Antonio L Rodrigues-Jr[I]

Antonio Ruffino-Netto[I]

Euclides Ayres de Castilho[II]

Spatial distribution of *M. tuberculosis*/HIV coinfection in São Paulo State, Brazil, 1991-2001

ABSTRACT

OBJECTIVE: To assess the spatial pattern of tuberculosis incidence in relation to the AIDS epidemic, with the aim of investigating the geographical influence on causality.

METHODS: All AIDS cases from State of São Paulo, notified to the Brazilian Ministry of Health between 1991 and 2001, were included. The cases were stratified by municipality, by administrative health regions, AIDS transmission categories, gender and years since diagnosis. A Gaussian geostatistical model was used to construct a thematic risk map, utilizing the tuberculosis incidence among AIDS cases as the response variable.

RESULTS: Exploratory analysis showed two patterns of AIDS incidence: one for the state capital, and another, with increasing risk, for the other municipalities. The more populous regions presented higher risk of tuberculosis transmission, with a pattern that matched the land occupation pattern, from east to west. The health regions with the highest AIDS incidence coefficients (per 10,000 inhabitants) were Santos (53.5), São José do Rio Preto (43.1), Ribeirão Preto (42.4) and São Paulo (40.3). The health regions with greatest tuberculosis incidence among AIDS cases were Santos (44.9%), Franco da Rocha (39.9%), Osasco (39.6%) and São Paulo (38.9%).

CONCLUSIONS: The results allow the conclusion that geographical coordinates presented an association with tuberculosis risk, but not with AIDS risk.

KEYWORDS: AIDS-related opportunistic infections, epidemiology. Tuberculosis, epidemiology. Acquired Immunodeficiency Syndrome, epidemiology. Epidemiologic surveillance. Residence characteristics. Incidence.

[I] Departamento de Medicina Social. Faculdade de Medicina de Ribeirão Preto. Universidade de São Paulo (USP). Ribeirão Preto, SP, Brasil

[II] Departamento de Medicina Preventiva. Faculdade de Medicina. USP. São Paulo, SP, Brasil

Correspondence:
Antonio Luiz Rodrigues-Jr
Departamento de Medicina Social
Av. Bandeirantes, 3900
14049-900 Ribeirão Preto, SP, Brasil
E-mail: alrj@fmrp.usp.br

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INTRODUCTION

The acquired immunodeficiency syndrome (AIDS) has altered the recent epidemiological history of tuberculosis, affecting people of all socioeconomic classes.[13] Individuals infected by HIV (HIV+) are 25 times more susceptible to tuberculosis than those who are not infected (HIV-),[7] and patients with coinfection of HIV and *Mycobacterium tuberculosis* present twice the risk of death presented by HIV+ patients without tuberculosis.[9]

Between 1980 and August 1995, 71,000 AIDS cases were notified in Brazil. Over the same period, the estimated incidence of tuberculosis was 80,000 to 90,000 cases per year. It has been estimated that, out of a total of around 400,000 people infected with HIV, 30% were coinfected with *M. tuberculosis.*[7] Kritski & Dalcomo[8] (1993) reported an increase in the incidence of tuberculosis in Brazil among people infected with HIV from 8% in 1984 to 20% in 1994. Another Brazilian study, in the state of Ceará in 1997, found that 30.6% of the AIDS cases also had tuberculosis, and that this increased to 76.8% one year later.[7] Recent studies on the AIDS epidemic have shown increased incidence among people in lower socioeconomic classes, which makes them more vulnerable to opportunistic diseases. Corbett et al[2] (2003) reported that there were 114,000 cases of tuberculosis in Brazil in 2000, and estimated the prevalence of HIV+ individuals as 3.3% (3,762 cases).

The World Health Organization (WHO) recommends epidemiological monitoring and intensification of the early detection of AIDS as tuberculosis control strategies, through giving priority to active searches among people with persistent coughs and fever. Such a strategy depends on integration among health programs and among the health information systems.[14] Lima et al[10] (1997) found that 43% of their AIDS cases had tuberculosis (217 out of 505 cases), and that this had not been registered by the tuberculosis information system in state of São Paulo in 1993.

The present study had the objective of studying the tuberculosis incidence among AIDS cases by using a geostatistical approach to assess the spatial distribution pattern.

METHODS

This study was of retrospective type, using secondary data. The population of each municipality was considered to be a dynamic cohort in which the members (residents) were, on average, exposed to the same causal factors for tuberculosis and AIDS over the course of time. The tuberculosis incidence among AIDS cases (comorbidity), and the hypothesis that the spatial location would be associated with it, were observed[4]. The information on AIDS cases notified to the Ministry of Health between 1991 and 2001 was utilized, and the political-administrative divisions of municipalities produced by the Instituto Brasileiro de Geografia e Estatística (Brazilian Institute for Geography and Statistics - IBGE) were adopted, for defining the observational units for the study.[5]

Over the whole country, 224,003 AIDS cases were notified. Among these, 7,800 cases were excluded because these individuals were less than 13 years old, given that diagnosing tuberculosis is more complex. Among the remaining 216,203 adult cases, 22.4% presented tuberculosis. The municipalities of São Paulo presented 100,494 AIDS cases, which corresponded to 44.9% of the epidemic in Brazil. After excluding the 3,203 children aged less than 13 years, it was found there were 25,147 adult cases of tuberculosis. Because São Paulo is the most populous state and has the highest economic production in the country, its municipalities were stratified into 24 administrative health regions (DIR). This stratification respects the historical and geographical characteristics of the human occupation, thus resulting in a dendritic network based on central locations, in accordance with Christaller's theory.[3] This theory states that some municipalities are more productive than others, and that there is a regionalized structure for the consumption of goods and services. The main regional centers for each stratum, as represented by main offices of the DIRs, were adopted as the central locations and are shown in Table 1.

A partition between the state capital and the other municipalities was included, because of the differences between the epidemiological patterns for AIDS.[12] Two categories of AIDS cases were considered: those that presented a positive diagnosis of tuberculosis were named notified cases, while those that did not present a known diagnosis of tuberculosis but which presented cough, fever, asthenia and disseminated mycobacteriosis were named probable cases. These criteria for defining cases reflect the impact of tuberculosis on the AIDS epidemic,[1] which is measured by the incidence coefficient. The sum of these cases (notified and probable) has been called the corrected incidence of the comorbidity. The information from the records that was taken into account included the municipality of residence, gender, date when AIDS was diagnosed and category of HIV exposure. The geographical coordinates (latitude and longitude) for each municipality were obtained from the Universal Transverse Mercator (UTM) sys-

Table 1 - Characteristics of the health regions (DIRs) in relation to tuberculosis and AIDS. São Paulo state, 1991 to 2001.

DIR	Central locations	Population density Inhabitants/ km²	Coefficient of AIDS incidence ($x10^4$)	Coefficient of tuberculosis incidence among AIDS cases	Probable tuberculosis cases	Total coefficient of tuberculosis incidence among AIDS cases
I	São Paulo - capital	6,452.0	40.3	0.3011	3,484	0.3891
II	Santo André	2,694.0	24.2	0.2278	323	0.2878
III	Moji das Cruzes	720.7	17.5	0.2314	192	0.2852
IV	Franco da Rocha	486.3	15.6	0.3141	47	0.3989
V	Osasco	1,045.7	17.9	0.3115	319	0.3955
VI	Araçatuba	35.5	20.4	0.1552	72	0.2114
VII	Araraquara	72.2	26.8	0.1894	128	0.2499
VIII	Assis	45.0	13.0	0.1966	23	0.2405
IX	Barretos	45.7	31.3	0.0900	116	0.1867
X	Bauru	52.2	22.2	0.1609	175	0.2465
XI	Botucatu	31.5	11.5	0.2210	21	0.2610
XII	Campinas	333.2	20.3	0.2702	311	0.3211
XIII	Franca	58.5	15.5	0.1671	77	0.2570
XIV	Marília	48.7	15.5	0.2455	37	0.2900
XV	Piracicaba	135.9	18.8	0.1735	134	0.2358
XVI	Presidente Prudente	29.2	13.1	0.2005	50	0.2587
XVII	Registro	17.1	9.0	0.2091	29	0.3409
XVIII	Ribeirão Preto	100.4	42.4	0.1776	533	0.3016
XIX	Santos	545.0	53.5	0.3719	541	0.4491
XX	São João da Boa Vista	84.6	12.9	0.2486	70	0.3266
XXI	São José dos Campos	100.0	43.1	0.1748	142	0.2096
XXII	São José do Rio Preto	46.9	34.6	0.1148	346	0.1953
XXIII	Sorocaba	69.0	19.3	0.1784	276	0.2597
XXIV	Taubaté	81.1	27.7	0.2392	118	0.2896

DIR: Health Region

tem, using the SAD-69 ellipsoid and the Córrego Alegre datum. The digital geographical base for the municipalities of São Paulo state was obtained from the Instituto Nacional de Pesquisas Espaciais (National Institute for Space Research - INPE). The incidence coefficients for each municipality took into consideration the sizes of their populations in 1996, thus representing the population at the halfway point of their follow-up. These figures were obtained from IBGE. The central coordinates of the localities were utilized for estimating the risk, by means of a spatial stochastic process of Gaussian, stationary, heteroscedastic and anisotropic nature.[4]

The coefficients of tuberculosis incidence among AIDS cases, from the central location theory, were analyzed using the geostatistical model. A model of spatial continuity of the event was adopted, in which a semivariogram function translated the distribution of the dependencies between the observation units, thus serving as evidence for an association between the physical space and the incidence of the disease.[4] The estimation of the risk of tuberculosis among AIDS cases was done using the generalized weighted least-squares method ("conventional kriging"). In this model, the distances from each municipality to the central locations acted as weights. The free software "R" was used in the geostatistical calculations.[5,6,11]

RESULTS

Table 1 presents the epidemiological and demographic measurements, and Figure 1 shows the proportional distribution of the AIDS transmission categories for each DIR. It was observed that there was high incidence of AIDS cases with unknown transmission category, in the heavily populated DIRs (regions I, II, III, V and XII). Regions I, II, III and IV are grouped adjacent to each other, covering an area in which more than 17 million people share the space, with innumerable contacts between them. The large numbers of AIDS cases with unknown transmission category in these regions may reflect a deficiency in the capacity of the epidemiological surveillance system to identify the HIV transmission category. DIR-I (the state capital) and DIR-II represented the municipalities with the highest population concentrations and highest incidence of tuberculosis among notified AIDS cases.

AIDS cases in São Paulo state were 2.6 times more frequent among males than among females. Among such cases with tuberculosis, the proportion was 3.4 times greater for males. Likewise, among the probable tuberculosis cases, the proportion was 3.1 times greater. Among the 25,147 AIDS cases with tuberculosis the transmission category of injectable drug users was reported in 37.0%, the heterosexual category in 31.9% and the unknown transmission category in 13.9%. If the probable tuberculosis cases were confirmed, the total number of AIDS cases with tuberculosis would be 32,711, made up of 35.7% in the transmission category of injectable drug users, 31.2% in the heterosexual category and 14.9% in the unknown category.

Table 2 presents the coefficients of tuberculosis

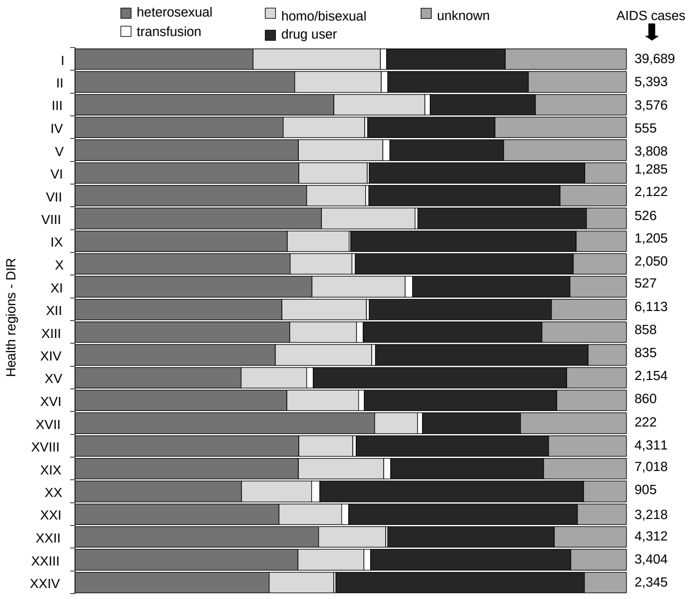

Figure 1 - Proportional distribution of AIDS cases according to transmission categories and Health Regions (DIR). São Paulo state, 1991 to 2001.

incidence among AIDS cases, for DIR-I and for the other DIRs, considering the male and female populations. The corrected incidence coefficient of the comorbidity per 10,000 inhabitants was 15.7 for the state capital (DIR-I) and 7.1 for the other DIRs. The results showed that the injectable drug users of male gender living in the capital presented the highest incidence of the comorbidity ($7.8x10^4$). In the corrected incidence of the comorbidity (25,147 notified cases and 7,564 probable cases), 77.1% were males. These were stratified as 30.2% with injectable drug use, 17.1% with heterosexual transmission, 17.0% with homosexual transmission, 11.8% with unknown transmission and 1% with vertical transmission. Among the women who presented tuberculosis (33.1%), the most frequent transmission category was heterosexual (14.0%).

Figure 2a shows the annual series of AIDS incidence coefficients for DIR-I, from 1991 to 2001. Figure 2b shows the same time series for the other DIRs together. Different epidemiological patterns for AIDS incidence can be seen: one for the capital, which shows stability with a tendency towards decreasing incidence, and another for the remaining municipalities, which shows a trend of increasing incidence. For both patterns, the incidence of the comorbidity decreased over this period, since the AIDS diagnosis was formerly based on the Caracas criteria and is now made via laboratory tests. Moreover, it can be seen that the numbers of probable cases that did not present a diagnosis of tuberculosis decreased with time, both for DIR-I and for the other DIRs. The thematic map of Figure 3 shows the estimated spatial distribution of the risk of tuberculosis among AIDS cases, in São Paulo state.

DISCUSSION

Around half of the AIDS notifications in Brazil come from São Paulo state, which represented close to one fifth of the population of Brazil in 1996. Thus, this is a high incidence coefficient. Two epidemiological patterns can be seen in the state: one pattern for the capital, which presents incidence that is apparently stable or slightly declining, and another for the other municipalities, which is clearly increasing. The pattern in the capital may be the result from the impact of prevention programs and from the participation of NGOs in combating the epidemic. For the state capital, the IBGE estimated a population concentration

Table 2 - Coefficient of tuberculosis incidence among AIDS cases, considering the state capital (DIR-I) and the other health regions (DIRs) according to AIDS transmission categories and gender. São Paulo state, 1991 to 2001.

Gender	Transmission category	DIR-I Notified	DIR-I Probable	Other DIR Notified	Other DIR Probable	Corrected incid. coeffic.*
Male						
	Heterosexual	4.03	0.99	2.13	0.53	3.33
	Homo/Bisexual	5.05	2.04	1.39	0.46	3.32
	Transfusion	0.20	0.07	0.10	0.03	0.16
	Drug user5	6.40	1.39	4.06	1.09	5.90
	Unknown	3.73	1.10	0.87	0.44	2.30
	Subtotal	19.41	5.59	8.54	2.56	15.01
Female						
	Heterosexual	3.24	0.99	1.54	0.46	2.65
	Homo/Bisexual	—	—	—	—	—
	Transfusion	0.06	0.04	0.03	0.02	0.07
	Drug user	1.27	0.30	0.60	0.20	1.03
	Unknown	0.84	0.32	0.20	0.13	0.58
	Subtotal	5.41	1.65	2.37	0.81	4.33
Total		12.13	3.54	5.44	1.68	9.59
Corrected incidence coefficient*		15.67		7.13		9.59

*For the corrected coefficient, the notified and probable tuberculosis incidence among AIDS cases were considered

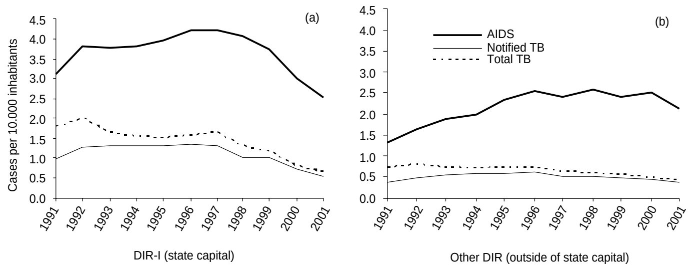

Figure 2 - Historical series of AIDS incidence coefficients and the impact of tuberculosis (TB) among AIDS cases, for the state capital (a) and other Health Regions (DIRs) outside of the state capital (b). São Paulo state, 1991 to 2001.

of 6,451.8 inhabitants/km^2 in the population count of 1996. The city of São Paulo is where the AIDS epidemic began in 1981. For the other DIRs, i.e. for the other municipalities in the state, a population concentration of 156.6 inhabitants/km^2 was estimated.

This division does not reflect a realistic partition of the risks, since the AIDS transmission mechanisms are not circumscribed to the physical limits of the municipalities. However, it helps in evaluating the human dynamics in these spaces as determinants for AIDS and tuberculosis. This partition allows the state capital to be considered to be an important link for the propagation of transmittable diseases like AIDS and tuberculosis. Despite these trends for the AIDS epidemic, the tuberculosis incidence coefficients have decreased because of the progressive introduction of laboratory tests for detecting HIV, in replacement for the Caracas/Rio de Janeiro criteria. However, the real prevalence of *M. tuberculosis* and HIV coinfection is unknown, since the national program for sexually transmitted diseases (STD) and AIDS only records the opportunistic diseases present at the time when AIDS is diagnosed. HIV+ individuals present 25 times greater risk of having tuberculosis. Intensified attention needs to be given to individuals with persistent coughing and fever, by means of actively searching among the notified AIDS cases, and also communication needs to be stimulated between the local tuberculosis and AIDS control programs.

The highest AIDS incidence coefficients per 10,000 inhabitants were found in the regions DIR-XIX (53.5), DIR-XXI (43.1), DIR-XVIII (42.4) and DIR-I (40.3). The Santos and Ribeirão Preto health regions presented very similar proportions, although in Santos there was a greater percentage of cases in the homosexual/bisexual transmission category and a lower percentage in the injectable drug user category. These differences are caused by the migratory flow of formal and informal market activities, and by the trade outflow route towards the coast and abroad. The greatest total tuberculosis incidence among AIDS cases was found in DIR-XIX (44.9%), DIR-IV (39.9%) and DIR-V (39.6%). The municipality of Santos presented the highest incidence coefficients, both for AIDS and for tuberculosis in AIDS cases, while DIR-I and DIR-XVIII presented 38.9% and 30.2% tuberculosis incidence among AIDS cases, putting them in fourth and eighth places, respectively. These figures give the idea that tuberculosis is an important disease in the regions with high population concentrations, as can be seen in Table 1.

The geostatistical method with adaptation to the central location theory showed coherence, by means of the semivariogram function, which showed an increasing trend only in the direction of 0º, thus indicating that the spatial autocorrelation occurred in the easterly direction. This is coherent with the land occupation pattern, which is from east to west. This pattern was not observed with the semivariogram for the AIDS incidence coefficient data, thus showing that there is no association between the value observed and the geographical location. These results confirm the theoretical pattern for AIDS, since there is no transmission caused by physical proximity (very close or adjacent neighbors). HIV is transmitted by people's attitudes, which are reflected in their social behavior and not by proximity to the carrier of the agent. On the other hand, *M. tuberculosis* is indeed transmitted by proximity to individuals carrying the bacillus. These analogies enable it to be considered that the geostatistical model

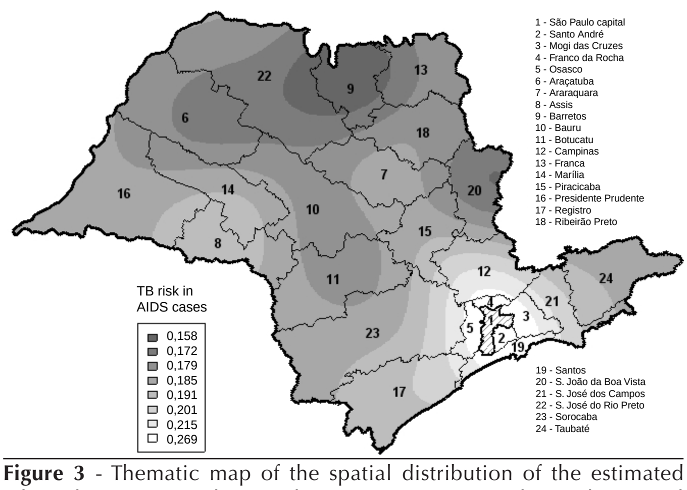

Figure 3 - Thematic map of the spatial distribution of the estimated tuberculosis (TB) incidence risk in AIDS cases, considering the central localities structure (main offices of the Health Regions (DIRs)). São Paulo state, 1991 to 2001.

adopted does not lead to ecological fallacies, when structured with central locations. It showed multi-disciplinary coherence between geostatistics, human geography and epidemiology.

According to Corrêa[3] (1996), the central locations can easily be determined, since they form part of the hierarchical structure of power, i.e. the administrative apparatus of the state, thus forming a network of dendritic type, through which public policies are implemented. In the present study, the main offices of the DIRs were adopted as sample in a continuous process across the physical space. Therefore, the geostatistical model assumed that the distances from each municipality to the central locations would define a system of regional influences that would be concordant with the lines of reasoning of human geography. This resulted in the numerical model for the spatial distribution of the risk of tuberculosis in AIDS cases in São Paulo state.

An individual with AIDS will only become infected by *M. tuberculosis* if there is exposure to the etiological agent, by means of other individuals carrying the bacillus. In the present study, the localities in which contacts occurred were identified, which by inference may reflect the areas of greatest risk of tuberculosis transmission, independent of whether these are individuals with AIDS, given the nonexistence of a databank at state or national level, regarding tuberculosis cases. Prevention is possible, and its impact on tuberculosis control is recognized by several DIRs. The recent visibility of tuberculosis caused by the AIDS epidemic has created an opportunity to mobilize segments of society and health service providers towards combating these two public health problems.

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