



Small-scale stable clusters of elevated tuberculosis incidence in Moscow, 2000–2015: Discovery and spatiotemporal analysis



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ABSTRACT

Objectives: To find residential areas with high incidence rate of tuberculosis in Moscow using spatio-temporal analysis of incidence data.

Methods: We analyzed the spatial patterns of residence locations of smear or culture positive patients with pulmonary tuberculosis in Moscow. To identify clusters with high local incidence rates, the neighborhoods of detected cases were studied. We assessed the spatial and temporal stability of clusters.

Results: For 19 033 cases diagnosed with smear or culture positive pulmonary tuberculosis among residents of Moscow in 2000–2015 we identified 18 small-scale clusters of increased incidence rate responsible for 3% of all registered cases identified on a territory inhabited by only 1% of the population. Locations of clusters were sufficiently stable in space throughout the whole period. The local incidence rate inside clusters was significantly (3–4 times) higher than the city average during the whole observation period. The presence of clusters was associated with the incidence rate in the surrounding area. Socio-demographic characteristics of patients in clusters were not significantly different from the average characteristics of patients in the city.

Conclusions: The detected small-scale clusters of increased incidence may be used to target active case finding for tuberculosis. The causes and mechanisms of cluster formation and stability need further study.

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Introduction

Tuberculosis (TB) notification rates among Moscow residents declined from 30.8 in 2002 to 14.5 in 2015 (cases per 100 000 population per year). Similarly, the notification rate of infectious smear or culture positive TB among residents declined from 15.1 in 2002 to 6.7 in 2015 (cases per 100 000 population per year) (Bogorodskaya et al., 2016). Despite the significant reduction in the incidence in Russia and Moscow during the past years, tuberculosis remains an important issue. In Moscow, two-thirds of cases of pulmonary tuberculosis are detected during regular screening of population groups with a high risk of infection by TB mycobacteria

(such as people living with HIV/AIDS, people contacting TB patients, persons with diabetes etc.) and with high potential for spreading the TB infection (for example, jobs involving communication with a large number of people, i.e. persons at high risk of transmission if they become ill – retailers, teachers, etc.). A possible way to improve tuberculosis control could be to monitor residential areas with high incidence rates. In order to find such locations, we performed a spatio-temporal analysis of data on the incidence of tuberculosis in Moscow.

The specific of the Moscow healthcare system is an emphasis on active case finding for tuberculosis during regular health examinations. The frequency of health examinations varies from 6 months for groups with high risk of being infected by TB, including people living together with identified tuberculosis patients (mandatory) and workers of children's institutions as a high risk group for TB transmission, to 2 years for the general population (optional). Tuberculosis survey is also mandatory for migrants seeking or renewing their annual work permit. As a

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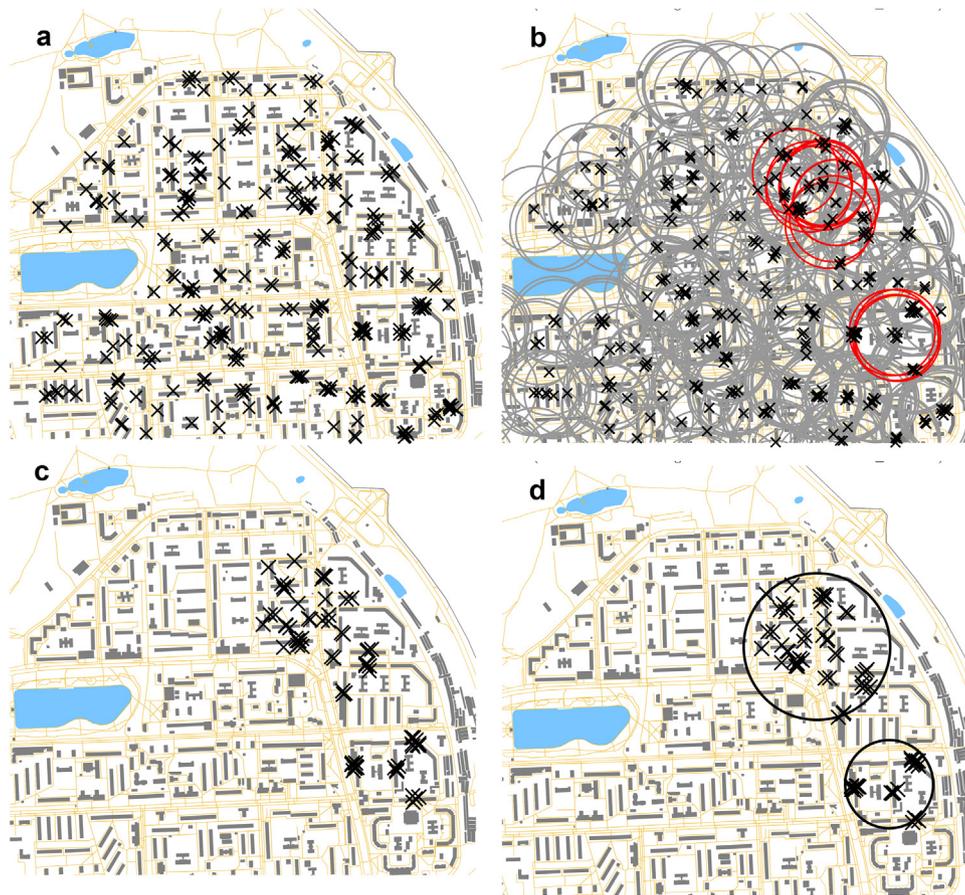


Figure 1. Procedure to identify clusters of increased tuberculosis incidence. (a) Use locations of disease cases (e.g. coordinates of houses). (b) Draw a screening circle around each case and count cases inside it thus estimating the local density of cases. Select circles with the local density above a predefined threshold (red) (see Figure 3b and c). (c) Collect all cases from selected circles. (d) Apply a distance-based method of spatial clusterization. Find center and surrounding circle for each cluster.

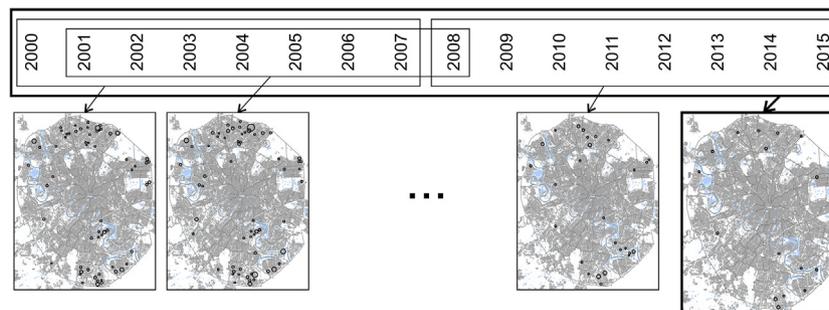


Figure 2. Illustration of the moving time window method for analysis of case clusters location stability. Upper part: timeline (in years) with 8-year intervals (2000–2007, 2001–2008 etc.) and 16-year interval (2000–2015). Lower part: smaller maps show clusters of cases derived from the 8-year intervals (black circles), and the bigger map is derived from the 16-year time interval. The procedure of cluster detection and stability estimation is described in Methods.

result, in 2015, two-thirds of cases were detected during the active case finding, and the proportion of cases with lung destruction decreased from 49% in 2000 to 38% in 2015.

An active case finding strategy is effective if targeted to epidemiologically significant population groups (such as staff of children's medical and educational institutions), or to groups and areas with a significantly increased TB notification rate (e.g. family members and those who were in close contact with a tuberculosis patient, personnel of tuberculosis institutions) (Decree 892). Since monitoring of epidemiologically significant groups in Moscow has

already been implemented, it is necessary to identify areas with high incidence rates.

We follow the Russian national standard and refer to infectious smear or culture positive pulmonary tuberculosis as MTB+ (Aivilov et al., 2015). Notification rate of tuberculosis with MTB+ ranges across Moscow municipalities from 3.4 to 20.2 (cases per 100 000 population per year) (see Figure 3a) (mean TB notification rate for years 2010–2014, data for 107 selected municipalities). The average notification rate of TB with MTB+ in Moscow in 2010–2014 was 10.3 (cases per 100 000 population per year).

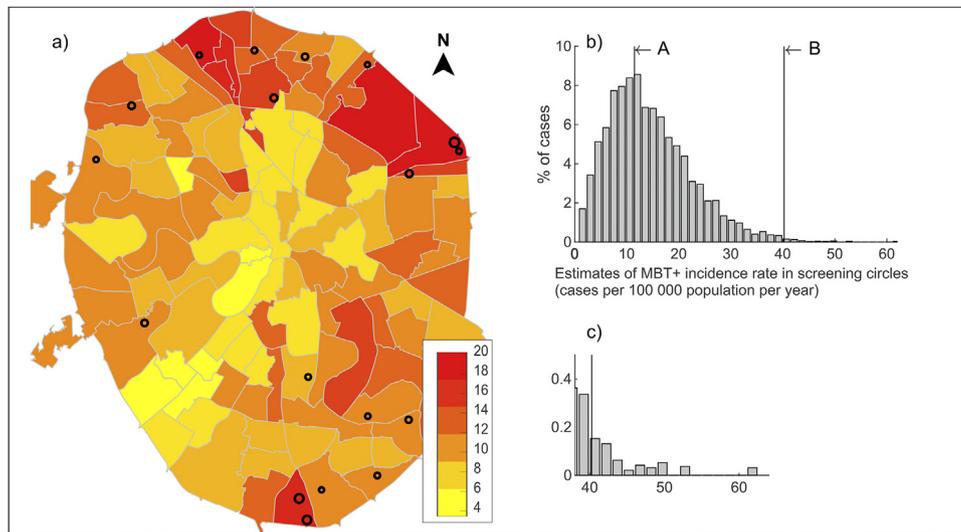


Figure 3. Identification of clusters of increased MTB+ incidence. (a) Choropleth map of average MTB+ incidence rates in Moscow municipalities (cases per 100 000 population per year) (years 2000–2015). 18 clusters of increased MTB+ incidence rates are marked with circles. (b) Distribution of local estimates of MBT+ incidence rates in 2000–2015 in screening circles of $R = 200$ m, line A – the average incidence rate of residents, line B – the threshold incidence rate for selection of cases for cluster analysis (40 cases per 100 000 population per year) (c) Zoom of the histogram tail with 649 cases composing 18 clusters of increased tuberculosis incidence.

If we select the top 10% of municipalities with the highest TB notification rates, we observe rates from 10.1 to 20.2 (cases per 100 000 population per year). These municipalities host from 32 to 182 thousand inhabitants, 1 million or 8% population of Moscow in total. Therefore, screening the entire municipality population is not optimal and can be not effective. A possible alternative will be to search for clusters of tuberculosis incidence inside the municipalities.

A recent review (Shaweno et al., 2018) notes that the apparent spatial clustering of TB is a sign of transmission and/or local risk factors. The authors also conclude that the spatial distribution of the incidence of tuberculosis is significantly heterogeneous and the patterns of detectable heterogeneity are dependent on the methods used for spatial analysis of data. Most of the papers devoted to cluster analysis of the incidence of TB use software based on the approach described in Kulldorff et al. (2005). Typically, data is analyzed on the level of administrative units, and one or several administrative units form a cluster (Touray et al., 2010; Nunes, 2007; Tiwari et al., 2006). The increase in infection transmission rate in such clusters is usually attributed to socio-economic factors.

Infection requires a relatively prolonged contact, for example, communication between a source of mycobacteria and a sensitive individual (Shaweno et al., 2018). Therefore, the priority targets of diagnostic and preventive measures are household members living together with the identified case.

An example of the discovery of clusters presumably due to not only socio-economic factors (such as poor background increasing activation frequency) but also increased infection rate is given in (Munch et al., 2003).

The aim of this article is to search and examine clusters of increased TB incidence in the residential areas of Moscow to facilitate future targeted interventions where needed.

Methods

Territory and cases

Moscow in 2010–2015 consisted of 146 municipalities, some of which merged into the city during the reform of 2011–2012. The population density and living conditions in the “new” Moscow

municipalities, which merged into the city in 2011–2012, differ significantly from the “old” areas in terms of average population density, proportion of residential areas, and organization of TB control.¹ For this study, we limited the data to 107 “old” municipalities that are fully (105) or partially (2) within the Moscow Ring Road. 10.6 million people inhabited this territory in 2014.

We analyzed all 19033 cases of infectious smear or culture positive pulmonary tuberculosis (MTB+) registered in 2000–2015 among the resident population of the considered territory. The individual case data included residential addresses that were geocoded down to a residential building using the Yandex geocoding web-service (LLC Yandex).

Local incidence rates

To estimate the characteristic size of “hotspots” of tuberculosis infection related to the place of residence we considered that the average MTB+ notification rate among the residents of Moscow was 11.5 (cases per 100 000 population per year) in 2000–2015. To find areas with a notification rate of at least 3 times the average we need to detect on average one case per year for every 2900 people. A typical Moscow apartment building hosts 500–2000 people; therefore, a cluster should include at least 2–6 apartment buildings. Estimates for blocks with typical apartment buildings in Moscow show that 2–6 houses are located within a circle with a radius of about 200 m.

The maximum “hotspot” size was estimated from the spatial structure of residential buildings. Moscow is mainly built up with residential quarters with a characteristic size of about 1 km surrounded by industrial areas, parks, and highways. Consequently, the spot radius should be less than 500–400 m to avoid including parts of non-residential areas.

Given these estimates, we implemented a simple yet effective estimate of “local” incidence rates. We counted the number of MTB+ cases in “screening circles” of radius $R = 200$ m around the location of each MTB+ case. The population density for quarters is estimated at

¹ For example, in 2015, the population density in the biggest areas of the “New Moscow” (Troitsky and Novomoskovsky Administrative Okrugs combined) was around 200 people/km² and the population density of the “Old Moscow” was around 11100 people/km², or 55 times higher.

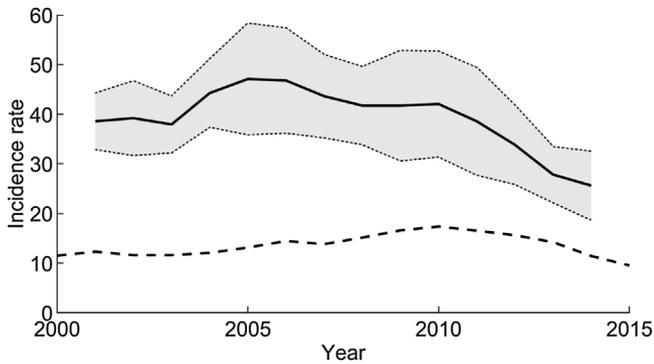


Figure 4. Dynamics of average MTB+ incidence rate in clusters (thick black line), 95% CI (gray area) (smoothed with a 3-year moving average) and the average MTB+ notification rate in Moscow (dashed line).

30000 persons/km². A circle of radius 200 m has an area of 0.126 km² and an average population of 4145 people. From this, the local incidence rates in the vicinity of case locations were estimated.

Detection of clusters

We estimated the local incidence rates for all screening circles and selected circles with incidence rates more than 3.5 times above the city average (40 cases per 100 000 population per year). Then we selected all MTB+ case points inside the selected circles and clustered them.

For clusterization we used a DBSCAN data clustering algorithm proposed by Ester et al. (1996) with parameters: minimum cluster size equal to 10 cases and maximum distance between cases for the clustering equal to 200 m. The algorithm starts with an arbitrary case. If the 200 m neighborhood of the case contains 10 or more cases, a cluster is started. Otherwise, the case is ignored. If a case is found to be a part of a cluster, and its 200 m neighborhood contains at least 10 cases, this new case and its 200 m neighborhood become a part of that cluster. This process continues until the high incidence cluster is completely defined. Then, a new examined case is processed, possibly leading to the discovery of a new cluster. Thus, the algorithm produces clusters satisfying the given conditions. For each case cluster, its center of mass and enclosing circle were found. Figure 1 illustrates the procedure.

Spatio-temporal analysis of clusters

To assess the stability of selected clusters, the following approach was used:

- We considered shorter periods (8 years) of the whole data time interval (16 years).
- We took “sliding” 8-year periods of consecutive years (2000–2007, 2001–2008, etc.) within the interval of years 2000–2015.
- Within each 8-year period, we identified clusters of increased MTB+ incidence (Figure 2) and found their centers. The procedure and parameters for the periods was the same as for the whole time interval.
- The “stability” of 16-year clusters was estimated as a percentage of 8-year clusters with centers falling inside the circles of 16-year clusters (Figure 5, small red circles inside large black circles).

Socio-economic factors and the presence of clusters

We collected openly available characteristics of municipalities such as population (all and by age- and sex groups, pensioner and

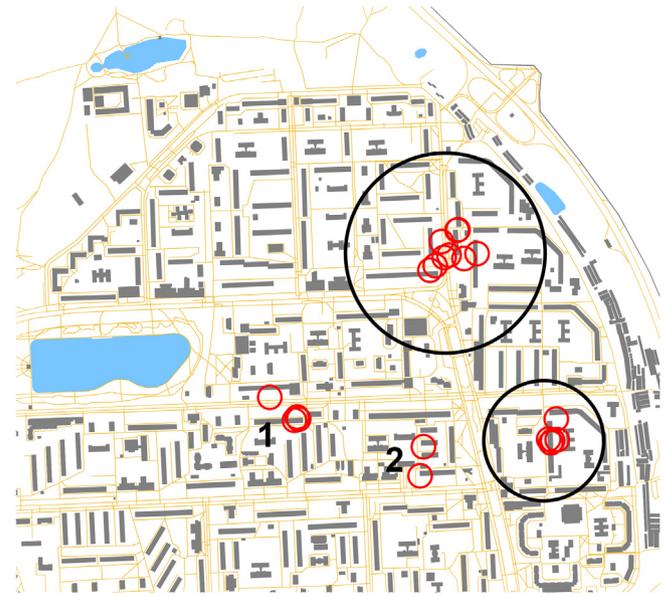


Figure 5. An example of the spatio-temporal dynamics of clusters of increased tuberculosis incidence. Large circles are the 16-year data clusters; small red circles are the centers of clusters derived from the 8-year period data. Shown are 21 centers: nine in the upper cluster, six in the lower cluster, four in the unstable group marked with “1”, and two in the unstable group marked with “2”.

working), area (whole and residential), living space and flat prices, share of population with higher education, subsidies (individual and family) and their derivatives (such as relative areas, population density, proportions of population by groups, population change etc.). We compared the socio-economic characteristics of municipalities with and without clusters and used the Student’s t-test to determine if the mean of characteristic depends upon the presence of clusters significantly.

Results

The principal result of this work is the method to find clusters of increased tuberculosis incidence in a vast populated area. The method allowed us to identify compact groups of apartment buildings, whose residents suffer from an increased incidence of tuberculosis. Figure 3b shows a distribution of local incidence rates estimated in “screening circles” of 19033 MBT+ cases registered in 107 selected Moscow municipalities in 2000–2015. The MBT+ incidence rate estimated in a screening circle was up to 62 cases per 100 000 population per year. To search for clusters of infection we selected the circles with high case count. In 648 circles the local incidence rate was higher than 40 cases per 100 000 population per year (Figure 3b, line B). Figure 3c zooms on the distribution of the incidence around these 648 cases. Figure 3a shows circles corresponding to these 648 cases. Clusterization resulted in 18 clusters in 16 municipalities with 27–49 cases per cluster. The incidence rate outside the clusters is definitely lower than inside them (Figure 4).

Table 1 shows the characteristics of the clusters of increased incidence rate. The number of MTB+ cases in clusters for years 2000–2015 is 648 or 3.4% of the total number of MTB+ cases (19033). The average number of MTB+ cases per year in a cluster is 2.25. A small number of cases questions the statistical confidence of identified clusters. To test this we compare the dynamics of the average incidence rate in clusters, 95% CI and the dynamics of average MTB+ notification rate in Moscow (Figure 4). The MTB+ incidence rate in clusters is significantly different from the average incidence rate in Moscow.

Table 1
Characteristics of clusters of increased MBT+ incidence shown in Figure 3.

Municipality name	MBT+ cases registered in 2000–2015	Average cases in cluster per year	Estimate of incidence rate in cluster ^a	Mean MBT+ incidence rate in surrounding municipality ^a
Altufevsky	35	2.19	46.8	18.8
Biryulevo East	28	1.75	48.2	17.3
Biryulevo West (1) ^b	54	3.38	34.5	19.9
Biryulevo West (2)	47	2.94	28.1	19.9
Brateevo	45	2.81	52.5	13.5
Golyanovo (1)	27	1.69	38.7	18.1
Golyanovo (2)	63	3.94	32.6	18.1
Dmitrovsky	27	1.69	42.7	16.7
Mariino	28	1.75	43.5	8.0
Nagatino-Sadovniki	28	1.75	40.3	16.5
Orekhovo-Borisovo South	30	1.88	41.7	13.1
Otradnoye	51	3.19	46.5	16.6
Ochakovo-Matveyevskoe	32	2.00	34.8	15.2
Izmailovo North	37	2.31	34.0	19.2
Medvedkovo North	31	1.94	35.1	17.0
Strogino	27	1.69	44.8	11.7
Tushino South	30	1.88	30.7	14.7
Yaroslavsky	28	1.75	49.9	15.3

^a Per 100 000 population per year in 2000–2015.

^b Two clusters in the same municipality.

Table 2
Comparison of epidemiological and socio-economic indicators in municipalities with and without clusters.^a

	Mean MBT+ incidence rate in 2000–2015	The proportion of the population with higher education	The proportion of the population receiving utility subsidies ^c	The market price of housing (\$/m ² , 2015)	Housing capital, per person (\$, in 2015 prices) ^d
Municipalities without incidence clusters (91)	10.6 ± 3.8	0.5 ± 0.1	0.05 ± 0.01	3221 ± 911	65587 ± 31035
Municipalities with incidence clusters (16)	15.74 ± 3.04	0.43 ± 0.06	0.05 ± 0.01	2624 ± 140	42515 ± 6600
p^b	$p < 0.01$	$p < 0.01$	$p = 0.83$	$p = 0.01$	$p < 0.01$

^a $m \pm \sigma$, where m is average, σ is an estimate of the variance of a random variable.

^b Reliability of the hypothesis that random samples belong to distributions with the same mean.

^c Share of the municipality population with low income and receiving utility subsidies.

^d Average apartment cost (per m²) in the municipality times the average living space (m²) per inhabitant.

Spatio-temporal dynamics of clusters of increased incidence

Figure 5 shows the result of analyzing the location stability of two clusters. Both clusters did not change position, i.e. were stable, during 16 years of observation. In addition, the area of the upper, larger cluster, if calculated from data of 8-year periods of consecutive years, was characterized by a high incidence. The stability of this cluster is estimated at 100%. The lower cluster is smaller and 6 of 9 centers of 8-year period clusters fall inside it. The stability of the second cluster is thus estimated at 67%. The average stability of these two clusters is 83%. In addition, note two conglomerations of 8-year period cluster centers – marked with “1” composed of 4 centers and marked with “2” of two centers. All 18 clusters demonstrate 77% “stability” for the 8-year periods and 73% for the 10-year periods. Thus, the discovered clusters have stable locations and consistently high incidence rates.

Socio-economic factors and the presence of clusters of increased incidence

Figure 3a shows that the clusters of increased incidence rate are unevenly distributed throughout the city: 11 out of 18 clusters are located in the Southern and Northern parts of the city, and there is not a single cluster in the Central and South-Western parts. The parts and their constituent municipalities differ in their socio-economic characteristics. Table 2 lists the difference between municipalities with and without clusters. The municipalities with

clusters are characterized by the significantly higher MBT+ incidence rates (15.7 vs 10.6 per 100 000 population), lower proportion of people with higher education (0.43 vs 0.5) and lower housing capital (\$42515 vs \$65587 per person). The incidence rate in municipalities is positively correlated with the share of low-income people receiving utility subsidies (Karkach et al., 2017), but this indicator did not differ significantly in municipalities with and without clusters. When registering patients, personal and social characteristics such as age, sex, education, marital status, employment, and job, disability, criminal record, etc. were recorded. A comparison of these characteristics for patients in clusters and in surrounding municipalities did not reveal significant differences in any of the indicators. This is an indirect indication that the causes for the cluster formation must be sought among the characteristics of the cluster territory.

Discussion

The aim of our study was to search for local clusters of increased incidence of tuberculosis on a scale smaller than the municipality. The exact localization down to a few multi-storey residential buildings whose residents are characterized by an increased incidence of tuberculosis will allow targeting effective measures to identify and treat active and latent tuberculosis infection. We assumed two possible causes and factors for the formation of such clusters.

- an increase in the incidence of residents in the vicinity of major markets and shopping centers where migrants work and rent housing.
- an increase in the incidence in deprived blocks.

These assumptions are consistent with the results of many works. For example, Munch et al. (2003) found increased tuberculosis incidence near wine bars. The authors suggest that tuberculosis infection occurs in these bars. In (Chan-Yeung et al., 2005) a higher density of tuberculosis cases was detected in areas with an older, less educated and poorer population.

To search for areas with high local incidence rates we used a modification of the spatial scan statistic method with the center of the scanning circular window at the location of cases (Waller and Gotway, 2004). To diminish the effect of build-up heterogeneity, quarter boundaries, parks, and highways a fixed scanning window radius of 200 m was used.

This approach allowed us to identify small-scale clusters of elevated tuberculosis incidence that are stable in time and space. They are characterized by the following features:

- they are small in size ($R = 180\text{--}250$ m) and occupy a part of the residential quarter;
- have no obvious physical boundaries with adjacent residential buildings that could account for the difference in the incidence rate in the cluster and in the surrounding territory;
- inside or in the vicinity of clusters there are no features that elevate the probability of infection/activation of tuberculosis such as markets, train stations, tuberculosis clinics, wine bars, etc.

We found that shifting the threshold level (line B in Figure 3b) to the left increases the number of discovered clusters, but the spatial and temporal stability of newly identified additional cluster decreases.

All identified clusters are located in municipal quarters and have a certain population density of about 30 000 people per km^2 . Using this population density estimate, we estimated the incidence in clusters and compared it with the incidence in municipalities. This comparison showed that clusters are detected under the condition of a relatively high average MTB+ incidence rate (>15.7 cases per 100 000 population per year) in the surrounding area. Comparison of available characteristics of cases identified in the clusters and on average in Moscow unexpectedly did not reveal significant differences. In particular, these groups did not differ in gender, age, level of education, shares of the unemployed, employees and workers.

The small share of the population living inside stable clusters (about 1%) indicates a rather “uniform” distribution of morbidity in residential areas of a city with 10 million population. This agrees with the absence of ethnic enclaves and residential areas with a high proportion of the population below the poverty level in Moscow.

There is also no indication of differences in characteristics of the healthy population between clusters and surrounding areas. The persistence of increased incidence rates in clusters (at least for 16 years) suggests that the rate of transmission of infection is higher in the clusters. What exactly favors increased transmissibility of *M. tuberculosis* in the clusters needs further study.

From the point of view of tuberculosis management, identification of incidence clusters allows targeting actions and is important for increasing the effectiveness of timely case-finding and eventually TB treatment.

Detection of evidence of transmission of TB to residents of neighboring houses and apartments is the reason for screening additional risk groups. It is also necessary to determine the conditions for the formation of local clusters.

Declarations of interest

None.

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