Drug-Resistant Tuberculosis, Clinical Virulence, and the Dominance of the Beijing Strain Family in Russia

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Drug-sensitive and resistant tuberculosis (TB) rates continue to increase globally and multidrug-resistant TB (MDR-TB) has become a serious public health problem in many regions including countries of the former Soviet Union such as Russia, with an incidence rate reaching 83.0/100 000 in 2002. Molecular epidemiological techniques have contributed to the understanding of TB transmission and identified related Mycobacterium tuberculosis-strain families such as the “Beijing,” which may have distinctive properties. This family includes strain W responsible for MDR-TB outbreaks in the United States and other low TB-incidence countries.

Studies have demonstrated high Beijing-strain prevalence in Asia and former Soviet Union countries. Explanations for the rapid dissemination of Beijing strains have included a putative higher virulence, enhanced transmissibility, an ability to escape from BCG vaccine–induced protection, greater mutability, and an association with multidrug resistance rendering cure more difficult and prolonging infectivity. However, by contrast, only a very weak association with

Context Tuberculosis and multidrug-resistant tuberculosis is a serious public health problem in Russia.

Objective To address the extent of “Beijing strain” transmission in the prison/civil sectors and the association of drug resistance, clinical, and social factors with the Beijing genotype.

Design and Setting Cross-sectional population-based molecular epidemiological study of all civilian and penitentiary tuberculosis facilities in the Samara region, Russia.

Patients Consecutively recruited patients with bacteriologically proven tuberculosis (n=880).

Main Outcome Measure Proportion of Beijing strains and association with drug resistance, human immunodeficiency virus infection, imprisonment, radiological, clinical, and other social factors.

Results Beijing-family strains (identified by spoligotyping and composed of 2 main types by mycobacterial interspersed repetitive unit analysis) were predominant: 586/880 (66.6%; 95% confidence interval [CI], 63.4%-69.7%) with a significantly higher prevalence in the prison population (rate ratio [RR], 1.3; 95% CI, 1.2-1.5) and those aged younger than 35 years (RR, 1.2; 95% CI, 1.0-1.3). Comparable proportions were co-infected with the human immunodeficiency virus (10%), concurrent hepatitis B and C (21.6%), drank alcohol (90%), smoked (90%), and had a similar sexual history. Drug resistance was nearly 2-fold higher in patients infected with Beijing strains compared with non-Beijing strains: multidrug resistance (RR, 2.4; 95% CI, 1.9-3.0), for isoniazid (RR, 1.8; 95% CI, 1.5-2.1), for rifampicin (RR, 2.2; 95% CI, 1.7-2.7), for streptomycin (RR, 1.9; 95% CI, 1.5-2.3), and for ethambutol (RR, 2.2; 95% CI, 1.6-3.2). Univariate analysis demonstrated that male sex (odds ratio [OR], 1.5; 95% CI, 1.1-1.9), advanced radiological abnormalities (OR, 5.6; 95% CI, 1.1-6.3), and previous imprisonment (OR, 2.0; 95% CI, 1.5-2.7) were strongly associated with Beijing-strain family disease. Multivariate analysis supported previous imprisonment to be a risk factor (OR, 2.0; 95% CI, 1.4-3.3) and night sweats to be less associated (OR 0.7; 95% CI, 0.5-1.0) with Beijing-strain disease.

Conclusions Drug resistance and previous imprisonment but not human immunodeficiency virus co-infection were significantly associated with Beijing-strain infection. There was evidence that Beijing isolates caused radiologically more advanced disease.

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resistance and the above factors was noted by Lillebaek et al.\textsuperscript{15}

Many TB cases originate among prisoners in Russia where there are almost 1 million incarcerated persons (approximately 0.7% of the total population).\textsuperscript{16} For example, the TB incidence rate was nearly 25-fold higher among prisoners compared with the civil population in the Tomsk region.\textsuperscript{16} In the Samara region, the incidence of TB among civilians and prisoners at the time of the study was 86.1/100,000 and 2,190.0/100,000, respectively, with incidence in pretrial detention centers of 1,889.9/100,000. Overcrowding, inadequate ventilation, and long periods of incarceration facilitate transmission. Poor patient adherence to treatment during and after incarceration and high loss to follow-up after release from prison encourage the development of drug resistance, which facilitates transmission into the general population.\textsuperscript{13-17,18}

We performed one of the largest (and the largest in Russia) population-based molecular epidemiological studies to systematically address: (1) Beijing strain transmission in the prison and civil sectors in the Samara region; and (2) correlation of drug resistance, clinical, and social factors with Beijing genotype to support or contradict immunopathological studies suggesting that Beijing strains had either enhanced pathogenicity or association with drug resistance.

\section*{METHODS}

\subsection*{Patients and Study Design}

Consecutive pulmonary TB patients aged 18 years and older, from all civilian TB dispensaries (18) and the prison TB hospital (admitting all TB cases in the prison sector) were included over 1 year (September 2001-September 2002). All patients provided written consent. Patients were interviewed by a team of trained Russian health staff who recorded clinical (including details of radiological examination) and social data. A structured questionnaire was used to collate data that were supplemented and verified with information from the medical notes.

The questionnaire and study were developed and approved by Federal Tuberculosis Institutions, Samara TB Service and Ethics Committee, and the Samara Health Ministry under whose auspices the study was conducted. The following data were collected: age, sex, accommodation, previous imprisonment, presence of TB symptoms and signs (cough, phlegm, hemoptysis, weight loss, night sweats, fever, shortness of breath, chest pain, fatigue, and body mass index), investigations including chest radiograph (cavitation, lung areas affected, and nature of pathology), blood pressure, erythrocyte sedimentation rate, and human immunodeficiency virus (HIV) status (HIV testing was performed routinely on all TB patients), history of treatment, history of TB contacts, social and sexual health history (including alcohol consumption, smoking history, history of sexually transmitted infections, and sexual activity).

Strains of Mycobacterium tuberculosis were isolated at the Regional TB laboratory, and drug susceptibility testing was performed with the resistance ratio method using Lowenstein–Jensen media in Samara, Russia and London, England. Spoligotyping was used to identify Beijing family isolates and performed as previously described.\textsuperscript{19} Mycobacterial interspersed repetitive unit (MIRU) analysis at 12 loci\textsuperscript{20} was also performed on 113 Beijing isolates selected proportionally from patients in the prison and civilian TB facilities.

\section*{Statistical Analysis}

Data were analyzed using Epilinfo version 6 (US Centers for Disease Control and Prevention, Atlanta, Ga), and SPSS version 10 (SPSS Inc, Chicago, Ill), statistical software packages. Pearson $\chi^2$ or Fisher 2-tailed test and the Mann-Whitney $U$ test were used to compare categorical and continuous variables, respectively.

\begin{table}
\centering
\caption{Prevalence of Beijing Family Strains in the Sample}
\begin{tabular}{lcccc}
\hline
 & \textbf{Beijing Strains} & \textbf{Civilians} & \textbf{Prisoners} & \textbf{Prisoners by Age, y}$^*$ \\
\hline
\textbf{No./total} & 586/880 & 253/586 & 333/586 & 270/582 & 312/582 \\
\% (95\% CI) & 66.6 (63.4-69.7) & 43.2 (39.2-47.2) & 56.8 (52.8-60.8) & 46.0 (42.4-50.5) & 53.6 (49.5-57.6) \\
\hline
\begin{tabular}{l}
\textbf{Attributable risk, \% (95\% CI)$^*$} \\
\end{tabular} & 13.7 (7.8-19.5) & 7.2 (1.3-13.1)$^\ddagger$ & 1\% (1.2-1.5) & 1.2 (1.0-1.3)$^\ddagger$ \\
\begin{tabular}{l}
\textbf{Rate ratio (95\% CI)} \\
\end{tabular} & 1.3 (1.2-1.5) & 1.2 (1.0-1.3)$^\ddagger$ & \\
\hline
\end{tabular}
\end{table}

\begin{table}
\centering
\caption{Dominant MIRU-12 Loci Profiles in Civilian and Prison Tuberculosis Patients Infected With the Beijing-Strain Family}
\begin{tabular}{lrrrr}
\hline
\textbf{Loci}$^*$ & \textbf{MIRU Type 1$^\ddagger$} & \textbf{MIRU Type 2$^*\ddagger$} \\
\hline
2 & 2 & 2 & \\
4 & 2 & 2 & \\
10 & 3 & 3 & \\
16 & 3 & 3 & \\
20 & 2 & 2 & \\
23 & 5 & 5 & \\
24 & 1 & 1 & \\
26 & 5 & 7 & \\
27 & 3 & 3 & \\
31 & 5 & 5 & \\
39 & 3 & 3 & \\
40 & 3 & 3 & \\
\hline
\end{tabular}
\end{table}
Table 3. Clinical and Social Characteristics of Tuberculosis Patients (N = 880) Infected With Beijing Strains vs Non-Beijing Strains

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Beijing, No./Total (%) (n = 586)</th>
<th>Non-Beijing, No./Total (%) (n = 294)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>36.3 (11.5)</td>
<td>38.4 (13.1)</td>
</tr>
<tr>
<td>Women</td>
<td>29/584 (5.0)</td>
<td>33/290 (11.4)</td>
</tr>
<tr>
<td>Signs and symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present cough for &gt;3 wk</td>
<td>438/584 (75.0)</td>
<td>215/289 (74.4)</td>
</tr>
<tr>
<td>Produce phlegm</td>
<td>486/584 (83.2)</td>
<td>243/289 (84.1)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>38/507 (7.5)</td>
<td>23/247 (9.3)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>213/583 (36.5)</td>
<td>122/287 (42.5)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>204/582 (35.1)</td>
<td>125/289 (43.3)</td>
</tr>
<tr>
<td>Fever</td>
<td>167/580 (28.8%)</td>
<td>94/289 (32.5)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>323/584 (55.3%)</td>
<td>157/286 (54.9)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>257/580 (44.3)</td>
<td>116/289 (40.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>435/582 (74.7)</td>
<td>216/289 (74.7)</td>
</tr>
<tr>
<td>BMI, mean (SD)§</td>
<td>21.0 (3.6)</td>
<td>21.1 (2.5)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, median (SD)</td>
<td>20.0 (17.3) [2-80]</td>
<td>23.7 (17.0) [2-77]</td>
</tr>
<tr>
<td>Form of TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>42/540 (7.8)</td>
<td>26/256 (10.2)</td>
</tr>
<tr>
<td>Disseminated</td>
<td>20/540 (3.7)</td>
<td>10/256 (3.9)</td>
</tr>
<tr>
<td>Infiltrative</td>
<td>332/540 (61.5)</td>
<td>164/256 (64.1)</td>
</tr>
<tr>
<td>Fibrocavernous</td>
<td>120/540 (22.2)</td>
<td>48/256 (18.8)</td>
</tr>
<tr>
<td>Caseous pneumonia</td>
<td>3/539 (0.6%)</td>
<td>1/256 (0.4%)</td>
</tr>
<tr>
<td>TB treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previously treated</td>
<td>478/584 (81.8)</td>
<td>214/290 (73.8)</td>
</tr>
<tr>
<td>Underwent surgery</td>
<td>39/504 (7.7)</td>
<td>12/290 (4.1)</td>
</tr>
<tr>
<td>Segment resection</td>
<td>27/39 (69.2)</td>
<td>10/12 (83.3)</td>
</tr>
<tr>
<td>Current treatment for &gt;4 wk</td>
<td>372/582 (63.9)</td>
<td>163/290 (56.2)</td>
</tr>
<tr>
<td>Concurrent blood-borne viral infections and liver diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV positive</td>
<td>38/379 (10.0)</td>
<td>18/191 (9.4)</td>
</tr>
<tr>
<td>HCV/HBV infection</td>
<td>124/575 (21.6)</td>
<td>58/288 (20.1)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>131/526 (24.9)</td>
<td>55/256 (21.5)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>83/578 (14.4)</td>
<td>39/289 (13.1)</td>
</tr>
<tr>
<td>Social characteristics¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous imprisonment</td>
<td>434/583 (74.4)</td>
<td>172/289 (59.5)</td>
</tr>
<tr>
<td>Homeless #</td>
<td>16/503 (2.8)</td>
<td>1/281 (0.4)</td>
</tr>
<tr>
<td>Live in own apartment</td>
<td>383/580 (66.0)</td>
<td>219/288 (76.0)</td>
</tr>
<tr>
<td>Smoking</td>
<td>524/583 (89.9)</td>
<td>250/289 (86.5)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>530/583 (90.9)</td>
<td>253/289 (87.5)</td>
</tr>
<tr>
<td>Sexual health¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unprotected sex in last 6 mo</td>
<td>128/577 (22.2)</td>
<td>65/288 (22.6)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>31/574 (5.4)</td>
<td>21/289 (7.3)</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>43/574 (7.5)</td>
<td>23/289 (8.0)</td>
</tr>
<tr>
<td>Herpes</td>
<td>23/505 (4.6)</td>
<td>0</td>
</tr>
<tr>
<td>Recreational drug use</td>
<td>185/576 (32.1)</td>
<td>82/289 (28.4)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; HCV/HBV, hepatitis C and B virus; HIV, human immunodeficiency virus; TB, tuberculosis.

*The total response for each parameter forms the denominator. P<.05 in reported variables unless otherwise indicated.
†For 2 patients infected with a Beijing strain data were not available.
‡For 4 patients infected with a non-Beijing isolate clinical data were not available.
§BMI calculated as weight in kilograms divided by the square of height in meters.
P=.05.
∥Social/sexual data were not available for 3 patients infected with the Beijing strain and for 5 patients infected with the non-Beijing family strain.
¶For prisoners this refers to the period prior to imprisonment.

RESULTS

Nearly all eligible individuals participated in the study (<2% did not participate). Beijing family strains were dominant overall among the 880 patients recruited (253 civilians and 333 prisoners; 586/880, 66.6%; 95% confidence interval [CI], 63.4%-69.7%) of all isolates (Table 1). A significantly higher prevalence was seen in the prison population (rate ratio [RR], 1.3; 95% CI, 1.2-1.5), and was more common in those aged younger than 35 years compared with older patients (RR, 1.2; 95% CI, 1.0-1.3). Two MIRU-12 loci profiles were predominant (Table 2) as recently described in a smaller study of isolates in St Petersburg. In this study, however, MIRU type 2 was more common among prisoners while MIRU type 1 was more common among civilian patients.

The number and proportion of Beijing and non–Beijing-infected patients with TB symptoms and signs, chest radiological appearances, social problems, and sexually transmitted diseases are given in Table 3. Comparable proportions in the 2 groups were co-infected with HIV (≈10%) and hepatitis B/C (≈20%), drank alcohol, smoked, and had a similar history of sexually transmitted diseases (Table 3). The number of episodes of imprisonment for Beijing and non–Beijing-infected patients is given in the Figure. Nearly three quarters of patients infected with Beijing strains had been in prison at some time and many had been
imprisoned more than once, typically 2 to 4 times, while more than half of patients infected with non-Beijing strains had a history of imprisonment. Recreational drug use with opiates was common, usually intravenously in both groups. Prison appears to be the major site for contacts with TB cases.

A risk factor analysis was conducted for Beijing-strain family-associated infection. Univariate analysis demonstrated that male sex (OR, 1.5; 95% CI, 1.1-1.9), older age (OR, 1.3; 95% CI, 1.1-1.7), homelessness (OR, 5.6; 95% CI, 1.1-6.3), and previous imprisonment (OR, 2.0; 95% CI, 1.5-2.7) were strongly associated with Beijing-strain family–associated disease (Table 4). Advanced radiological damage (multiple zones affected with fibrotic changes and widespread cavitation) was also significantly associated based on univariate analysis (OR, 3.3; 95% CI, 1.3-8.4). There was less association based on univariate analysis with night sweats (OR, 0.7; 95% CI, 0.5-0.9). Multivariate analysis (Table 4) supported previous imprisonment to be a risk factor (OR, 2.0; 95% CI, 1.4-3.3).

The number of prison episodes did not differ significantly between Beijing and non-Beijing–infected patients, suggesting that a single episode was sufficient to acquire Beijing-strain TB. Previous treatment for longer than 4 weeks and male sex failed to reach statistical significance (the latter presumably related to the confounding effect of imprisonment on sex, because the majority of prisoners were men). Although homelessness failed to reach significance on multivariate analysis, living in one’s own apartment (ie, the reverse of homelessness in terms of independent stable accommodation and a surrogate marker of wealth) was less associated with Beijing infection (Table 4). There were no significant differences in BCG vaccination rates in patients infected with Beijing strains (88.6%; 452/510) and in non-Beijing strains (90.6%, 213/235; 95% CI for the difference, −2.6% to 6.6%); vaccination status was unknown for 74 and 55 patients, respectively.

Drug susceptibility testing on 561 visible isolates detected high levels of resistance with significantly higher rates of resistance among strains belonging to the Beijing family (Table 5). Resistance to isoniazid, rifampicin, multidrug resistance, streptomycin, and ethambutol were more than 2-fold higher in Beijing- vs non-Beijing–infected patients (Table 5).

**COMMENT**

The high prevalence of drug-resistant Beijing–associated TB and increasing rates of both legal and illegal migration from Russia to the United States and Western Europe makes this study relevant to all physicians treating patients with TB. The expansion of the European Union includes states of the former Soviet Union with a substantial ethnically Russian population that until recently could freely migrate within the Russian Federation and cases of MDR-TB in former Russian nations have been identified.

Beijing family strains comprised two thirds of the isolates in this population spanning the entire prison and civilian TB systems. Drug resistance rates were significantly higher, particularly for MDR-TB among those infected with the Beijing genotype. Co-infection with HIV did not appear to have a significant impact on Beijing-associated characteristics and high rates of co-infection (approximately 10%) were seen in both groups. High rates of concurrent hepatitis B and C infection as well as HIV were seen overall, reflecting on the importance of intravenous drug abuse in this population.

There was some evidence that clinical presentation differed between the Beijing- and non–Beijing-infected groups. Although a smaller study in the Netherlands showed no difference in radiological appearance, this study did...
show that Beijing-infected patients were more likely to have radiological features of advanced disease supporting in vivo studies demonstrating a different immunopathological response in Beijing-infected mice.24 There was a lower likelihood of night sweats in Beijing-associated disease. The underlying cause of night sweats remains unclear but is presumably associated with a heightened T\(_{H1}\) cytokine response, which might be reduced in Beijing infection. The study by Lopez et al.,24 which demonstrated that BALB/c mice infected with Beijing isolates exhibited a more severe pathology also noted a high but transient tumor necrosis factor \(\alpha\) (TNF-\(\alpha\)) and low interferon \(\gamma\) output. Consistent with these observations were the findings of a study in which a biologically active lipid species (a polyketide synthase–derived phenolic glycolipid [PGL]) produced by Beijing strains inhibited the release of proinflammatory cytokines including tumor necrosis factor \(\alpha\); PGL appeared to be responsible for the “hyperlethal” of Beijing strains in murine models.25

Beijing-infected patients were more likely to have been treated previously. Whether this implies greater treatment failure or relapse due to intrinsic properties of Beijing strains per se or is due to the association with drug resistance requires further study.

The younger age of those infected with Beijing strains would support recent and active transmission, particularly among prisoners who are younger than civilian TB patients and who are more likely to be homeless or to share communal accommodation before imprisonment and on release.

Definitive TB contacts were identified in 250/582 (43.0%) of cases for Beijing and 98/289 (33.9%) for non-Beijing–individuals with the majority occurring in the prison (145/243, 59.7% and 50/92, 54.3%), respectively. Nevertheless, there was no other significant difference in the nature of TB contact between Beijing and non–Beijing-infected groups. Although 2 MIRU types predominated in both the prison and civilian sector, the proportion of each type differed (ie, MIRU type 223325153533 was more common among civilians and type 223325173533 was more common in prisoners with TB). The exact significance of this is unclear but the allelic difference may confer variation in pathogenicity or transmissibility within the populations (ie, sub-Beijing families may have different and advantageous properties, which confounds comparison of all patients infected with Beijing and non-Beijing strains). A larger comparative analysis of patients with the 2 types is needed to resolve this.

The higher rates of drug resistance among Beijing isolates in the prison (nearly twice as high as in the civilian population) supports imprisonment as the principal source of drug resistance. The principal source of drug resistance. Smaller molecular epidemiological studies in the former Soviet Union\(^6^-^9,^19\) demonstrated that a high proportion of TB strains overall belonged to the Beijing family but were limited to either prison or civilian patients or did not include knowledge of patients’ HIV or clinical status.

When introduced de novo, Beijing-strain family isolates have been shown to spread successfully. For example, on Gran Canaria, 1 of the 7 Canary Islands,\(^26\) rapid dissemination of the Beijing genotype was observed over a 3-year period from its introduction onto the island in 1993. It has been postulated that Beijing isolates are more virulent and also that they may be escape mutants circumventing BCG-induced immune protection. In a country such as Russia with a historical policy of multiple BCG vaccinations throughout childhood, it is possible that the widespread prevalence of Beijing isolates in this setting is because of an evolutionary advantage over other strains. Nevertheless, we have not discovered significant differences between the BCG status of patients infected with Beijing and non-Beijing strains. The widespread prevalence of Beijing isolates in this setting is, therefore, likely to be a combination of high levels of drug resistance that reduce cure rates and maintain a pool of infectious cases, and the opportunity for institutional spread particularly in prison and intrinsic properties of the Beijing family itself in the interaction with the host.

Given the existing epidemiology, rapid and inexpensive methods for diagnosing rifampin-, isoniazid-, and multidrug-resistant TB are urgently required, coupled with improved institutional cross-infection procedures for both TB and HIV. Correction of current weaknesses in the system for TB health care delivery, accompanied by the implementation of a directly observed therapy short course

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**Table 5. Comparison of Resistance Levels in Beijing Compared With Non-Beijing Strains (n = 561)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Beijing Strain*</th>
<th>Non-Beijing Strain*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Resistant/</td>
<td>% Resistant (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>262/349</td>
<td>75.1 (70.2-79.5)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>224/349</td>
<td>64.2 (58.9-69.2)</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>216/349</td>
<td>61.9 (56.6-67.0)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>202/350</td>
<td>57.7 (52.4-63.0)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>122/349</td>
<td>35.0 (30.0-40.2)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MDR-TB, multidrug-resistant tuberculosis; RD, rate difference; RR, rate ratio.

*Among all patients for which there was a viable culture, n = 561 for streptomycin and n = 560 for remainder (one subculture was contaminated).
(DOTS-style program), supplemented by rapid diagnosis of resistance and appropriate regimens for the treatment of highly drug-resistant TB are required. Delivery of antiretroviral therapy for those with HIV infection is essential.

This was a large prospective population-based study but larger clinical and immunopathological studies are needed with more discriminating molecular epidemiological tools to verify enhanced virulence of the Beijing family (or other strain-family groups) in humans.

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Author Contributions: Dr Drobniewski had full access to all of 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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Acquisition of data: Drobniewski, Balabanova, Ruddy, Zakharova, Fedorin.

Analysis and interpretation of data: Drobniewski, Balabanova, Nikolayevsky.

Drafting of the manuscript: Drobniewski, Balabanova, Nikolayevsky.

Critical revision of the manuscript for important intellectual content: Drobniewski, Balabanova, Ruddy, Kuznetzov, Zakharova, Melentyev, Fedorin.

REFERENCES


