CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com *Research Article*

INVESTIGATING SPILLOVER OF MULTI-DRUG RESISTANT TB FROM A PRISON: A SPATIAL AND MOLECULAR EPIDEMIOLOGICAL ANALYSIS

[1]Dr. Iram Masood, [2]Dr. Aamina Ahmed, [3]Dr. Hafiz Muhammad Usman Ashraf

[1]WMO, BHU Kund, Khushab.

[2]WMO, RHC Lawa.

[3]House Officer, ABSTH, Gujrat.

Abstract:

Congregate settings may serve as institutional amplifiers of tuberculosis (TB) and multidrug-resistant tuberculosis (MDR-TB). We analyze spatial, epidemiological, and pathogen genetic data prospectively collected from a prison, where inmates experience a high risk of MDR-TB, to investigate the risk of spillover into the surrounding community.

Using hierarchical Bayesian statistical modeling, we address three questions regarding the MDR-TB risk: (i) Does the excess risk observed among prisoners also extend outside the prison? (ii) If so, what are the magnitude, shape, and spatial range of this spillover effect? (iii) Is there evidence of additional transmission across the region?

The region of spillover risk extends for 5.47 km outside of the prison (95% credible interval: 1.38, 9.63 km). Within this spillover region, we find that nine of the 467 non-inmate patients (35 with MDR-TB) have MDR-TB strains that are genetic matches to strains collected from current inmates with MDR-TB, compared to seven out of 1080 patients (89 with MDR-TB) outside the spillover region (p values: 0.022 and 0.008). We also identify eight spatially aggregated genetic clusters of MDR-TB, four within the spillover region, consistent with local transmission among individuals living close to the prison.

We demonstrate a clear prison spillover effect in this population, which suggests that interventions in the prison may have benefits that extend to the surrounding community.

Keywords: ***Antibiotic resistance, Bayesian statistics, Spatial analysis, Spillover analysis, Transmission***

Corresponding author:

Dr. Iram Masood,

Rawalpindi Medical College.

QR code

Please cite this article in press Iram Masood et al., ***Investigating Spillover of Multi-Drug Resistant TB from A Prison: A Spatial and Molecular Epidemiological Analysis.,*** *Indo Am. J. P. Sci, 2018; 05(12).*

INTRODUCTION:

In 2016, the latest year for which estimates are available, there were 490,000 incident cases of multidrug-resistant tuberculosis (MDR-TB). Individuals with MDR-TB have a disease that is resistant to at least isoniazid and rifampicin and they are at substantially elevated risk of treatment non-response, treatment-related side effects, and mortality, even if drug resistance is recognized and treatment with appropriate second-line drug regimens is available. MDR-TB arises as a consequence of failed treatment or by direct transmission from an individual infectious with MDR-TB. Measures of the relative importance of failed treatment and direct transmission as drivers of MDR-TB are not easy to obtain in the setting of complex epidemics, where reports of treatment history and prior drug susceptibility results are often unreliable or unavailable (Alexander and De, 2013).

Nonetheless, an analysis based on programmatic data and an inference based on fitting transmission dynamic models to data reveal that direct transmission of MDR-TB is now the dominant mechanism driving incidence in most settings. Therefore, the success of interventions that aim to mitigate the rise of MDR-TB will depend critically on their ability to identify where transmission occurs and who is at the highest risk of infection. It has been suggested that specific types of congregate settings, especially hospitals and prisons, can serve as institutional amplifiers of TB, and in particular, MDR-TB. This hypothesis suggests that the high incidence rates of TB and MDR-TB reported in congregate settings can lead to spillover risk in the community, especially in settings where there is a rapid turnover of members in the congregate setting or there are opportunities for interaction between community members and those in the congregate setting (Callaway, 2014).

METHODS AND MATERIALS:

The data was collected in the context of a population-wide implementation study of the Microscopic Observation Drug Susceptibility assay, a rapid test for TB and MDR-TB. Full details of the field methods are available in a previous publication. All isolates included in this study have been tested for susceptibility to isoniazid and rifampin and have been genotyped by 15-loci MIRU-VNTR. In total, approximately 71% of all culture-positive isolates had genotyping and geographic data and were included in this analysis.

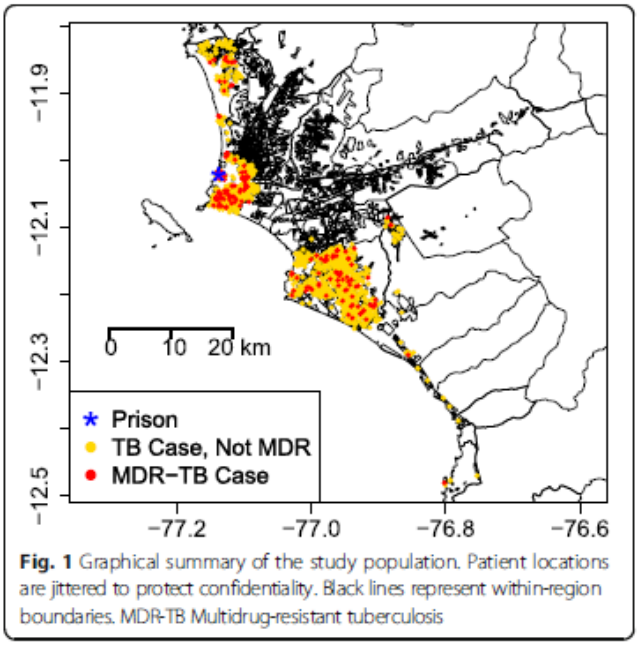

Fig. 1 Graphical summary of the study population. Patient locations are jittered to protect confidentiality. Black lines represent within-region boundaries. MDR-TB Multidrug-resistant tuberculosis

Source: (Bharadwa et al., 2018)

For this analysis, we used individual-level information about the patients including sex (male or female), sputum smear positivity indicator (yes or no), previous TB treatment status (yes or no), average socioeconomic status of their city block (lower, middle, and upper tertiles), population density of their city block (number of people per city block), age category (<25, 25‑64, or 65+ years), prisoner status (yes or no), and longitude and latitude of residence at time of diagnosis. In total, our analysis includes 1587 TB patients after removing those with missing covariate information. Of these patients, 115 shared a residence with at least one other patient in the study. Table 1 displays the summary information for this population by MDR-TB status.

Table 1 Study population characteristics

Characteristic	Tuberculosis type	
	Multidrug-resistant	Drug susceptible
Total	164	1423
Prisoner status (yes)	7 (0.04)	33 (0.02)
Sex (male)	102 (0.62)	897 (0.63)
Smear positive (yes)	147 (0.90)	1271 (0.89)
Previous treatment (yes)	79 (0.48)	346 (0.24)
Socioeconomic status category		
Upper tertile	9 (0.05)	73 (0.05)
Middle tertile	65 (0.40)	485 (0.34)
Lower tertile	90 (0.55)	865 (0.61)
Age category		
[18–25)	36 (0.22)	376 (0.26)
[25–65)	120 (0.73)	951 (0.67)
65+	8 (0.05)	96 (0.07)
Population density (per city block)	127.99 (57.84)	121.90 (57.38)
Distance to prison (kilometers)	15.07 (12.10)	18.36 (11.57)

Counts with proportions in parentheses are shown for categorical variables.
Means with standard deviations in parentheses are shown for continuous variables

Source: (Bharadwa et al., 2018)

Spillover risk analysis

We develop hierarchical Bayesian statistical models that simultaneously account for the potential of elevated MDR-TB risk for an individual due to a number of sources including (i) individual-level risk factors, (ii) proximity to the prison (representing potential spillover), and (iii) spatial proximity to other MDR-TB cases (representing the possibility of local transmission). In our analyses, each TB patient is categorized as having MDR-TB or drug-susceptible TB (i.e., any phenotype that is not MDR-TB) and we model the probability that a patient has MDR-TB as a function of these different sources of risk. We are primarily interested in determining if proximity to the prison has any impact on an individuals' MDR-TB risk and formally test this hypothesis through the inclusion of $\lambda g(\| si - sp \|; \theta)$. We test a number of competing options that each make a different assumption regarding the range and shape of the potential spillover effect, and formally compare the models using two Bayesian model selection techniques: the Watanabe- Akaike information criterion (WAIC) (Bharadwa et al., 2018).

We are also interested in understanding if there is additional residual risk associated with proximity to other MDR-TB cases. Therefore, we introduce random effects that aim to detect pockets of increased MDR-TB risk due to spatial location alone. The w(si) parameters are spatially correlated random effects that account for any residual spatial variability in MDR-TB risk (after controlling for individual-level characteristics and proximity to the prison). The vector of spatially correlated random effects, , is modeled using a Gaussian process prior distribution with spatially structured covariance matrix which describes the variance/covariance of the random effects. This specification allows us to determine if there are highly localized regions of MDR-TB risk, possibly due to transmission (Bharadwa et al., 2018).

.

Molecular analysis

The spatially correlated random effects identify areas that have excess residual MDR-TB risk. To determine if this excess risk may be due to local transmission, we further interrogate these regions using 15-loci MIRU-VNTR genotypes. If multiple genetically matched isolates are identified in a single high MDR-TB risk region, we deem local

transmission to be probable. Specifically, we first identify estimated spatial random effects whose upper 95% credible intervals are larger than 0, indicating a statistically significant increased local risk of MDR-TB (Bharadwa et al., 2018).

Prior specification

To specify the model fully within the Bayesian framework, prior distributions must be selected for each of the unknown model parameters. When possible, we select weakly informative prior distributions for the data to drive the inference rather than our prior beliefs.

Computing and model fitting

Each of the proposed models is fitted in the Bayesian setting using Markov chain Monte Carlo sampling techniques with R statistical software. For each model, we collect 90,000 samples from the joint posterior distribution of the model parameters after a burn-in period of 10,000 iterations. To reduce the autocorrelation in the Markov chains and ease the computational burden of summarizing 90,000 posterior samples resulting in a final set of 5000 posterior samples. Convergence was assessed through visual inspection of individual parameter trace plots and by monitoring the Geweke diagnostic measure (Bharadwa et al., 2018).

RESULTS:

Data Description

We have a total of n = 1,587 TB patients in m= 1,509 unique spatial locations. As shown in Table 1, 164 of the TB patients have MDR-TB (10.3%). The factor most closely associated with increased risk of MDR-TB is previous treatment for TB; 18.6% of previously treated individuals have MDR-TB compared to 7.3% of treatment naive individuals. We note that previous TB treatment status among those with MDR-TB is an imperfect proxy for transmitted MDR-TB. Individuals without previous treatment are assumed to have MDR-TB as a consequence of direct transmission, but those with previous treatment may have MDR-TB as a result of transmission or acquisition during their prior treatment. Current imprisonment is also associated with MDR-TB. Among the 40 inmates with TB, 17.5% have MDR-TB compared to 10.2% of individuals in the general population.

Spillover Risk Analysis

The prisoner indicator model provides an improved fit over the constant spillover risk model, indicating that the assumption of constant risk in the area surrounding the prison may not accurately reflect the true nature of the spillover. However, a substantial improvement in model fit is observed when different shapes of spillover risk are considered. The exponential and Gaussian spillover risk models have an improved fit overall compared with the prisoner indicator model. This indicates that there may be a spillover effect and that the resulting excess risk decreases as distance from the prison increases, before becoming 0.

The WAIC result of this model comparable overall, so we examine the inference for λ, the parameter controlling the magnitude of the spillover risk, to make our final model selection. While the posterior mean of λ is comparable between both models, the 95% credible interval of the parameter for the exponential spillover risk model is slightly below 0. The corresponding interval from the Gaussian spillover risk model excludes 0 (Table 2). Therefore, we further explore the results of the Gaussian spillover risk model in the remaining analyses but note that the results are generally comparable between both models. In Table 2, we present the posterior inference for each of the parameters in the Gaussian spillover risk model. Parameters whose 95% credible intervals are strictly larger than 0: indicate an increased risk of MDR-TB for patients in those categories, with a similar interpretation for strictly negative results. As expected, patients who have been previously treated for TB are more likely to have MDR-TB than patients with no previous treatment history. No other individual-level risk factors are associated with increased or decreased risk of MDR-TB.

Table 2 Inference from the Gaussian spillover risk model

Parameter	Mean	SD	Quantile 0.025	Quantile 0.975
Intercept	−2.23	0.71	−3.90	−1.20
Previous treatment: yes vs. no	0.81	0.24	0.44	1.35
Sex: female vs. male	0.11	0.16	−0.17	0.46
Smear positive: yes vs. no	0.11	0.22	−0.29	0.58
Socioeconomic status:				
Middle vs. upper	−0.19	0.30	−0.81	0.39
Lower vs. upper	−0.40	0.31	−1.10	0.15
Population density	0.01	0.09	−0.17	0.19
Age category				
[25–65) vs. [18–25)	−0.01	0.16	−0.33	0.31
65+ vs. [18–25)	−0.27	0.32	−1.00	0.30
Spillover magnitude (λ)	0.49	0.28	0.01	1.13
Spillover range (θ), kilometers	5.47	1.83	1.38	9.63
Regression parameter variance (σ_β^2)	0.90	0.86	0.18	3.10
Spatial variance parameter (σ_w^2)	1.71	1.55	0.11	5.53

Posterior means, posterior SDs, and posterior quantiles are presented. Parameters whose 95% credible intervals do not include 0 are shown in bold, indicating an increased (positive effect) MDR-TB risk for a patient with the particular characteristic

MDR-TB multidrug-resistant tuberculosis, *SD* standard deviation

Source: (Bharadwa et al., 2018)

Result of Molecular Analysis

Through incorporation of the MIRU-VNTR genotyping data, we also investigate the particular TB strains that are present within the estimated buffer of increased MDR-TB risk surrounding the prison. In total, there are 467 non-prisoner TB patients within 5.47 km (posterior mean of θ) of the prison. Of the TB strains observed in this spillover region, 249 (49%) do not have an exact MIRU-VNTR match. Nine MDR-TB patients outside the prison (but within the spillover buffer) share a common strain with an inmate with MDR-TB. In contrast, outside this prison spillover buffer, where there are over twice as many TB patients (1080), only seven MDR-TB patients share a common strain with inmates with MDR-TB ($p = 0.022$ from a two-sample test of proportions). When sub-setting to only those patients with MDR-TB, we find nine out of the 35 MDR-TB patients within the prison spillover buffer share a common strain with an inmate compared to seven out of 89 MDR-TB patients outside the prison spillover buffer ($p = 0.008$). This provides further evidence to support the idea of potential MDR-TB spillover from the prison.

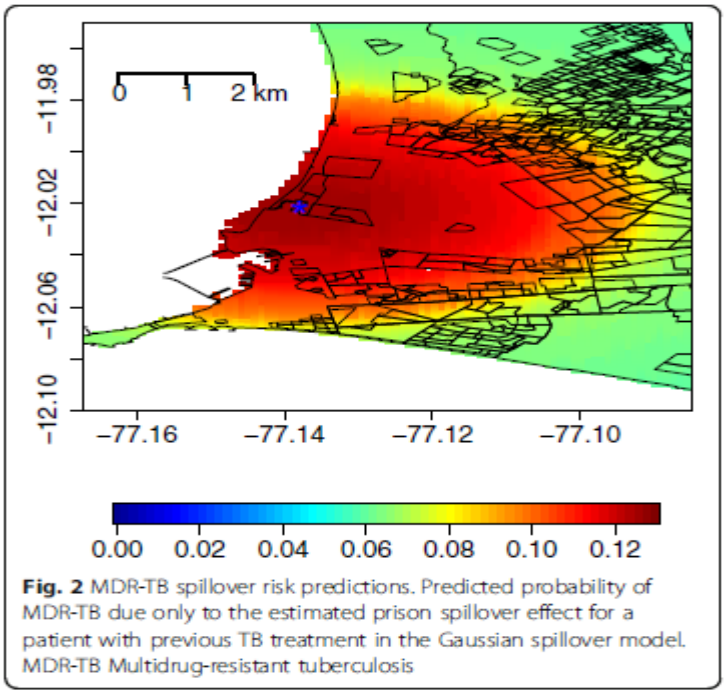

Fig. 2 MDR-TB spillover risk predictions. Predicted probability of MDR-TB due only to the estimated prison spillover effect for a patient with previous TB treatment in the Gaussian spillover model. MDR-TB Multidrug-resistant tuberculosis

Source: (Bharadwa et al., 2018)

Discussion

The availability of spatial and pathogen genetic data offers new opportunities to describe the transmission dynamics of pathogens across spatial scales, and these types of data have been combined to gain a better understanding of how MDR-TB is

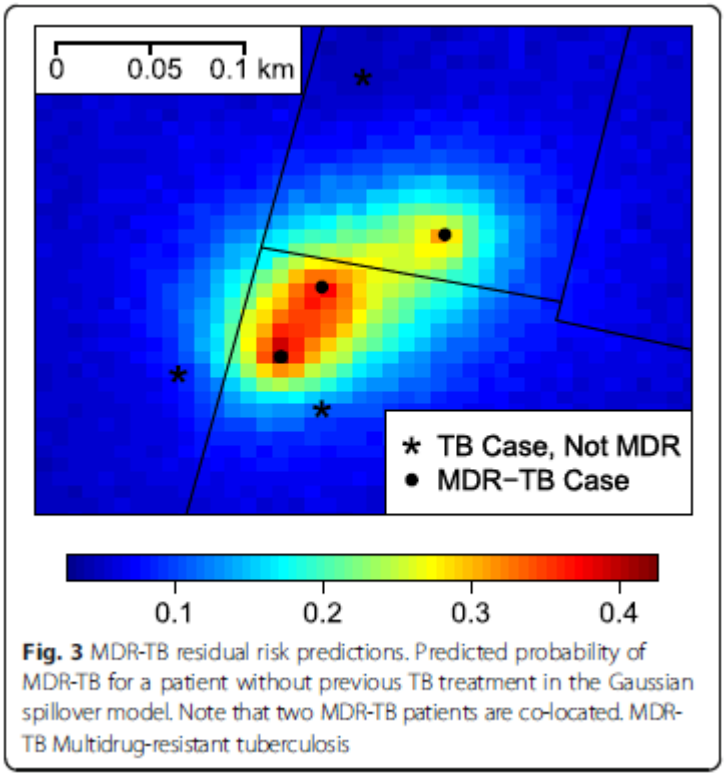

Fig. 3 MDR-TB residual risk predictions. Predicted probability of MDR-TB for a patient without previous TB treatment in the Gaussian spillover model. Note that two MDR-TB patients are co-located. MDR-TB Multidrug-resistant tuberculosis

Source: (Bharadwa et al., 2018)

types of data have been combined to gain a better understanding of how MDR-TB is transmitted within cities and over larger geographic areas, but the role of prisons in propagating epidemics of MDR-TB in the community has not previously been confirmed. In this study, we found that the risk of MDR-TB was elevated among individuals diagnosed with TB in the area surrounding the prison (Pinto and Carvalho, 2017).

This spillover effect dissipated as distance from the prison increased, and the effect was non-significant at a distance of approximately 5 km. The individual covariate known to be most associated with MDR-TB (i.e., previous treatment for TB) remained a significant risk factor, but the distribution of cases reporting previous treatment did not explain the spatial concentration of MDR-TB around the prison location. As there is little reason to believe that risk of acquired resistance should be related to proximity to the prison, this spatial pattern suggests that the majority of MDR-TB cases among previously treated individuals in this area may be the result of transmitted resistance (Pinto and Carvalho, 2017).

Our approach allowed us to identify foci of residual risk of MDR-TB, for which interrogation of molecular epidemiological data revealed several probable hot spots of MDR-TB transmission with strains that are were also found within the prison. In summary, our analysis suggests that those living in the area closest to the prison experience a higher risk of MDR-TB spillover, and once such strains appear outside the prison, they can be transmitted further in the community.

Our study has several notable limitations. First, we do not have data on whether individuals with TB in the community had previously been imprisoned or had known exposure to prisoners or ex-prisoners. This would have been useful in understanding the mechanism of increased risk experienced by those living closest to the prison. Second, our analysis is based solely on household location. As transmission of Mycobacterium tuberculosis may well occur outside the home, use of home location serves at best as a proxy of transmission risk. Third, we had sufficient data to include 71% of culture-positive isolates in this analysis, and it is possible that selection bias could occur if individuals without bacteriological confirmation of TB or missing drug susceptibility testing or spatial data were at a systematically different risk of MDR-TB than those included in the analysis. Fourth, we have used MIRU-VNTR data to identify strains that are genetically clustered and thus, may be related in chains of transmission. While MIRU-VNTR is an important tool for identifying potential transmission clusters, whole-genome sequencing can break up apparent MIRU-VNTR clusters and may have allowed us to infer transmission events better (Pinto and Carvalho, 2017).

CONCLUSION:

We leveraged epidemiological, spatial, and pathogen genetic data to test the hypothesis that high rates of MDR-TB previously documented within a prison have led to a spillover risk in the surrounding community. Using Bayesian hierarchical spatial statistical modeling, we found strong evidence to support the hypothesis that the excess risk extends beyond the walls of the prison. In combination with existing work, our results suggest that such institutions have potential to amplify epidemics and that efforts to control transmission within institutions can also have important indirect effects on reducing risk in the surrounding community.

REFERENCES:

1. Alexander, P. and De, P. (2013). The Emergence of Extensively Drug-Resistant Tuberculosis (TB): TB/HIV Coinfection, Multidrug-Resistant TB and the Resulting Public Health Threat from Extensively Drug-Resistant TB, Globally and in Canada. Canadian Journal of Infectious Diseases and Medical Microbiology, 18(5), pp.289-291.
2. Bharadwa, R., Quadros, S., Faruqi, N., Pinto, M. and Rodrigues, S. (2018). Isolation of Multi Drug Resistant Mycobacteria from Extrapulmonary samples in a Tertiary Care Hospital: A Retrospective Analysis. Annals of International medical and Dental Research, 4(2).
3. Callaway, E. (2014). Russia's drug-resistant TB spreading more easily. Nature, 23(3), p.114.
4. McDiarmid, M. (2016). Multi-drug Resistant TB. Journal of Occupational and Environmental Medicine, 37(4), p.523.
5. Melzer, M. (2016). Molecular analysis of drug resistant TB. Thorax, 57(6), pp.562-563.
6. Mitnick, C., Rodriguez, C., Hatton, M., Brigden, G., Cobelens, F., Grobusch, M., Horsburgh, R., Lange, C., Lienhardt, C., Oren, E., Podewils, L., Seaworth, B., van den Hof, S., Daley, C., Gebhard, A. and Wares, F. (2016). Programmatic Management of Drug-Resistant Tuberculosis: An Updated Research Agenda. PLOS ONE, 11(5), p.e0155968.
7. Mitnick, C., Rodriguez, C., Hatton, M., Brigden, G., Cobelens, F., Grobusch, M., Horsburgh, R., Lange, C., Lienhardt, C., Oren, E., Podewils, L., Seaworth, B., van den Hof, S., Daley, C., Gebhard, A. and Wares, F. (2016). Programmatic

Management of Drug-Resistant Tuberculosis: An Updated Research Agenda. PLOS ONE, 11(5), p.e0155968.

8. Pinto, C. and Carvalho, A. (2017). The HIV/TB coinfection severity in the presence of TB multi-drug resistant strains. Ecological Complexity, 32, pp.1-20.
9. Prasad, R. and Srivastava, D. (2013). Multi drug and extensively drug-resistant TB (M/XDR-TB) management: Current issues. Clinical Epidemiology and Global Health, 1(3), pp.124-128.
10. Warren, J., Grandjean, L., Moore, D., Lithgow, A., Coronel, J., Sheen, P., Zelner, J., Andrews, J. and Cohen, T. (2018). Investigating spillover of multidrug-resistant tuberculosis from a prison: a spatial and molecular epidemiological analysis. BMC Medicine, 16(1).