

Identifying Hotspots of Multidrug-Resistant Tuberculosis Transmission Using Spatial and Molecular Genetic Data

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Background. We aimed to identify and determine the etiology of “hotspots” of concentrated multidrug-resistant tuberculosis (MDR-tuberculosis) risk in Lima, Peru.

Methods. From 2009 to 2012, we conducted a prospective cohort study among households of tuberculosis cases from 106 health center (HC) areas in Lima, Peru. All notified tuberculosis cases and their household contacts were followed for 1 year. Symptomatic individuals were screened by microscopy and culture; positive cultures were tested for drug susceptibility (DST) and genotyped by 24-loci mycobacterial interspersed repetitive units-variable-number tandem repeats (MIRU-VNTR).

Results. 3286 individuals with culture-confirmed disease, DST, and 24-loci MIRU-VNTR were included in our analysis. Our analysis reveals: (1) heterogeneity in annual per-capita incidence of tuberculosis and MDR-tuberculosis by HC, with a rate of MDR-tuberculosis 89 times greater (95% confidence interval [CI], 54,185) in the most-affected versus the least-affected HC; (2) high risk for MDR-tuberculosis in a region spanning several HCs (odds ratio = 3.19, 95% CI, 2.33, 4.36); and (3) spatial aggregation of MDR-tuberculosis genotypes, suggesting localized transmission.

Conclusions. These findings reveal that localized transmission is an important driver of the epidemic of MDR-tuberculosis in Lima. Efforts to interrupt transmission may be most effective if targeted to this area of the city.

Keywords. drug resistance; MDR-tuberculosis; spatial analysis; tuberculosis.

There were approximately 480 000 incident cases of multidrug-resistant tuberculosis (MDR-tuberculosis) worldwide in 2013 [1]. MDR-tuberculosis, defined by resistance to at least isoniazid and rifampicin, is associated with poor treatment outcomes for individuals affected and poses a threat to effective tuberculosis control in many communities. While MDR-tuberculosis arises initially through selective pressure from ineffective or improperly administered treatment of drug-susceptible tuberculosis, once MDR strains of tuberculosis are present, they may be directly transmitted to others. In settings where MDR-tuberculosis is prevalent, interruption of the MDR transmission cycle depends on both preventing acquisition of resistance among individuals on treatment for less-resistant forms of disease and on prompt diagnosis and effective treatment of individuals with MDR-tuberculosis [2, 3].

Tuberculosis notification data show that direct transmission is the principal driver of the worldwide epidemic of MDR-

tuberculosis. Globally, approximately 20.5% of previously treated incident tuberculosis cases have MDR-tuberculosis, while approximately 3.5% of cases without previous treatment have MDR-tuberculosis [1]. Applying these risks of resistance to the percentages of new and retreatment cases among all those notified (6.5% previously treated vs 93.5% without previous treatment) reveals that while the per-capita risk of MDR is substantially lower among those without prior treatment, more than 70% of incident MDR-tuberculosis cases arise among the much larger pool of treatment-naïve individuals. Because resistance among those without prior treatment signals MDR transmission, these numbers suggest that successful containment of MDR-tuberculosis depends on interrupting its transmission.

There is a substantial gap between the numbers of estimated incident MDR-tuberculosis cases and the numbers actually notified (approximately 136 000 of 480 000), and a further gap between the numbers notified and those offered potentially effective second-line therapy (approximately 97 000 of these 136 000) [1]. While new tools for rapid detection of resistance (eg, Xpert MTB/RIF [4]) offer hope for reducing delays to detection, universal access to drug susceptibility testing (DST) is not currently available in most high-burden settings. Identifying novel, practical approaches for improving detection of

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MDR-tuberculosis and delivery of appropriate therapy is a priority for countries currently expanding their programs to address MDR epidemics [5, 6].

Spatial variation in biological and social risk factors for tuberculosis can lead to dramatically different patterns of infection over short spatial scales. If regional tuberculosis epidemics are characterized by patches of concentrated risk rather than spatially uniform risk, strategies targeted at the highest burden areas may be more effective than blanket screening and treatment. We aimed to identify and describe spatial heterogeneity in the risk of MDR-tuberculosis in Lima, Peru. We anticipate that the identification of high-risk areas may allow for targeted interventions to more effectively control transmission in these areas.

To address these questions, we conducted a cohort study of tuberculosis cases and their household contacts in contiguous areas of Lima to document the spatial distribution of tuberculosis. We utilized universal DST and *Mycobacterium tuberculosis* genotyping among these cases to (1) identify areas of elevated MDR risk, and (2) describe patterns of spatial aggregation of specific tuberculosis genotypes.

METHODS

Study Setting and Design

We conducted a population-based prospective cohort study within households of tuberculosis index cases in contiguous areas of Lima Ciudad and Lima Este. Between September 2009 and August 2012, we identified all adults (>15 years old) diagnosed with incident pulmonary tuberculosis at any of 106 participating public health centers located in our study catchment area of approximately 3.3 million inhabitants. This area includes 12 of the 43 districts of metropolitan Lima, all within Lima Ciudad or Lima Este, and reflects a mix of urban and peri-urban areas and informal settlements. Within 1 month of diagnosis of tuberculosis in these “index patients,” a study nurse visited the patient’s home and invited all other individuals in the household to participate in a baseline assessment of tuberculosis infection and disease. These household contacts were followed for incident infection and disease for 12 months. Informed consent was obtained from all study participants. The study design is described in further detail in [8].

All enrolled index cases and suspected cases among household contacts were assessed for tuberculosis disease by smear and culture. A history of prior tuberculosis treatment was assessed by self-report during a directed questionnaire. Study nurses collected spatial information on households using handheld global positioning system (GPS) units. Strains from those with culture-confirmed disease were further tested for drug resistance [9–11], and DNA was extracted and genotyped by 24-loci mycobacterial interspersed repetitive units–variable-number tandem repeats (MIRU-VNTR) using standard methods [12]. We defined strains as being genetic matches if they

were exact matches at all 24 loci. Isolates were also assigned lineages using the MIRU-VNTRplus reference database [13].

Analytic Methods

We employed the following 2 approaches to mapping the distribution of tuberculosis cases in Lima:

Variation in Rates of Tuberculosis and MDR-Tuberculosis at the Health-Center Level

We created maps that illustrate per-capita rates of notified tuberculosis (resistant and drug-sensitive) and MDR-tuberculosis at the health-center (HC) level. Residents who received care at HCs were defined by the location of their household; estimates of the population within HC areas were derived from census data [14]. HC-level rates were estimated via Poisson regression using Gaussian process spatial smoothing. Because the exact geographic boundaries of HC catchment areas are not available digitally, we approximated these boundaries with a set of Voronoi polygons [15]. For additional details, see the [Supplementary Materials](#).

*Continuous Spatial Variation in Relative Risk of MDR-Tuberculosis and Spatial Aggregation of Specific *M. tuberculosis* Genotypes*

We also generated maps that highlight areas in continuous space with greater-than-expected risk of MDR or aggregation of specific *M. tuberculosis* genotypes. We refer to these as “hot-spot” maps, which present a visual representation of the relative risk of being a “case” or a “control” at each spatial location. Cases were defined by either drug resistance phenotype or MIRU-VNTR genotype, as follows: (1) in analyses probing for hotspots of increased MDR risk, we designated individuals with MDR-tuberculosis as cases, and all individuals with non-MDR disease as controls; (2) in analyses to identify hotspots of transmission of particular genotypes, we labeled all individuals with a specific MIRU-VNTR genotype as cases and individuals with any other genotype as controls.

To construct these hotspot maps, we used a nonparametric distance-based mapping (DBM) approach [16]. DBM is less sensitive to asymmetric spatial patterns of cases and controls than Kernel-density estimation [16] and thus provides an attractive alternative for detection of high-risk areas in real communities. For additional detail, see the [Supplementary Materials](#).

To visually highlight areas of elevated per-capita risk, we adopted the map coloring scheme outlined in a previous study in which DBM was used to identify areas of elevated MDR-tuberculosis risk [17]. This color scale was created by generating 100 synthetic datasets with randomly permuted case labels. Each synthetic dataset thus represents a realization of the scenario in which the overall ratio of cases to controls remains constant (and identical to the observed data) but in which the case/control status is independent of household location.

We applied the DBM algorithm to each of these randomized datasets and recorded the minimum and maximum score values

Table 1. Sample Characteristics

| Variable | All Tuberculosis | MDR | Non-MDR |
|-------------------------------|--------------------|------------------|-------------------|
| Treatment status | | | |
| Treatment naive | 2660 (81%) | 243 (63%) | 2417 (83%) |
| Previous treatment | 626 (19%) | 143 (37%) | 483 (17%) |
| Bacteriological status | | | |
| Smear-positive | 2426 (74%) | 268 (69%) | 2158 (74%) |
| Culture-positive | 860 (26%) | 118 (31%) | 742 (26%) |
| Total | 3286 (100%) | 386 (12%) | 2900 (88%) |

Percentages in the first 4 rows of each column represent the proportion of individuals with each type of tuberculosis in each group (treatment naive, previous treatment, smear-positive, culture-positive). All smear-positive cases are also culture-positive. Percentages in the final row represent the proportion of total tuberculosis cases.

Abbreviation: MDR, multidrug-resistant.

obtained using the same 100 × 100 grid. These values were then used to create a color scale for the map: dark blue indicated a score smaller than or equal to the value of the first percentile of the 100 sampled minimum values, light blue indicated values between the 2nd and 5th percentiles of the distribution of minimum values, light red indicated values between the 95th and 99th percentiles of the maximum values distribution, and dark red indicated a score at or above the 99th percentile value. Colors from turquoise to orange illustrated the range of values from the 5th percentile of the minimum distribution to the 95th percentile of the maximums. This random permutation approach

ensured that the resulting maps highlighted areas in which the proportion of individuals who are cases was greater than expected by random chance, irrespective of the local density of controls.

RESULTS

Among 3571 sputum smear or culture-positive cases, we were able to include data from 3286 individuals (92%) with culture-confirmed tuberculosis who had complete household GPS data, and for whom we had results of DST and 24-loci MIRU-VNTR. The per-capita incidence of culture-confirmed tuberculosis in our study was 74.12/100 000 (95% confidence interval [CI], 71.59, 76.61). We note that these values are lower than the overall rate of tuberculosis disease, because tuberculosis cases without bacteriological diagnosis are also included in official statistics; in our data, 1391/4962 (28%) of cases were smear and culture negative. Of these, 284 (20%) were secondary household cases. Descriptive statistics are presented in Table 1. For additional sample characteristics, see the [Supplementary Materials](#).

MDR cases in our cohort were dominated by the Latin American–Mediterranean (LAM) sublineage of the Euroamerican tuberculosis lineage [18], which accounted for 44% (175) of all identified MDR cases, followed by the Haarlem lineage with 19% (44 cases) and the Beijing lineage with 4% (17 cases).

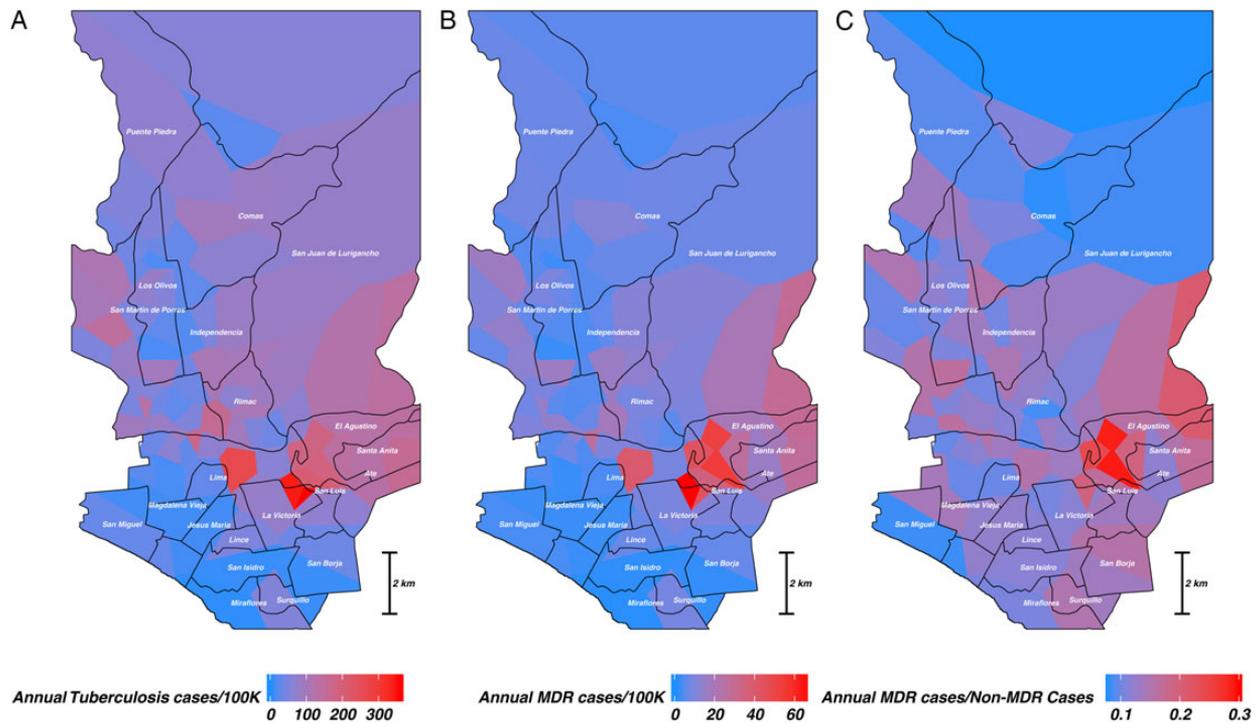


Figure 1. HC-level risks. Annual per-100 k rates of drug-sensitive and drug-resistant tuberculosis (A) and MDR tuberculosis (B), by HC catchment area. C, Ratio of the per-capita rate of MDR to non-MDR cases by HC. HC catchment areas are represented by polygons, with polygon fill color indicating the tuberculosis or MDR-tuberculosis rate in cases/100 K population. The boundaries of administrative districts of Lima are overlaid in black, and labeled in white. Abbreviations: HC, health center; MDR, multidrug-resistant.

The LAM sublineage also had the greatest overall proportion of MDR-tuberculosis cases among lineages represented by 10 or more cases, with 19% of LAM isolates identified as MDR.

As HCs were recruited into the study over time, some areas participated in the study for less time than others; this was accounted for in all analyses. Twelve percent of individuals included in our study had MDR disease; the risk of resistance was substantially higher among individuals reporting prior treatment for tuberculosis (odds ratio [OR] = 2.92, 95% CI, 2.29, 3.71). There were 1199 distinct MIRU-VNTR patterns among case isolates. We found that 865/1199 (72%) of these were unique, while 28% were exactly matched to at least 1 other isolate. Thirty-five genotypes were associated with more

than 10 cases; the most commonly observed genotype was isolated from 134 cases. The full distribution of cluster sizes is shown in Figure 1 in the [Supplementary Materials](#).

Variation in Rates of Tuberculosis and MDR-Tuberculosis at the Health-Center Level

The maps in Figure 1 show substantial geographic heterogeneity in the per-capita rate of tuberculosis (Figure 1A) and rate of MDR-tuberculosis (Figure 1B) across the 85 HC catchment areas in our dataset that reported culture-positive cases with complete records for geographic, genetic, and drug sensitivity during the study period. Several HC catchment areas had particularly high overall rates of tuberculosis as well as MDR-tuberculosis, with

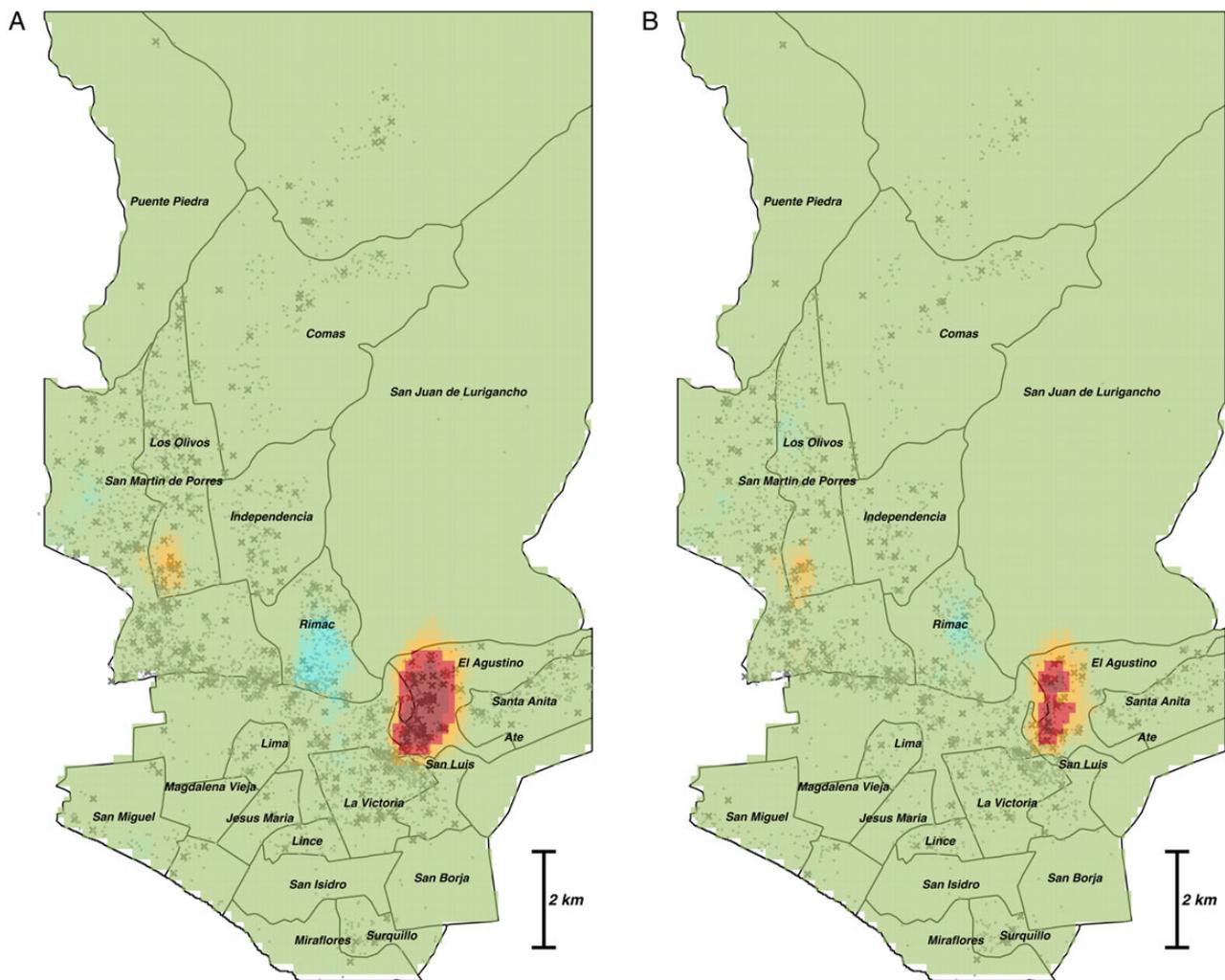


Figure 2. Tuberculosis phenotype hotspot maps. *A*, Area of concentrated MDR-tuberculosis risk measured using household GPS location and MDR phenotype. *B*, Areas of dark color show an area of elevated risk for MDR-tuberculosis among tuberculosis cases with no prior history of tuberculosis treatment, suggesting that these individuals were infected by another individual with MDR-tuberculosis. On both maps, darker areas indicate spatial concentration of MDR cases greater than expected by random chance, given the local density of tuberculosis cases. These values are obtained by randomly permuting case and control labels and recording the maximum and minimum scores from the distance-based mapping algorithm for each of a set of 100 of these randomized “null” maps. Dark areas highlight score values greater than the 99th percentile of the maximum values from the randomly permuted maps. Abbreviations: GPS, global positioning system; MDR-tuberculosis, multidrug-resistant tuberculosis. This figure is available in black and white in print and in color online.

the per-capita rate of disease in the most severely affected HC area many times larger than in the least affected area (rate ratio = 89, 95% CI, 54, 185). Comparison of Figures 1A and 1B reveals the co-occurrence of high rates of tuberculosis and MDR-tuberculosis in several areas. Figure 1C illustrates the ratio of the annual per-100 K rate of MDR to non-MDR tuberculosis cases by HC area. The average ratio of MDR to non-MDR cases was 0.12 (95% CI, .12, .15) while the maximum and minimum ratios were 0.37 (95% CI, .25, .59) and 0.02 (95% CI, .02, .07), respectively.

Spatial Variation in Risk of MDR-Tuberculosis

Figure 2A illustrates a single hotspot of elevated MDR-tuberculosis-risk, highlighted in light and dark red. Tuberculosis cases living within this area are considerably more likely have MDR-tuberculosis than those outside the area (OR = 3.19, 95% CI, 2.33, 4.36). To identify areas of high risk for transmitted MDR, we restricted the population of cases and controls to those tuberculosis cases in our dataset with no history of previous tuberculosis treatment. The map in Figure 2B shows an area nested within the region of increased MDR risk in Figure 2A

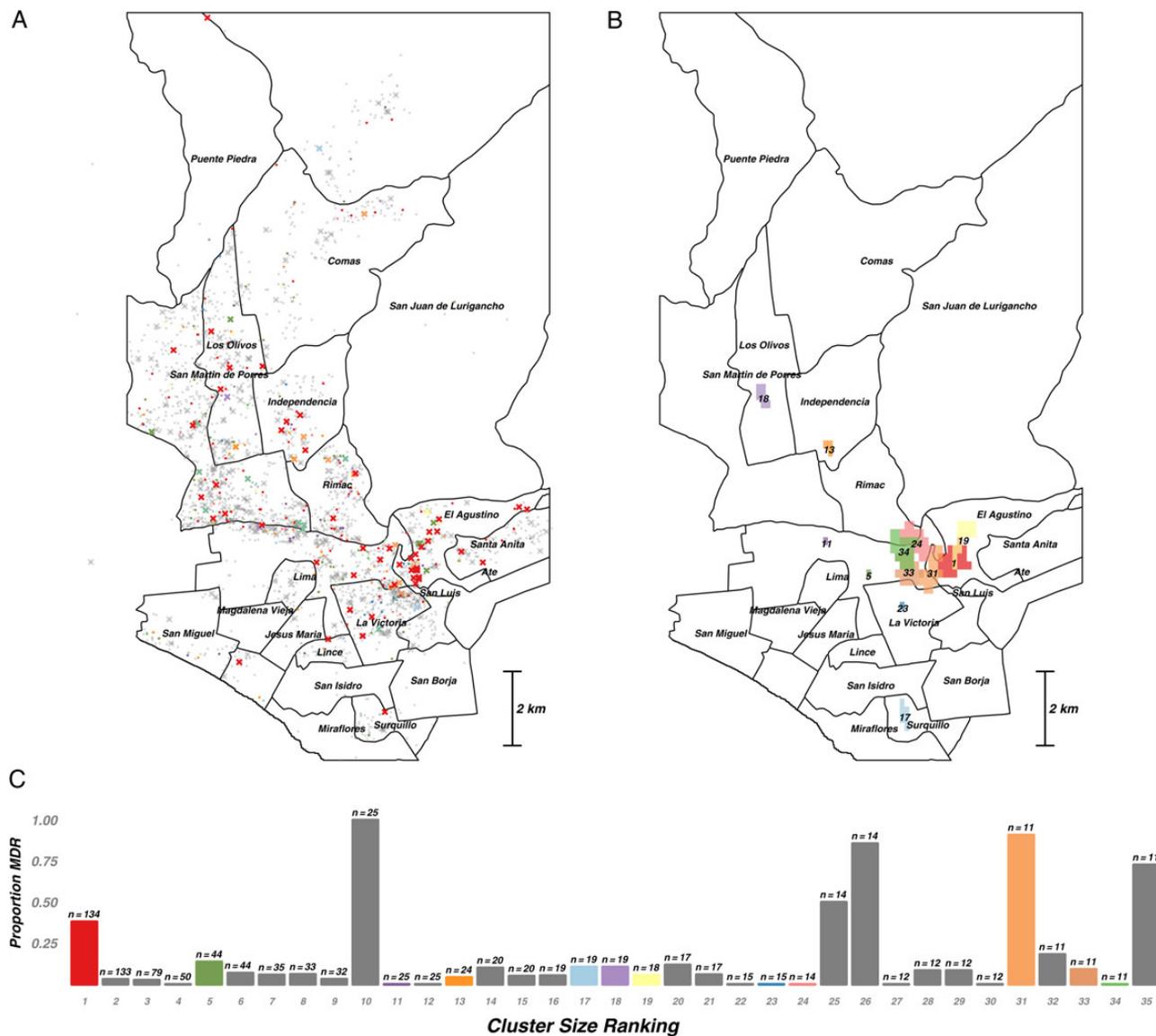


Figure 3. Tuberculosis genotype hotspot maps. A–C, Colors indicate genotype. A, GPS locations of the households of MDR cases are marked with an “x” and household GPS locations of all other cases are marked with a dot. Cases belonging to a genotype without spatial clustering detected by the hotspot mapping algorithm are colored in gray. Colored points in A illustrate the geographic distribution of cases of the 12 tuberculosis genotypes associated with genotype-specific hotspots in B (labeled in the same color). B, Location and size of genotype-specific hotspot areas. Hotspot labels in B correspond to genotypes in C. Both maps reflect the household location and genotype of only household index cases to ensure that results reflect community transmission. C, Proportion of cases of each genotype that are MDR. Bars in C are in descending order by the total number of cases belonging to each genotype with 10 or more cases in the dataset. Abbreviations: GPS, global positioning system; MDR, multidrug-resistant. This figure is available in black and white in print and in color online.

characterized by elevated risk of MDR among treatment-naive individuals. Treatment-naive individuals inside the highlighted area are also more likely to be MDR cases than treatment-naive individuals outside this area (OR = 2.80, 95% CI, 1.62, 4.85)

Spatial Aggregation of *M. tuberculosis* Genotypes

In order to understand possible mechanisms driving the locally elevated risk of MDR-tuberculosis identified in Figures 1 and 2, we probed for evidence of spatial aggregation of specific *M. tuberculosis* genotypes. This allowed us to highlight groups of cases potentially linked by transmission, regardless of retreatment status. To do this, we generated a set of hotspot maps for the set of 35 genotypes in our dataset that were observed more than 10 times. We included only household index cases in this analysis to focus on instances of community transmission; 158 secondary household cases were dropped. We also excluded a subset of 191 index cases missing MIRU genotypes and an additional 294 index cases with multiple copy numbers at 1 or more MIRU-VNTR loci from the genetic analysis. We then examined the distribution of genotypes in the area of elevated MDR risk identified in Figure 2A to determine the extent to which the genotypes of MDR-tuberculosis cases in this area corresponded to MDR-tuberculosis genotypes aggregated in the area of elevated MDR-tuberculosis risk.

Figure 3A illustrates the spatial locations of all study cases; colored markers represent genotypes for which we found evidence of spatial aggregation, while gray markers represent genotypes for which there was no evidence of spatial aggregation, and those with 10 or fewer isolates. In total, 12/35 of the largest genotypic clusters showed evidence of spatial aggregation, although in some cases the majority of cases of a given genotype still fall outside of a highlighted area of genotype-specific risk. Colored areas in Figure 3B indicate spatial aggregation of a particular genotype that is greater than expected by chance, similar to the light and dark red areas in Figure 2.

In Figure 3C, the 35 largest genetic clusters are ordered by size. The height of each bar indicates the proportion of isolates within that genotypic cluster that were MDR-tuberculosis. For the most abundant genotype, colored in bright red on Figure 3A, and labeled “1” in 3B, we see an area of increased risk in an area of eastern Lima known as Lima Este. This genotype belongs to the LAM sublineage and represents 14% (134/902) of all LAM isolates in our dataset and 32% (56/175) of MDR cases belonging to the LAM sublineage. Of the 56 MDR cases of this genotype in our dataset, 17 occur within the hotspot area highlighted in bright red in Figure 3B. The concentration of MDR cases in this area is considerably greater than outside of it: 31% (35/114) of the cases of this genotype outside the hotspot area are MDR cases, contrasted with 80% (16/20) within the hotspot. Adjusting for the impact of previous treatment on MDR risk, we find that the risk of MDR among cases of genotype 1 within the hotspot area in Figure 3B is considerably greater than among cases

Table 2. Distribution of Genotypes Among MDR Cases in High-Risk Area

| Cluster ID | Map ID | Cluster MDR | Previous Treatment | Genotype MDR |
|------------|--------|-------------|--------------------|--------------|
| 1 | 1 | 30% (17/56) | 65% (11/17) | 33% (17/51) |
| 2 | 5 | 7% (4/56) | 25% (1/4) | 67% (4/6) |
| 3 | 10 | 5% (3/56) | 33% (1/3) | 12% (3/25) |
| 4 | 31 | 4% (2/56) | 0% (0/2) | 20% (2/10) |
| 5 | 25 | 4% (2/56) | 0% (0/2) | 29% (2/7) |
| 6 | ... | 4% (2/56) | 50% (1/2) | 100% (2/2) |
| 7 | ... | 2% (1/56) | 0% (0/1) | 100% (1/1) |
| 8 | ... | 2% (1/56) | 0% (0/1) | 100% (1/1) |
| 9 | ... | 2% (1/56) | 0% (0/1) | 50% (1/2) |
| 10 | ... | 2% (1/56) | 100% (1/1) | 50% (1/2) |
| 11 | 19 | 2% (1/56) | 0% (0/1) | 100% (1/1) |
| 12 | 3 | 2% (1/56) | 100% (1/1) | 50% (1/2) |
| 13 | ... | 2% (1/56) | 100% (1/1) | 100% (1/1) |
| 14 | ... | 2% (1/56) | 100% (1/1) | 100% (1/1) |
| 15 | ... | 2% (1/56) | 100% (1/1) | 50% (1/2) |
| 16 | 26 | 2% (1/56) | 0% (0/1) | 8% (1/12) |
| 17 | ... | 2% (1/56) | 0% (0/1) | 100% (1/1) |
| NA | ... | 27% (15/56) | 13% (2/15) | 17% (15/86) |

The table lists the proportion of the 56 MDR cases in the high-risk area highlighted in light and dark red in Figure 2B belonging to each of 17 distinct genotypes, the proportion of these cases with previous treatment, and the proportion of MDR cases for that genotype which are located in the high-risk area. The column marked “Cluster ID” indicates the ID of the genotype within this elevated MDR risk area, in order of number of cases within this area. The column marked “Map ID” indicates the corresponding ID from Figure 3 for the 35 genotypes represented by more than 10 cases in the dataset. Genotypes not represented in Figure 3 are marked by a “...”. The final row, marked “NA,” contains counts for individuals within this area with missing or incomplete MIRU-VNTR information.

Abbreviations: ID, identification; MDR, multidrug-resistant; MIRU-VNTR, mycobacterial interspersed repetitive units–variable-number tandem repeats.

of genotype 1 outside of this area (OR = 7.69, 95% CI, 2.33–24.53). Cases of genotype 1 outside the hotspot area in Figure 3B are also more likely to be MDR cases than cases of other genotypes (OR = 6.89, 95% CI, 4.48, 6.89), even after adjusting for the impact of previous treatment (OR = 2.91, 95% CI, 2.12, 3.68). By contrast, the second-most abundant genotype in our dataset, with 133 cases, has a low proportion of MDR cases (3% compared with 12% in the study overall) and did not show evidence of spatial aggregation.

Table 2 shows the distribution of 17 unique genotypes among the 56 MDR-tuberculosis cases located within the area of elevated MDR risk, highlighted in light and dark red in Figure 2A. The table shows that all of the genotypes showing evidence of spatial aggregation in the area of elevated MDR risk in Figure 3B (genotypes 1, 19, and 31) had at least 1 MDR case. Genotype 1 comprises 30% (17/56) of the total MDR cases in this area, and 35% of these (6/17) reported no previous treatment. Among genotypes 19 and 31, there were 3 total MDR cases, none of which had previous treatment. Overall, 35/56 (62%) of MDR cases in this area had no previous treatment. This suggests that the majority of these individuals were infected by an MDR case of the same genotype, potentially within the area highlighted in Figure 2B. Thus, this may be an area of elevated MDR transmission, both across and within specific genotypes.

DISCUSSION

We identified an area of increased MDR-tuberculosis risk concentrated in neighborhoods in the eastern portion of Lima. This analysis provides a detailed account of the tuberculosis epidemic within the study area, because we recruited all cases notified within HCs and provided universal drug susceptibility testing and MIRU-VNTR genotyping for all bacteriologically positive cases. Our findings provide additional detail on the spatial distribution of MDR-tuberculosis and identify areas where transmission of particular genotypes appears to be spatially concentrated. We also expanded on the results of previous analyses of administrative data, which raised concerns about elevated risk of transmitted MDR-tuberculosis risk in Lima Este [5, 17]. We found that the increased risk of MDR due to transmission associated with living in this area was comparable to the increased risk of MDR associated with previous tuberculosis treatment in the study population as a whole. Earlier work shows how the techniques presented here can be readily adapted to applied contexts in which universal DST and genotyping are not available [17, 19, 20].

The genotype-specific results presented in Figure 3 strongly suggest that the elevated MDR risk among treatment-naive individuals in Lima Este (Figure 2B) is due to the transmission of MDR-tuberculosis, rather than to the systematic acquisition of resistance via treatment failure in this area. If risk in this area is driven by localized transmission, the potential direct and indirect benefits associated with improved detection and treatment of MDR in this area may be substantial. The concentration of MDR within genotype 1—even among treatment-naive cases outside of high-risk areas—is also worth highlighting: this suggests a pattern of transmission involving both spatially aggregated risks and connections between geographically disparate neighborhoods. Such results underscore the critical importance of understanding the extent and nature of geographic heterogeneity in risk for crafting effective interventions [21].

Some of the geographic heterogeneity in concentration of MDR genotypes may also be explained by strain-specific differences in infectivity. However, higher-resolution genomic data would be needed to establish transmission links between individual cases and spatial locations and to explore the possibility that specific clones had high reproductive fitness. In future analyses, joining geographic and genetic information with dynamic models that can highlight individual-level heterogeneity in tuberculosis transmission (eg, the role of superspreaders [22]) will be critical for determining whether the focus of intervention should be on individuals and their movements or concentrated on high-risk geographic areas.

Results showing the disproportionate impact such hotspot areas can have on population-level tuberculosis rates [7] speak to the urgent need to reduce MDR acquisition and transmission in these areas. For example, the identification of MDR hotspots

may be useful for targeting diagnostic resources to make them more effective for mitigating population-level risk than when they are applied uniformly [23]. Recent findings from Lima have shown that poverty and economic instability increase the overall risk of inadequate and ineffective treatment, MDR-tuberculosis risk, and tuberculosis mortality [24]. Further research is necessary to better understand how these socioeconomic factors impact the rate of transmission and the rate at which drug-sensitive tuberculosis cases become MDR-tuberculosis infections in such areas, and how socioeconomic factors contribute to the establishment and maintenance of tuberculosis and MDR-tuberculosis hotspots.

There are several caveats in the interpretation of our results. In particular, the identification of an area in which a genotype is more concentrated than expected by chance should not be taken to represent the dominance of that genotype over all others. Instead, because of the way our study was scaled up, with HCs recruited over the study period, such genotypic maps should be interpreted on a genotype-by-genotype basis. That is, a map showing an area of concentrated risk for a particular genotype suggests that there is localized transmission of this genotype, but not necessarily that there is more transmission of this genotype than all other genotypes in this area. Nonetheless, the use of the genetic information allows us to confirm areas of transmission that span phenotypes (ie, MDR vs drug-sensitive) that may either not show up on phenotype-specific maps, or may join areas of risk highlighted on maps that focus on a single phenotype.

These findings hold out the possibility that case-finding strategies targeted at areas of concentrated risk may be more effective than blanket screening and treatment programs that do not adapt to spatial and biological variation. However, additional geographic analyses and mathematical modeling studies are essential to assess the potential of such strategies to curtail transmission, both within and outside such hotspot areas. As more tuberculosis programs move toward achieving the goal of universal screening for MDR-tuberculosis, studies such as these will be crucial for identifying and targeting areas of highest need at the earliest phases of scale-up.

Supplementary Data

Supplementary materials are available at <http://jid.oxfordjournals.org>. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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