Pyrazinamide (PZA) has important sterilizing activity in tuberculosis (TB) chemotherapy. We describe trends, risk factors, and molecular epidemiology associated with PZA-resistant (PZA\textsuperscript{r}) Mycobacterium tuberculosis in New York City (NYC). From 2001 to 2008, all incident culture-positive TB cases reported by the NYC Department of Health and Mental Hygiene (DOHMH) were genotyped by IS6110-based restriction fragment length polymorphism and spoligotype. Multidrug-resistant (MDR) isolates underwent DNA sequencing of resistance-determining regions of pncA, rpoB, katG, and fabG1. Demographic and clinical information were extracted from the NYC DOHMH TB registry. During this period, PZA\textsuperscript{r} doubled (1.6% to 3.6%) overall, accounting for 44% (70/159) of the MDR population and 1.4% (75/5511) of the non-MDR population. Molecular genotyping revealed strong microbial phylogenetic associations with PZA\textsuperscript{r}. Clustered isolates and those from acid-fast bacillus (AFB) smear-positive cases had 2.7 (95% confidence interval [CI] = 1.71 to 4.36) and 2.0 (95% CI = 1.19 to 3.43) times higher odds of being PZA\textsuperscript{r}, respectively, indicating a strong likelihood of recent transmission. Among the MDR population, PZA\textsuperscript{r} was acquired somewhat more frequently via primary transmission than by independent pathways. Our molecular analysis also revealed that several historic M. tuberculosis strains responsible for MDR TB outbreaks in the early 1990s were continuing to circulate in NYC. We conclude that the increasing incidence of PZA\textsuperscript{r}, with clear microbial risk factors, underscores the importance of routine PZA drug susceptibility testing and M. tuberculosis genotyping for the identification, control, and prevention of increasingly resistant organisms.
MATERIALS AND METHODS

All incident culture-positive TB cases reported and verified by the NYC DOHMH between January 2001 and December 2008 \((n=6,260)\) were included in the study (Fig. 1). Routine genotyping was performed by the Public Health Research Institute (PHRI) Tuberculosis Center at Rutgers University (\(\text{IS}_{6110}\)-restriction fragment length polymorphism [RFLP]) and New York State Wadsworth Center (spoligotype) \((19)\). All strains with genotyping results available \((n=5,877)\) were assigned a molecular lineage using the taxonomic designation previously described by Gagneux and Small \((20)\) and a strain code following a nomenclature system of the PHRI TB Center that has been described previously \((21, 22)\). Strains identified as Mycobacterium bovis \((n=68)\) or Mycobacterium africanum \((n=78)\) \((23)\) were omitted from our analysis. Clusters were defined as two or more strains sharing identical \(\text{IS}_{6110}\)-RFLPs and spoligotypes. DST was performed at the NYC DOHMH Public Health Laboratories and the New York State Wadsworth Center \((24)\) reference laboratories, which utilized the Bactec 460TB system \((\text{BD, Franklin Lakes, NJ})\) until 2003 and the BD Bactec MGIT 960 mycobacterial detection system thereafter. DST results were available for culture-positive TB cases for all first-line anti-TB agents: INH, RIF, ethambutol (EMB), and PZA. DST results for second-line drugs (SLD), including kanamycin, capreomycin, amikacin, fluoroquinolones, and ethionamide, were avail-

FIG 1 Study schema. MDR, resistant to at least isoniazid and rifampin; PZAR, PZA resistant; PZAS, PZA susceptible; mono-PZAR, resistant only to PZA and no other drug; MDR-PZAR, resistant to at least isoniazid, rifampin, and PZA; poly-PZAR, resistant to PZA and at least one other drug, excluding MDR-PZAR.

FIG 2 Distribution of PZAR, mono-PZAR, and MDR-PZAR TB in NYC from 2001 to 2008.


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PZA&lt;sup&gt;a&lt;/sup&gt; (n = 145)</th>
<th>PZA&lt;sup&gt;+&lt;/sup&gt; (n = 5,525)</th>
<th>Unadjusted OR</th>
<th>95% CI</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yr (IQR)</td>
<td>40 (30–50)</td>
<td>42 (30–57)</td>
<td>0.99</td>
<td>0.98–1.00</td>
<td>0.0118</td>
</tr>
<tr>
<td>Sex&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>89 (61.38%)</td>
<td>3,469 (62.79%)</td>
<td>0.94</td>
<td>0.67–1.32</td>
<td>0.7292</td>
</tr>
<tr>
<td>F</td>
<td>56 (38.62%)</td>
<td>2,056 (37.21%)</td>
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<td></td>
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<tr>
<td>U.S. born&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
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<td>Yes</td>
<td>47 (32.64%)</td>
<td>1,598 (29.03%)</td>
<td>1.18</td>
<td>0.83–1.69</td>
<td>0.3472</td>
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<tr>
<td>No</td>
<td>97 (67.36%)</td>
<td>3,906 (70.97%)</td>
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<td>History of TB</td>
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<td>Yes</td>
<td>8 (5.52%)</td>
<td>139 (2.52%)</td>
<td>2.26</td>
<td>1.09–4.71</td>
<td>0.0248</td>
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<td>No</td>
<td>137 (94.48%)</td>
<td>5,386 (97.48%)</td>
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<td>History of LTBI</td>
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</tr>
<tr>
<td>Yes</td>
<td>5 (3.45%)</td>
<td>320 (5.79%)</td>
<td>0.58</td>
<td>0.24–1.43</td>
<td>0.2308</td>
</tr>
<tr>
<td>No</td>
<td>140 (96.55%)</td>
<td>5,205 (94.21%)</td>
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<tr>
<td>History of homelessness</td>
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</tr>
<tr>
<td>Yes</td>
<td>18 (12.41%)</td>
<td>518 (9.38%)</td>
<td>1.37</td>
<td>0.83–2.26</td>
<td>0.2171</td>
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<tr>
<td>No</td>
<td>127 (87.59%)</td>
<td>5,007 (90.62%)</td>
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<td>History of substance abuse</td>
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<tr>
<td>Yes</td>
<td>19 (13.29%)</td>
<td>494 (9.15%)</td>
<td>1.52</td>
<td>0.93–2.49</td>
<td>0.0924</td>
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<tr>
<td>No</td>
<td>124 (86.71%)</td>
<td>4,903 (90.85%)</td>
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<td>History of alcohol abuse</td>
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<tr>
<td>Yes</td>
<td>24 (16.78%)</td>
<td>875 (16.20%)</td>
<td>1.04</td>
<td>0.67–1.63</td>
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<tr>
<td>No</td>
<td>119 (83.22%)</td>
<td>4,527 (83.80%)</td>
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<tr>
<td>History of Rikers treatment</td>
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<tr>
<td>Yes</td>
<td>3 (2.07%)</td>
<td>106 (1.92%)</td>
<td>1.08</td>
<td>0.34–3.44</td>
<td>0.8964</td>
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<tr>
<td>No</td>
<td>142 (97.93%)</td>
<td>5,419 (98.08%)</td>
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<td>HIV serostatus</td>
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<tr>
<td>Positive</td>
<td>31 (21.38%)</td>
<td>825 (14.93%)</td>
<td>1.39</td>
<td>0.92–2.11</td>
<td>0.1226</td>
</tr>
<tr>
<td>Negative</td>
<td>85 (58.62%)</td>
<td>3,145 (56.92%)</td>
<td>Reference</td>
<td></td>
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<tr>
<td>Unknown</td>
<td>29 (20.00%)</td>
<td>1,555 (28.14%)</td>
<td>0.69</td>
<td>0.45–1.06</td>
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<td>TB infection site</td>
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<td>Pulmonary</td>
<td>114 (78.62%)</td>
<td>3,882 (70.26%)</td>
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<tr>
<td>Extrapulmonary</td>
<td>14 (9.66%)</td>
<td>986 (17.85%)</td>
<td>0.48</td>
<td>0.28–0.85</td>
<td>0.0109</td>
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<tr>
<td>Both</td>
<td>17 (11.72%)</td>
<td>657 (11.89%)</td>
<td>0.88</td>
<td>0.53–1.48</td>
<td>0.6309</td>
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<td>Respiratory AFB smear status</td>
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<tr>
<td>Positive</td>
<td>104 (74.82%)</td>
<td>2,967 (57.77%)</td>
<td>2.17</td>
<td>1.48–3.2</td>
<td>&lt;0.0001</td>
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<tr>
<td>Negative</td>
<td>35 (25.18%)</td>
<td>2,169 (42.23%)</td>
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<td>Abnormal chest X-ray</td>
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<tr>
<td>Yes</td>
<td>59 (93.65%)</td>
<td>2,091 (88.87%)</td>
<td>1.85</td>
<td>0.67–5.13</td>
<td>0.2311</td>
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<tr>
<td>No</td>
<td>4 (6.35%)</td>
<td>262 (11.13%)</td>
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<td>Final culture conversion</td>
<td></td>
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<tr>
<td>Yes</td>
<td>106 (86.18%)</td>
<td>3,563 (85.92%)</td>
<td>1.02</td>
<td>0.61–1.72</td>
<td>0.9345</td>
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<td>No</td>
<td>17 (13.82%)</td>
<td>584 (14.08%)</td>
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<tr>
<td>Any cavitation</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32 (25.00%)</td>
<td>1,010 (21.62%)</td>
<td>1.21</td>
<td>0.81–1.81</td>
<td>0.3606</td>
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<tr>
<td>No</td>
<td>96 (75.00%)</td>
<td>3,661 (78.38%)</td>
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<tr>
<td>Any death&lt;sup&gt;d&lt;/sup&gt;</td>
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<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>23 (17.83%)</td>
<td>582 (11.18%)</td>
<td>1.72</td>
<td>1.09–2.70</td>
<td>0.0187</td>
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<tr>
<td>No</td>
<td>106 (82.17%)</td>
<td>4,623 (88.82%)</td>
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</table>

(Continued on following page)
able for all cases with reduced susceptibility to any first-line agent. M. tuberculosis isolates were classified as MDR if they were resistant to at least INH and RIF (3). Isolates were classified as poly-PZA’ if they were resistant to PZA and at least one other drug, excluding MDR isolates (Fig. 1).

Data collection. Demographic and clinical information was provided by the NYC DOHMH TB Registry, which contains information for each reported TB patient obtained by interview and medical-record abstraction performed by trained Bureau of Tuberculosis Control (RTBC) staff, using standard data collection forms. Demographic variables included age at TB diagnosis, sex, birthplace (United States or foreign born with country of birth), number of years since arrival in the United States for foreign-born patients, and race/ethnicity. Sociodemographic variables included reported homelessness; substance use (injection drug use), noninjection drug use (consolidated into yes or no); alcohol abuse; and history of TB treatment at Rikers Island Prison Complex. Clinical variables included initial chest radiography results (normal/abnormal and absence/presence of cavities), the anatomical site of TB disease, respiratory acid-fast bacillus (AFB) smear status, final culture conversion (final conversion from positive to negative culture), HIV status (infected, uninfected, or unknown); and death from any cause (yes or no). Finally, we evaluated the overall agreement between PZA susceptibility determined by phenotype (DST) and genotype (pncA sequence) among MDR isolates using a kappa statistic.

Ethical approval for this study was obtained from the Institutional Review Boards of the NYC DOHMH and Rutgers University (Newark, NJ).

### TABLE 1 (Continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PZA’ (n = 145)</th>
<th>PZA+ (n = 5,525)</th>
<th>Unadjusted OR</th>
<th>95% CI</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
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<td>Drug resistance</td>
<td></td>
<td></td>
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<tr>
<td>Mono</td>
<td>50 (34.48%)</td>
<td>461 (59.87%)</td>
<td>Reference</td>
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<tr>
<td>Poly</td>
<td>25 (17.24%)</td>
<td>220 (28.57%)</td>
<td>1.05</td>
<td>0.63–1.74</td>
<td>0.8568</td>
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<tr>
<td>MDR</td>
<td>70 (48.28%)</td>
<td>89 (11.56%)</td>
<td>7.25</td>
<td>4.73–11.13</td>
<td>&lt;0.0001</td>
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</table>

Molecular epidemiology

<table>
<thead>
<tr>
<th>Clustered</th>
<th>Yes</th>
<th>No</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>83</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>(57.24%)</td>
<td>(42.76%)</td>
</tr>
<tr>
<td>No.</td>
<td>2,414 (43.69%)</td>
<td>3,111 (56.31%)</td>
</tr>
<tr>
<td>OR</td>
<td>1.73</td>
<td>1.05</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.24–2.41</td>
<td>0.63–1.74</td>
</tr>
<tr>
<td>P</td>
<td>0.0012</td>
<td>0.32</td>
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Phylogenetic lineage

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<th>Lineage</th>
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<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18</td>
<td>44</td>
<td>73</td>
<td>490</td>
</tr>
<tr>
<td></td>
<td>(12.50%)</td>
<td>(30.56%)</td>
<td>(30.69%)</td>
<td>(9.80%)</td>
</tr>
<tr>
<td></td>
<td>490 (9.80%)</td>
<td>878 (15.95%)</td>
<td>347 (6.31%)</td>
<td>3,111 (56.31%)</td>
</tr>
<tr>
<td>OR</td>
<td>1.91</td>
<td>2.60</td>
<td>0.67</td>
<td>0.67</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.13–3.22</td>
<td>1.78–3.81</td>
<td>0.67–2.71</td>
<td>0.67–2.71</td>
</tr>
<tr>
<td>P</td>
<td>0.0159</td>
<td>&lt;0.0001</td>
<td>0.4063</td>
<td>0.4063</td>
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</table>

### TABLE 2 Adjusteda epidemiologic characteristics of pyrazinamide resistance

<table>
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<tr>
<th>Characteristic</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
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<tr>
<td>Age (yr)</td>
<td>0.99</td>
<td>0.98–1.01</td>
<td>0.2007</td>
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<tr>
<td>HIV positivity</td>
<td>1.39</td>
<td>0.80–2.43</td>
<td>0.2467</td>
</tr>
<tr>
<td>TB infection site</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Extrapulmonary vs pulmonary</td>
<td>0.84</td>
<td>0.33–2.14</td>
<td>0.7192</td>
</tr>
<tr>
<td>Both vs pulmonary</td>
<td>0.81</td>
<td>0.42–1.55</td>
<td>0.5272</td>
</tr>
<tr>
<td>AFB smear positivity</td>
<td>2.02</td>
<td>1.19–3.43</td>
<td>0.0094</td>
</tr>
<tr>
<td>History of TB</td>
<td>0.93</td>
<td>0.28–3.08</td>
<td>0.9932</td>
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<td>History of substance abuse</td>
<td>1.29</td>
<td>0.70–2.40</td>
<td>0.4164</td>
</tr>
<tr>
<td>Any death</td>
<td>1.77</td>
<td>0.89–3.52</td>
<td>0.0133</td>
</tr>
<tr>
<td>Clustered</td>
<td>2.73</td>
<td>1.71–4.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lineage 1 vs 4</td>
<td>3.45</td>
<td>1.72–6.95</td>
<td>0.0005</td>
</tr>
<tr>
<td>Lineage 2 vs 4</td>
<td>5.01</td>
<td>3.13–8.03</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lineage 3 vs 4</td>
<td>3.30</td>
<td>1.33–8.19</td>
<td>0.0101</td>
</tr>
</tbody>
</table>

a Adjusted for known TB risk factors, including age, HIV, and any univariate variable with a P value of <0.2.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-MDR TB Cases</th>
<th>MDR TB cases</th>
<th>Breslow-Day test for homogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PZA(^a) (n = 75)</td>
<td>PZA(^a) (n = 5,436)</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td></td>
<td>PZA(^a) (n = 70)</td>
<td>PZA(^a) (n = 89)</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>P value</td>
<td>$\chi^2$</td>
</tr>
<tr>
<td>Median age, yr (IQR)</td>
<td>40 (31–51)</td>
<td>42 (30–57)</td>
<td>0.99</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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</tr>
<tr>
<td>M</td>
<td>49 (65.33%)</td>
<td>3,425 (63.01%)</td>
<td>1.11</td>
</tr>
<tr>
<td>F</td>
<td>26 (34.67%)</td>
<td>2,011 (36.99%)</td>
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<tr>
<td>U.S. born</td>
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<tr>
<td>Yes</td>
<td>17 (22.67%)</td>
<td>1,563 (28.86%)</td>
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</tr>
<tr>
<td>No</td>
<td>58 (77.33%)</td>
<td>3,852 (71.14%)</td>
<td>0.72</td>
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<td>History of TB</td>
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</tr>
<tr>
<td>Yes</td>
<td>1 (1.33%)</td>
<td>132 (2.43%)</td>
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<tr>
<td>No</td>
<td>74 (98.67%)</td>
<td>5,304 (97.57%)</td>
<td>0.54</td>
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<tr>
<td>History of LTBI</td>
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</tr>
<tr>
<td>Yes</td>
<td>3 (4.00%)</td>
<td>313 (5.76%)</td>
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<tr>
<td>No</td>
<td>72 (96.00%)</td>
<td>5,123 (94.24%)</td>
<td>0.68</td>
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<tr>
<td>History of homelessness</td>
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</tr>
<tr>
<td>Yes</td>
<td>6 (8.00%)</td>
<td>506 (9.31%)</td>
<td>0.85</td>
</tr>
<tr>
<td>No</td>
<td>69 (92.00%)</td>
<td>4,930 (90.69%)</td>
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<td>History of substance abuse</td>
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<tr>
<td>Yes</td>
<td>5 (6.67%)</td>
<td>481 (9.06%)</td>
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<tr>
<td>No</td>
<td>70 (93.33%)</td>
<td>4,830 (90.94%)</td>
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<td>History of alcohol abuse</td>
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<tr>
<td>Yes</td>
<td>11 (14.67%)</td>
<td>853 (16.05%)</td>
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</tr>
<tr>
<td>No</td>
<td>64 (85.33%)</td>
<td>4,463 (83.95%)</td>
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<td>History of Rikers treatment</td>
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<tr>
<td>Yes</td>
<td>0 (0.00%)</td>
<td>104 (1.91%)</td>
<td>3</td>
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<tr>
<td>No</td>
<td>75 (100.00%)</td>
<td>5,332 (98.09%)</td>
<td>3</td>
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<td>HIV serostatus</td>
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<tr>
<td>Positive</td>
<td>11 (14.67%)</td>
<td>803 (14.77%)</td>
<td>0.94</td>
</tr>
<tr>
<td>Negative</td>
<td>45 (60.00%)</td>
<td>3,093 (56.90%)</td>
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<td>19 (25.33%)</td>
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<td>Pulmonary</td>
<td>55 (73.33%)</td>
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<td>Extrapulmonary</td>
<td>8 (10.67%)</td>
<td>976 (17.95%)</td>
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<tr>
<td>Both</td>
<td>12 (16.00%)</td>
<td>644 (11.85%)</td>
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<td>Respiratory AFB smear status</td>
<td>Positive (70.42%)</td>
<td>2914 (57.74%)</td>
<td>1.74</td>
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<td>Negative (29.58%)</td>
<td>21 (29.58%)</td>
<td>2,133 (42.26%)</td>
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<td>Abnormal chest X-ray</td>
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<td>Yes (91.18%)</td>
<td>31 (91.18%)</td>
<td>2,056 (88.81%)</td>
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<td>3 (8.82%)</td>
<td>259 (11.19%)</td>
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<tr>
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<td>54 (88.52%)</td>
<td>3,498 (85.90%)</td>
<td>1.27</td>
</tr>
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<td>No (11.48%)</td>
<td>7 (11.48%)</td>
<td>574 (14.10%)</td>
<td>1</td>
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<tr>
<td>Any cavitation</td>
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<tr>
<td>Yes (19.70%)</td>
<td>13 (19.70%)</td>
<td>992 (21.60%)</td>
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<tr>
<td>No (80.30%)</td>
<td>53 (80.30%)</td>
<td>3,601 (78.40%)</td>
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<tr>
<td>Any death</td>
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<tr>
<td>Yes (12.50%)</td>
<td>9 (12.50%)</td>
<td>568 (11.07%)</td>
<td>1.15</td>
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<td>63 (87.50%)</td>
<td>4,564 (88.93%)</td>
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<tr>
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<td></td>
<td></td>
<td></td>
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<td>Yes (40.00%)</td>
<td>12 (40.00%)</td>
<td>345 (57.02%)</td>
<td>0.50</td>
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<td>No (60.00%)</td>
<td>18 (60.00%)</td>
<td>260 (42.98%)</td>
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<td>INH-EMB</td>
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<tr>
<td>Yes (10.00%)</td>
<td>3 (10.00%)</td>
<td>28 (4.63%)</td>
<td>2.29</td>
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<tr>
<td>No (90.00%)</td>
<td>27 (90.00%)</td>
<td>577 (95.37%)</td>
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<td>INH-EMB-SLD</td>
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<td>1 (3.33%)</td>
<td>6 (0.99%)</td>
<td>3.44</td>
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<tr>
<td>No (96.67%)</td>
<td>29 (96.67%)</td>
<td>599 (99.01%)</td>
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<td>22 (32.35%)</td>
<td>22 (25.00%)</td>
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<td>46 (67.65%)</td>
<td>66 (75.00%)</td>
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<tr>
<td>EMB-SLD</td>
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<td></td>
<td></td>
</tr>
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<td>Yes (52.94%)</td>
<td>36 (52.94%)</td>
<td>23 (26.14%)</td>
<td>3.18</td>
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<tr>
<td>No (47.06%)</td>
<td>32 (47.06%)</td>
<td>65 (73.86%)</td>
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<tr>
<td>Yes (50.67%)</td>
<td>38 (50.67%)</td>
<td>2,363 (43.47%)</td>
<td>1.34</td>
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<tr>
<td>No (49.33%)</td>
<td>37 (49.33%)</td>
<td>3,073 (56.53%)</td>
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<tr>
<td>Phylogenetic lineage</td>
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<tr>
<td>1 17 (22.97%)</td>
<td>17 (22.97%)</td>
<td>488 (9.01%)</td>
<td>3.10</td>
</tr>
<tr>
<td>2 9 (12.16%)</td>
<td>9 (12.16%)</td>
<td>846 (15.63%)</td>
<td>0.95</td>
</tr>
<tr>
<td>3 6 (8.11%)</td>
<td>6 (8.11%)</td>
<td>341 (6.30%)</td>
<td>1.57</td>
</tr>
<tr>
<td>4 42 (56.76%)</td>
<td>42 (56.76%)</td>
<td>3,739 (69.06%)</td>
<td></td>
</tr>
</tbody>
</table>

a NA, not applicable.
b M, male; F, female.
c Cochran–Mantel-Haenszel nonzero correlation statistic.
d Drug resistance analysis excludes drug-susceptible M. tuberculosis strains and is independent of PZA. The INH category excludes strains with additional RIF, EMB, or SLD. INH-EMB excludes strains with additional RIF or SLD. INH-EMB-SLD excludes strains with additional RIF. The EMB category excludes strains with additional SLD.
RESULTS

PZA resistance trends and associated risk factors among NYC TB cases. Culture-positive TB cases in New York City steadily declined from 950 cases in 2001 to 649 in 2008 ($R^2 = 0.9$). During this time, a total of 6,260 culture-positive TB cases were reported, 5,670 (91%) of which were due to *M. tuberculosis* infection and had genotype and DST results available (Fig. 1). Of these, 145 (2.6%) cases involved infection with PZA’ *M. tuberculosis*. The annual *M. tuberculosis* PZA’ prevalence was between 1.6% and 3.6%, resulting in an average of 18 cases per year. The burden of PZA’ fluctuated considerably, peaking in 2002, 2005, and 2008 (Fig. 2). From 2001 to 2005, MDR-PZA’ (resistance to PZA, INH, and RIF only) accounted for an average of 60% of all PZA’ in NYC, whereas mono-PZA’ accounted for an average of 24%. Between 2006 and 2008, there was a shift in the relative proportions of mono-PZA’ and MDR-PZA’. While the overall proportion of PZA’ remained relatively constant during the study period ($R^2 = 0.2$), by 2008, mono-PZA’ accounted for 60% of PZA’ in NYC, whereas MDR-PZA’ accounted for less than 30% of PZA’.

The univariate analysis of epidemiologic risk factors associated with PZA’ is presented in Table 1. Predictors of PZA’ included AFB smear positivity, history of TB, death, and strain clustering. Among drug-resistant strains ($n = 915$), MDR was strongly associated with PZA’ (OR = 7.25; 95% confidence interval [CI] = 4.73 to 11.13) compared to any monoresistance. In the multivariate analysis (Table 2), AFB smear positivity (OR = 2.02; 95% CI = 1.19 to 3.43) and clustering (OR = 2.73; 95% CI = 1.71 to 4.36) maintained significant associations with PZA’ TB caused by PZA’ *M. tuberculosis*.

**PZA resistance trends and risk factors among the NYC MDR population.** PZA resistance was high among patients with MDR TB, accounting for 44% (70/159) of all MDR cases, while only 1.4% (75/551) of the non-MDR population was PZA’. Table 3 shows the odds ratios for PZA’ according to clinical and demographic characteristics, stratified by patients with MDR and non-MDR TB. Factors independently associated with PZA’ among patients with MDR TB in the stratified analysis were EMB-SLD resistance and AFB smear positivity. AFB smear positivity was the only significant characteristic among patients with non-MDR TB (Table 3). In the multivariate MDR TB analysis, only EMB-SLD resistance (OR = 3.48; 95% CI = 1.57 to 7.69) maintained significance (Table 4), while a history of latent *M. tuberculosis* infection (LTBI) trended toward significance (OR = 0.12; 95% CI = 0.01 to 1.07).

**Molecular epidemiology of PZA resistance.** Overall, PZA’ isolates accounted for 3.5% of lineage 1 (18/508), 4.8% of lineage 2 (44/922), 2.5% of lineage 3 (9/356), and 1.9% of lineage 4 (73/3861). Significant lineage-specific PZA’ associations were identified in the univariate analysis, where lineage 1 and lineage 2 *M. tuberculosis* isolates were approximately twice as likely to be PZA’ as lineage 4 isolates (Table 1). These associations maintained significance in the multivariate model and indicate a phylogenetic *M. tuberculosis* lineage association with PZA’ lineage 1 (OR = 3.45; 95% CI = 1.72 to 6.95), lineage 2 (OR = 5.01; 95% CI = 3.13 to 8.03), and lineage 3 (OR = 3.30; 95% CI = 1.33 to 8.19) compared to lineage 4 (Table 2). Among the non-MDR population, phylogenetic lineage 1 was the only PZA’ predictor that maintained significance in the multivariate model (OR = 3.27; 95% CI = 1.64 to 6.51) (Table 4).

**MDR TB case-control study.** To examine PZA’ risk factors among the 159 MDR cases, we performed a case-control study. Sixty percent of MDR isolates (96/159) were considered genotypically clustered (identical IS6110-RFLPs and spoligotypes), with clusters ranging in size from 2 to 21 members. In contrast, only 43.6% (2,401/5,511) of the non-MDR strains were genotypically clustered (Table 3). Forty-four percent of MDR isolates (70/159) were PZA’ based on DST, 64% (45/70) of which belonged to a genotypic cluster. The genetic markers *pncA*, *katG*, and *rpoB* were used to further resolve clustering within the MDR population. Sequence data for the fabG1 promotor did not provide additional cluster resolution and are not shown.

Complete sequence data (*katG*, *rpoB*, and *pncA*) were available for 88% (140/159) of MDR *M. tuberculosis* isolates (Fig. 1), while *pncA* sequence data were available for 143 isolates. Analysis of the *pncA* CDS-promoter region of MDR isolates identified 83 (58%) mutants. In total, there were 37 unique *pncA* mutations, which included insertions, deletions, and nonsynonymous substitutions. Some discordances between PZA’ determined by DST and the presence of *pncA* mutations (PZA’-*pncA*) were observed (109/143; kappa = 0.54). However, the majority of these were accounted for by a single family of Beijing strains (termed W; n = 54) (29/54; kappa = 0.17), many of which carried a specific *pncA* mutation known to exhibit discordance with phenotypic PZA’ (16, 28), as discussed below. Concordance between the *pncA* sequence and PZA DST results was significantly higher when W strains were excluded and the remaining 89 strains were evaluated (80/89; kappa = 0.79).

Table 5 shows the resolution of genotypic clusters, using DNA sequence data to distinguish primary transmission from independent acquisition of MDR TB. Identical sequences for *katG*, *rpoB*, and *pncA* confirmed the genotyping assignment of seven clusters (n = 38). Conversely, diverse *pncA* mutations were identified within four genotypic clusters possessing identical IS6110-RFLPs, spoligotypes, and mutations in *katG* and *rpoB*, while a fifth cluster with identical *katG* and *pncA* sequences (P strain; spoligotype S00086) was resolved by different *rpoB* mutations.

**Table 4 Adjusted* epidemiologic characteristics of pyrazinamide resistance among MDR and non-MDR TB cases**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MDR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>0.98</td>
<td>0.95–1.01</td>
<td>0.1518</td>
</tr>
<tr>
<td>HIV positivity</td>
<td>1.38</td>
<td>0.57–3.37</td>
<td>0.4724</td>
</tr>
<tr>
<td>TB infection site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary vs pulmonary</td>
<td>0.83</td>
<td>0.16–4.23</td>
<td>0.8211</td>
</tr>
<tr>
<td>Both vs pulmonary</td>
<td>0.44</td>
<td>0.12–1.60</td>
<td>0.2149</td>
</tr>
<tr>
<td>AFB smear</td>
<td>1.79</td>
<td>0.64–4.87</td>
<td>0.2556</td>
</tr>
<tr>
<td>History of LTBI</td>
<td>0.12</td>
<td>0.01–1.07</td>
<td>0.0572</td>
</tr>
<tr>
<td>EMB-SLD</td>
<td>3.48</td>
<td>1.57–7.69</td>
<td>0.0021</td>
</tr>
<tr>
<td><strong>Non-MDR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>0.99</td>
<td>0.98–1.01</td>
<td>0.5188</td>
</tr>
<tr>
<td>HIV positivity</td>
<td>0.95</td>
<td>0.46–1.98</td>
<td>0.8891</td>
</tr>
<tr>
<td>TB infection site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary vs pulmonary</td>
<td>0.89</td>
<td>0.28–2.81</td>
<td>0.8379</td>
</tr>
<tr>
<td>Both vs pulmonary</td>
<td>1.37</td>
<td>0.63–2.97</td>
<td>0.4256</td>
</tr>
<tr>
<td>AFB smear</td>
<td>1.82</td>
<td>0.93–3.58</td>
<td>0.0820</td>
</tr>
<tr>
<td>Lineage 1</td>
<td>3.27</td>
<td>1.64–6.51</td>
<td>0.0008</td>
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</tbody>
</table>

* Adjusted for known TB risk factors, including age, HIV, and any univariate variable with a P value of <0.2.
DISCUSSION

The prevalence of PZA$^+$ has been reported to range from 0.8 to 10% among patients with non-MDR TB and from 10 to 85% among patients with MDR TB worldwide (4, 29, 30). During the study period, TB caused by PZA$^+$ M. tuberculosis in NYC was 50% higher than the national average and 20% higher among patients with MDR TB (31). Moreover, the MDR TB burden in NYC was 2-fold higher than national estimates. Thus, the high prevalence of MDR TB could be an explanation for the high proportion of MDR-PZAr among these patients, we sought to determine PZA$^+$ risk factors in the MDR TB population. Concurrency to EMB and SLDs was the only PZA$^+$ risk factor that maintained statistical significance in the adjusted case-control model. While a strong association between MDR-PZAr and EMB$^+$ has been associated with the inappropriate use of standard short-course therapy in patients with MDR TB (36), we do not have sufficient evidence here to address this question. A larger study found AFB smear positivity, clustering, and death to be independently associated with PZA$^+$. Together, these risk factors suggest that patients infected with PZA$^+$ strains were infectious, transmitting, and not responding well to treatment. A history of TB was also independently associated with PZA$^+$, perhaps suggesting that a proportion of patients experienced relapses of drug-resistant TB, though relapse data were not available for this analysis (34, 35). Given the clinical importance of MDR TB and the high proportion of PZA$^+$ among these patients, we sought to determine PZA$^+$ risk factors in the MDR TB population. Concurrent resistance to EMB and SLDs was the only PZA$^+$ risk factor that maintained statistical significance in the adjusted case-control MDR model. While a strong association between MDR-PZAr and EMB$^+$ has been associated with the inappropriate use of standard short-course therapy in patients with MDR TB (36), we do not have sufficient evidence here to address this question. A larger proportion of MDR-PZAr among clustered versus nonclustered strains suggests that primary transmission was responsible for more PZA$^+$ than acquired resistance within the MDR TB population.

Based on our molecular examination of MDR strains, we were able to further refine our cluster analysis. In particular, we identified MDR TB clusters with IS6110-RFLP; spoligotype; and katG, rpoB, and pncA mutations identical to those previously described in New York City TB laboratory on June 17, 2017 by guest http://aac.asm.org/ Downloaded from

<table>
<thead>
<tr>
<th>Infection</th>
<th>Genotypic cluster</th>
<th>RFLP (spoligotype)</th>
<th>Lineage (spoligotype)</th>
<th>Count</th>
<th>Cluster</th>
<th>Count</th>
<th>Cluster</th>
<th>Count</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
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<td>Primary transmission</td>
<td>W (S00034)</td>
<td>2 (Beijing, ST523, ST623)</td>
<td>22</td>
<td>S315T_H526Y 21$^a$</td>
<td>ACC(T)47GCC(A) 21$^a$</td>
<td>28, 37</td>
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<td>W665 (S00034)</td>
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<td>S315T_H526Y 3</td>
<td>ACC(T)47GCC(A) 3</td>
<td>3</td>
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<tr>
<td></td>
<td>P1 (S00086)</td>
<td>4 (X, Harlem, LAM, Uganda)</td>
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<td>S315T_H526Y 2</td>
<td>CTG(L)85CCG(P) 2</td>
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<td>WT_H526D 5 WTb</td>
<td>WTb 5</td>
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<td>WT 2</td>
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<tr>
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<td>BW230 (S00241)</td>
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<td>WT 2</td>
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<td>Independent acquisition</td>
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<td>290 Δ G 2</td>
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<tr>
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<td>W148 (S00034)</td>
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<td>S315T_S531L 3</td>
<td>CAT(H)71CGT(R) GGA(G)108CGA(R) 1</td>
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<tr>
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<td>W1 (S00034)</td>
<td>2 (Beijing, ST523, ST623)</td>
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<td>ACC(T)47GCC(A) 2</td>
<td>28, 43</td>
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<td>S315T_H526Y 2</td>
<td>ACC(T)47GCC(A) 1</td>
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<td></td>
<td>P (S00086)</td>
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<td>CTG(L)85CCG(P) 3</td>
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<td>Both</td>
<td>H (S00009)</td>
<td>4 (X, Harlem, LAM, Uganda)</td>
<td>11</td>
<td>S315T_S531L 9 WT_WT 1 WT_L511P 1 WT 1</td>
<td>40, 41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unresolved</td>
<td>W738 (S00034)</td>
<td>2 (Beijing, ST523, ST623)</td>
<td>3</td>
<td>S315T_WT 2 S315T_S531L 1</td>
<td>TCG(S)67CCG(P) 1$^a$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AB (S00145)</td>
<td>4 (X, Harlem, LAM, Uganda)</td>
<td>2</td>
<td>S315T_V146F 2 WT_S531L 1 WT 2</td>
<td>AGC(T)142ATG(M) 1$^a$</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>W269 (S00034)</td>
<td>2 (Beijing, ST523, ST623)</td>
<td>2</td>
<td>S315T_S531L 1</td>
<td>AGC(T)141CCG(P)$^a$ 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ One bad sequence.
$^b$ WT, wild type.
$^c$ Also contains a lineage-specific synonymous mutation (TCC[S]65TCT[S]).
in a number of historic NYC drug-resistant outbreak strains (28, 37), e.g., strain C (S00030) (38), strain H (S00009), strain BW (S00241) (39), and strain P (S00086) (40, 41). The sequence-based confirmation of MDR genotypic clusters strongly suggests primary transmission and shows evidence that these historic strains were continuing to circulate and reactivate within NYC during the study period. For example, a 21-member cluster of the W (S00034; Beijing family) MDR-PZA' strain contained genetic markers identical to those of a highly clonal strain that was responsible for a large NYC MDR outbreak in the early 1990s (28, 37). Smaller clusters of historic W variant strains previously described (28, 37, 42, 43) were also identified. Our data suggest that PZA' also appeared independently in MDR TB (i.e., not as a result of primary transmission) (44). For example, the P strain was likely transmitted as a katG-pncA mutant prior to becoming MDR, which indicates PZA' was at times acquired prior to MDR development, as seen in other strains (45, 46).

In addition to clustering, further microbial phylogenetic lineage effects were observed. In the general NYC TB population, PZA' was associated with lineage 1 (East African/Indo-Oceanic), lineage 2 (East Asian/Beijing), and lineage 3 (East Africa/Central Asia) compared to lineage 4 (Euro-American). PZA' associations with lineages 1 and 2 were consistent with lineage effects reported in the national study conducted by the CDC (31). Our data indicate that PZA' among patients with MDR TB was associated with lineage 2, while PZA' was associated with lineage 1 among patients with non-MDR TB. Phylogenetic M. tuberculosis lineages are strongly associated with geographic locations. Therefore, the observed phylogenetic associations in this study are curious and may be a proxy for the importation of PZA' from specific non-U.S. locations. Additional studies would be needed to examine these microbial associations in light of social networks and neighborhood level effects.

Limitations of this study include moderate amounts of HIV data (70%), which is a well-established risk factor for drug-resistant TB. In addition, many demographic variables were self-reported, including a history of TB/LTBI, alcohol or substance abuse, and homelessness, which may have been subject to information bias and misclassification, though it is likely nondifferential. Furthermore, due to the technical complications of PZA-DST (8, 18), our findings may have been subject to some PZA' misclassification. However, pncA sequence data have been shown to be a useful tool to confirm PZA'-DST results (47). The most common pncA-PZA' inconsistency we observed was that of W strains with a pncA mutation in codon 47 (ACC [Thr] → GCC [Ala]). This specific mutation has been shown to correlate poorly with PZA-DST in several previous studies (12, 16, 28, 48, 49), suggesting that the mutation confers borderline resistance at PZA concentrations used routinely in PZA-DST (16). Also, the molecular data suggest that IS6110-RFLP analysis and spoligotyping may have slightly overestimated the extent of clustering and primary transmission.

Despite a steady decline in the total number of TB cases in NYC from 2001 to 2008, the incidence of PZA' increased. Patients with PZA' TB were more infectious and actively transmitting and had poor clinical outcomes compared to patients with TB caused by PZA' M. tuberculosis. Among the MDR TB population, PZA' was acquired somewhat more frequently via primary transmission than independently. In addition, concurrent EMB-SLD resistance was the only risk factor for PZA' among patients with MDR TB. These observations have important clinical and public health implications for control of drug-resistant TB. Specifically, the strength of microbial risk factors for PZA' highlights the importance of routine PZA-DST, genotyping, and confirmatory sequence analysis for ensuring appropriate drug therapy and disrupting transmission. Finally, as clinical trials of new regimens to shorten treatment of drug-susceptible and MDR TB are expanding, these results support the need to consider PZA' in trial design (50–53).

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REFERENCES


