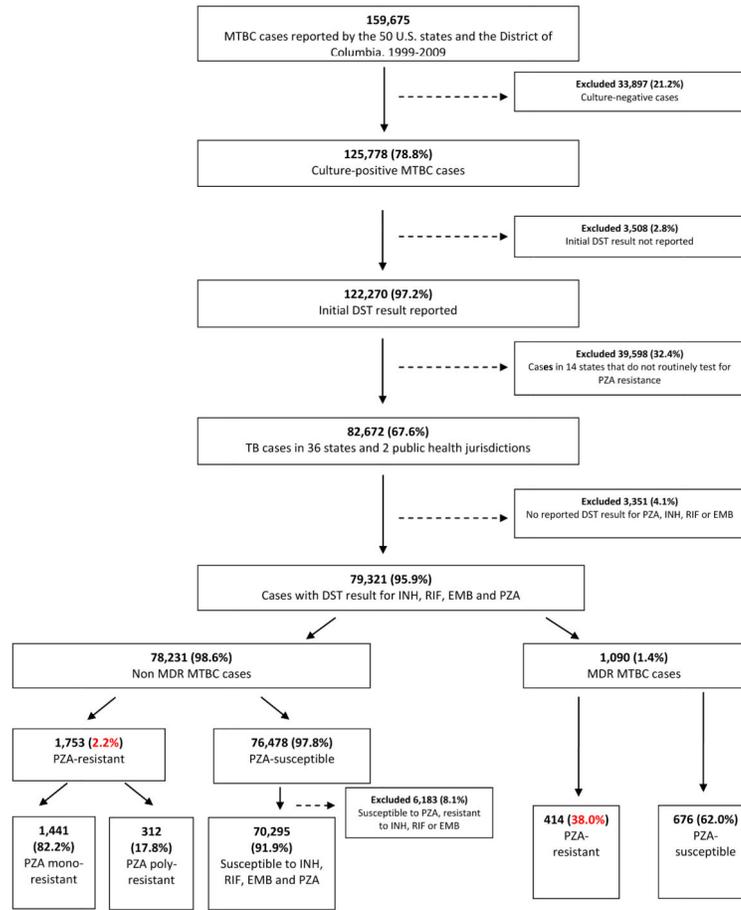


Figure 1. Selection of MTBC cases with resistance to pyrazinamide (PZA) reported in NTSS, 1999-2009

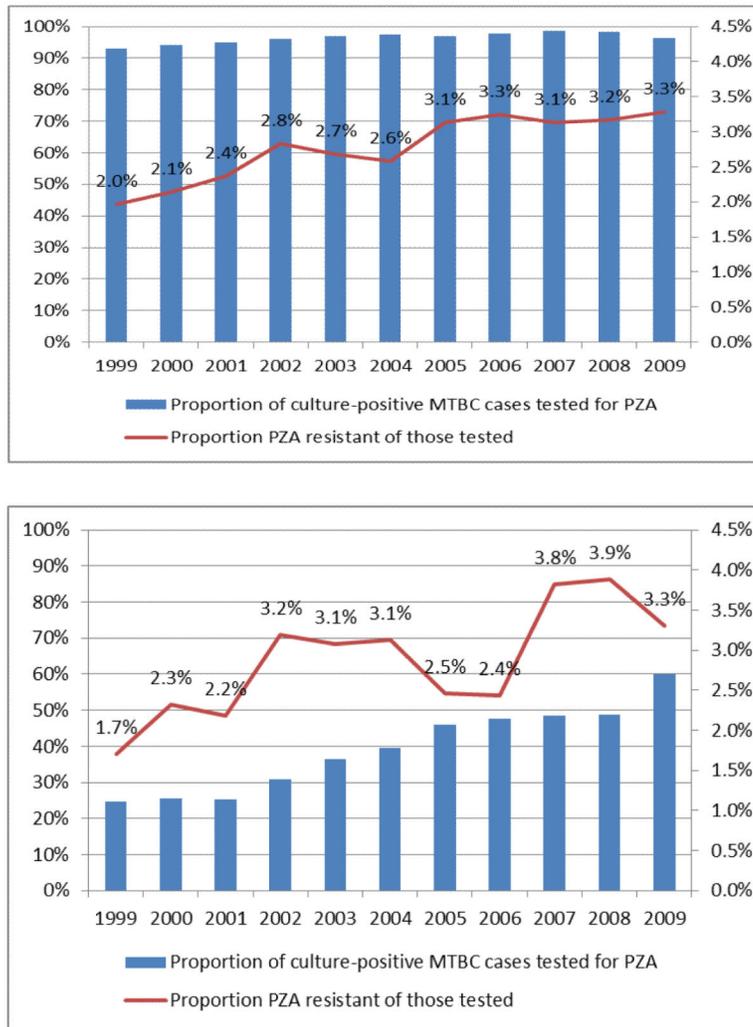


Figure 2. Proportion of culture-positive MTBC cases with a reported PZA drug susceptibility test result, and proportion reported as resistant to PZA among those tested, 1999-2009 (N=122,270)

A. Data for 36 states and 2 public health jurisdictions with 85% TB cases with reported DST result for PZA (N=82,672)

Note. Overall 2.7% of cases had resistance to PZA. Proportions of resistance to PZA significantly increased (APC=5.0, CL: 3.2, 6.7; P<0.001).

B. Data for 14 states with <85% TB cases with reported DST result for PZA (N=39,598)

Note. Overall 2.9% of cases had resistance to PZA. Proportions of resistance to PZA significantly increased (APC=5.4, CL: 1.2, 9.6; P=0.02).

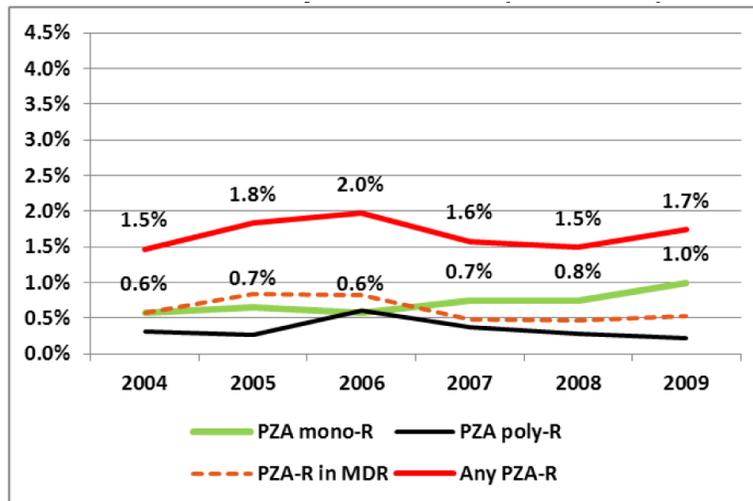
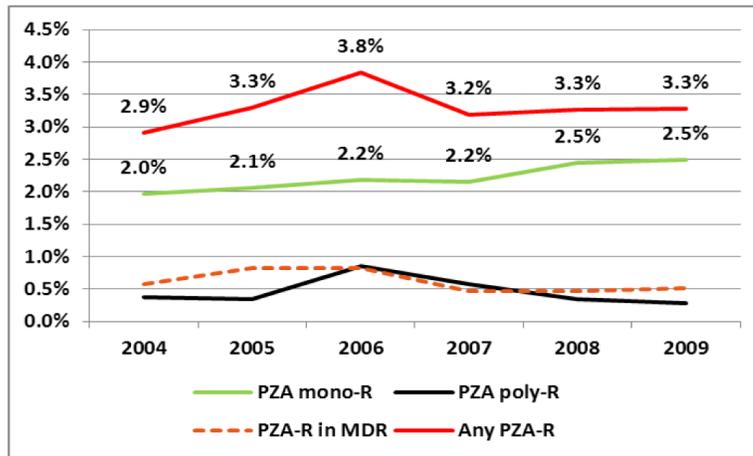
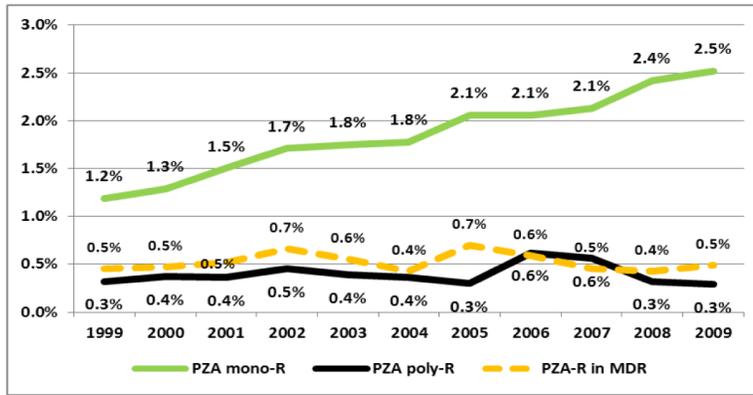


Figure 3. Trends in proportions of PZA resistance in MTBC and *M. tuberculosis*. Percent reflects proportion of cases with specific resistance pattern among all cases tested for PZA drug susceptibility in each sub-set.
 A. All MTBC cases, with or without available genotype, 1999-2009 (N=79,321)

Increase in proportions of PZA-mono-resistance was significant (APC during 1999-2002: 12.9, CL: 5.0, 19.7, P=0.005; APC during 2002-2009: 6.0, CL: 4.3, 7.6; P<0.001), while no significant change in proportions of PZA-poly-resistance (APC=2.4, CL: -3.6, 8.7; P=0.40) and PZA resistance in MDR (APC=-0.04, CL: -4.2, 4.3; P=0.98) observed.

B. MTBC cases with available genotype *M. bovis* included, 2004-2009 (N=28,080)

For mono-resistance APC=9.0, CL: 2.5, 15.9; P=0.02; for poly-resistance APC=0.3, CL: -37.7, 61.5; P=0.99; for PZA resistance in MDR TB cases APC=-4.4, CL: -19.7, 13.8; P=0.51; for any PZA resistance APC=5.0, CL: -4.5, 15.3; P=0.23

C. M. tuberculosis cases only, 2004-2009 (N=27,428)

For mono-resistance APC=11.0, CL: 2.6, 20.1; P=0.02; for poly-resistance APC=-7.2, CL: -31.4, 25.6; P=0.53; for PZA resistance in MDR TB cases APC=-8.5, CL: -23.2, 8.8; P=0.23; for any PZA resistance APC=-0.1, CL: -8.4, 9.0; P=0.97.

Socio-demographic and clinical characteristics associated with initial resistance to PZA in MTBC cases (N=73,138)

Table 1

Characteristics	Prevalence Ratio (95% Confidence Interval)					
	No. (%)	PZA-mono-R (n=1,441)	PZA-poly-R MDR (n=414)	PZA-mono-R vs. Drug susceptible	PZA-poly-R vs. Drug susceptible	PZA-R in MDR vs. PZA-S in MDR
Sex						
Female	122 (2.2)	122 (0.5)	207 (42.7)	1.20 (1.08-1.33)	1.04 (0.83-1.31)	1.25 (1.08-1.46)
Male	826 (1.9)	190 (0.4)	206 (34.1)	1.00	1.00	1.00
Age categories, years						
0-4	77 (10.1)	5 (0.7)	7 (70.0)	5.07 (4.04-6.38)	1.31 (0.54-3.18)	1.84 (1.21-2.81)
5-14	85 (13.6)	6 (1.1)	9 (60.0)	6.83 (5.50-8.47)	1.98 (0.88-4.47)	1.58 (1.03-2.42)
15-24	204 (2.6)	30 (0.4)	71 (40.8)	1.29 (1.10-1.52)	0.70 (0.47-1.03)	1.07 (0.87-1.33)
25-44	503 (2.0)	138 (0.6)	196 (38.0)	1.00	1.00	1.00
45-64	309 (1.5)	73 (0.4)	98 (34.9)	0.74 (0.65-0.86)	0.64 (0.48-0.85)	0.92 (0.76-1.11)
65	263 (1.6)	60 (0.4)	33 (35.1)	0.81 (0.70-0.94)	0.67 (0.50-0.91)	0.92 (0.69-1.24)
Race/ethnicity						
Hispanic	982 (5.3)	107 (0.6)	111 (38.5)	4.31 (3.64-5.09)	2.62 (1.74-3.95)	0.97 (0.73-1.28)
Asian	197 (1.0)	128 (0.7)	178 (38.2)	0.83 (0.67-1.02)	2.87 (1.92-4.29)	0.96 (0.74-1.25)
Non-Hispanic Black	95 (0.5)	45 (0.2)	79 (35.4)	0.40 (0.31-0.52)	1.02 (0.64-1.63)	0.89 (0.66-1.20)
American Indian	8 (0.7)	2 (0.2)	0 (0)	0.55 (0.27-1.11)	0.73 (0.17-3.06)	Undefined
Non-Hispanic multiple	1 (0.8)	1 (0.8)	3 (100)	0.69 (0.10-4.87)	3.66 (0.50-26.66)	2.51 (1.98-3.19)
Unknown	2 (0.8)	0 (0)	2 (50.0)	0.63 (0.16-2.52)	undefined	1.26 (0.46-3.44)
Non-Hispanic White	156 (1.2)	29 (0.2)	41 (39.8)	1.00	1.00	1.00
Country of birth						
Foreign-born nationals	1017 (2.4)	237 (0.6)	316 (37.2)	1.62 (1.45-1.82)	2.15 (1.66-2.79)	0.92 (0.77-1.10)
U.S.-born	419 (1.5)	74 (0.3)	96 (40.5)	1.00	1.00	1.00
Occupation during 2 years prior to diagnosis						
Unemployed	779 (2.1)	155 (0.4)	229 (40.4)	1.10 (0.98-1.22)	0.93 (0.74-1.17)	1.14 (0.97-1.34)
Employed/not seeking empl.	553 (1.9)	130 (0.5)	148 (35.4)	1.00	1.00	1.00
Health care worker	26 (1.2)	7 (0.3)	19 (37.3)	0.65 (0.44-0.96)	0.74 (0.34-1.57)	1.05 (0.72-1.54)
Other employment	553 (1.9)	130 (0.5)	148 (35.4)	1.00	1.00	1.00
Yes	15 (0.8)	4 (0.2)	6 (33.3)	0.39 (0.23-0.65)	0.47 (0.18-1.27)	0.87 (0.45-1.69)
No	1425 (2.0)	308 (0.4)	408 (38.2)	1.00	1.00	1.00

Characteristics	No. (%)		Prevalence Ratio (95% Confidence Interval)			
	PZA-mono-R (n=1,441)	PZA-poly-R (n=312)	PZA-R/MDR (n=414)	PZA-mono-R vs. Drug susceptible	PZA-poly-R vs. Drug susceptible	PZA-R in MDR vs. PZA-S in MDR
Homeless in the year prior to diagnosis	Yes	9 (0.2)	15 (34.9)	0.28 (0.19-0.41)	0.41 (0.21-0.80)	0.91 (0.60-1.38)
	No	1393 (2.1)	300 (0.5)	392 (38.2)	1.00	1.00
Substance use (alcohol, IDU, non-IDU)	Yes	139 (1.1)	33 (0.3)	50 (38.2)	0.50 (0.42-0.59)	0.54 (0.38-0.78)
	No	1299 (2.2)	279 (0.5)	363 (37.9)	1.00	1.00
Prior TB diagnosis	Yes	35 (1.1)	22 (0.7)	96 (48.5)	0.54 (0.39-0.76)	1.63 (1.06-2.52)
	No	1397 (2.1)	289 (0.4)	313 (35.6)	1.00	1.00
Location of TB disease	Extrapulmonary (EP) alone	630 (4.7)	70 (0.5)	46 (39.0)	4.34 (3.88-4.86)	1.36 (1.04-1.78)
	Pulmonary & EP	256 (3.6)	39 (0.6)	32 (34.8)	3.29 (2.84-3.80)	1.39 (0.99-1.96)
	Pulmonary alone	552 (1.1)	203 (0.4)	334 (38.0)	1.00	1.00
Sputum microscopy result for AFB	Positive	426 (1.3)	137 (0.4)	237 (38.8)	0.65 (0.58-0.74)	1.01 (0.79-1.30)
	Negative	544 (2.0)	112 (0.4)	140 (35.5)	1.00	1.00
Sputum culture result for MTBC	Positive	673 (1.3)	215 (0.4)	341 (37.7)	0.39 (0.34-0.45)	1.13 (0.77-1.68)
	Negative	260 (3.4)	28 (0.4)	39 (40.2)	1.00	1.00
HIV test result	Positive	113 (1.9)	23 (0.4)	50 (37.3)	1.45 (1.18-1.79)	0.92 (0.59-1.43)
	Unknown	929 (2.7)	160 (0.5)	188 (38.7)	2.08 (1.85-2.34)	1.12 (0.89-1.42)
	Negative	399 (1.3)	129 (0.4)	176 (37.5)	1.00	1.00
Vital Status at diagnosis	Alive	1412 (2.0)	300 (0.4)	408 (38.0)	1.25 (0.86-1.81)	0.62 (0.35-1.11)
	Dead	28 (1.6)	12 (0.7)	5 (33.3)	1.00	1.00

Note. MTBC=*Mycobacterium tuberculosis* complex. R=resistant, S=susceptible. IDU=injecting drug use. AFB=acid-fast bacillus.

Table 2

Independent predictors of PZA resistance in MTBC cases in multivariable regression analysis (N=73,138)

Characteristic		Adjusted prevalence ratio (95% CI)		
		PZA-mono-R vs. Drug susceptible	PZA-poly-R vs. Drug susceptible	PZA-R/MDR vs. PZA-S/MDR
Sex	Female vs. male	-	-	1.25 (1.08-1.46)
Age group, years	0-24	1.50 (1.31-1.71)	0.81 (0.57-1.15)	-
	45+	0.85 (0.74-0.97)	0.72 (0.56-0.92)	-
	25-44	1.00	1.00	-
Race/ethnicity	Hispanic	3.52 (2.96-4.18)	2.49 (1.67-3.71)	-
	Asian	0.59 (0.47-0.73)	2.68 (1.82-3.96)	-
	Black	0.37 (0.29-0.49)	0.96 (0.61-1.52)	-
	White/Other	1.00	1.00	-
Unemployed	Yes vs. No/Unknown	1.27 (1.14-1.42)	-	-
Substance use	Yes vs. No/Unknown	0.80 (0.67-0.97)	-	-
Homeless	Yes vs. No/Unknown	0.43 (0.28-0.65)	-	-
Resident of correctional facility	Yes vs. No/Unknown	0.41 (0.23-0.73)	-	-
HIV status	Positive	1.43 (1.15-1.77)	-	-
	Unknown	1.82 (1.61-2.06)	-	-
	Negative	1.00	-	-
Previous TB diagnosis	Yes	-	1.78 (1.15-2.75)	1.37 (1.16-1.62)
	Unknown	-	0.33 (0.05-2.38)	1.12 (0.56-2.22)
Site of TB disease	No	-	1.00	1.00
	EPTB	3.02 (2.60-3.52)	-	-
	EPTB&PTB	2.91 (2.50-3.39)	-	-
	PTB	1.00	-	-
Initial chest radiograph	Normal	1.88 (1.63-2.16)	1.56 (1.17-2.08)	-
	Unknown	1.48 (1.04-2.10)	1.20 (0.54-2.70)	-
	Abnormal	1.00	1.00	-

Note. R=resistant, S=susceptible.

Table 3

Independent predictors of PZA resistance in *M. tuberculosis* cases in multivariable regression analysis (N=27,428)

Characteristic		Adjusted prevalence ratio (95% CI)		
		PZA-mono-R vs. Drug susceptible	PZA-poly-R vs. Drug susceptible	PZA-R/MDR vs. PZA-S/MDR
Age group	0-24	-	0.53 (0.26-1.09)	-
	25-44	-	1.00	-
	45+	-	0.55 (0.35-0.84)	-
Race/ethnicity	Hispanic	0.95 (0.59-1.53)	1.12 (0.41-3.09)	-
	Asian	1.79 (1.18-2.70)	3.70 (1.49-9.22)	-
	Black	0.91 (0.56-1.48)	2.02 (0.75-5.47)	-
	White/Other	1.00	1.00	-
Foreign-born	Yes	-	2.37 (1.24-4.70)	0.72 (0.55-0.93)
	No	-	1.00	1.00
Previous TB diagnosis	Yes	-	2.42 (1.24-4.70)	-
	No	-	1.00	-
Site of TB disease	EPTB	1.42 (1.02-1.99)	-	0.97 (0.66-1.43)
	EPTB&PTB	1.24 (0.80-1.92)	-	0.60 (0.34-1.05)
	PTB	1.00	-	1.00

Note. R=resistant. S=susceptible

Table 4Association of PZA resistance with *M. tuberculosis* lineage in multivariable regression analysis (N=27,428)

Characteristic		Adjusted prevalence ratio (95% CI)	
		Non MDR TB cases N=26,982	MDR TB cases N=446
Phylogenetic lineage	EuroAmerican	1.24 (0.80-1.92)	0.83 (0.61-1.13)
	IndoOceanic	2.26 (1.53-3.36)	0.54 (0.32-0.90)
	East African Indian	1.17 (0.63-2.19)	0.82 (0.49-1.40)
	East Asian	1.00	1.00
Age group	0-24	0.90 (0.63-1.30)	1.12 (0.83-1.52)
	25-44	0.72 (0.57-0.93)	0.85 (0.64-1.13)
	45+	1.00	1.00
Race/ethnicity	Hispanic	0.85 (0.52-1.38)	1.14 (0.75-1.72)
	Asian	1.48 (0.89-2.46)	0.93 (0.63-1.39)
	Black	1.03 (0.67-1.59)	0.87 (0.55-1.40)
	White/Other	1.00	1.00
Foreign-born	Yes	1.20 (0.84-1.71)	0.71 (0.53-0.97)
	No	1.00	1.00
Previous TB diagnosis	Yes	1.40 (0.87-2.26)	1.14 (0.86-1.52)
	No	1.00	1.00
Site of TB disease	EPTB	1.09 (0.82-1.46)	1.06 (0.71-1.58)
	EPTB&PTB	1.05 (0.72-1.54)	0.60 (0.34-1.06)
	PTB	1.00	
HIV infection	Yes	0.80 (0.43-1.46)	1.00 (0.65-1.52)
	No/unknown	1.00	1.00