SPATIOTEMPORAL EPIDEMIOLOGY
IN TB CONTROL

CARLA NUNES

GOALS OF THIS RESEARCH LINE AT ENSP

BACKGROUND

— TB in Portugal
— Spatiotemporal epidemiology - definition

4 CASE STUDIES

— Identification of areas of risk of incidence - methodological
— Identification of risk areas of incidence and associated factors
— Identification of factors associated with treatment dropout
— Identification of factors associated with longer diagnostic times

CONCLUSIONS
Motivation

— Contribute to knowledge in the area of spatial epidemiology, in particular spatiotemporal clustering / modeling processes, and their value in Public Health;

— Contribute to the knowledge on the control of Tuberculosis and its determinants, in particular for sustained and scientifically robust local interventions.

Goals

— Describe / develop / discuss / apply spatiotemporal processes, strengths and limitations;
— Define critical points in the control of tuberculosis in Portugal and identify the associated local determinants.
  — Incidence, failure treatment (including drop-out), delay until diagnosis, diagnosis, contact screening and mortality (Brazil)

Setting: Portugal

TB NOTIFICATION AND INCIDENCE RATE (10^5)
PTB Incidence Rate (10^5) MUNICIPALITIES, 2000-2015

Spatial unit: municipalities (278)
Individual information
(2000-....)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Indicator</th>
<th>Numerator</th>
<th>Denominator</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTB</td>
<td>Incidence rate /100,000</td>
<td>New notified PTB cases / (2004-2006)</td>
<td>2005 resident population</td>
<td>DGH</td>
</tr>
<tr>
<td>Overcrowded accommodation</td>
<td>Percentage of overcrowded</td>
<td>Overcrowded primary family residence</td>
<td>Primary family residence</td>
<td>NIS (2001 Census)</td>
</tr>
<tr>
<td></td>
<td>accommodation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-standard accommodation</td>
<td>Percentage of non-standard</td>
<td>Non-standard primary family residence</td>
<td>Primary family residence</td>
<td>NIS (2001 Census)</td>
</tr>
<tr>
<td></td>
<td>accommodation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working-age</td>
<td>Percentage of working-age</td>
<td>Working-age individuals with no education</td>
<td>Resident working age population (15-64 years)</td>
<td>NIS (2001 Census)</td>
</tr>
<tr>
<td>individuals with no</td>
<td>individuals with no education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no-education level</td>
<td>Unemployment rate</td>
<td>Unemployed population</td>
<td>Resident working age population (15-64 years)</td>
<td>NIS (2001 Census)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-qualified workers</td>
<td>Percentage of non-qualified</td>
<td>Non-qualified workers employed</td>
<td>Population employed</td>
<td>NIS (2001 Census)</td>
</tr>
<tr>
<td></td>
<td>workers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prison population</td>
<td>Prison population /100,000</td>
<td>Prison population (average 2004-2006)</td>
<td>2005 resident population estimates</td>
<td>MIP/GPS</td>
</tr>
<tr>
<td></td>
<td>Immigrants</td>
<td>Immigrants</td>
<td>2005 resident population estimates</td>
<td>NIS (2001 Census)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WHO, 2008</td>
</tr>
</tbody>
</table>


Ecological information

SEMINAR

SPATIOTEMPORAL EPIDEMIOLOGY IN TB CONTROL

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4 CASE STUDIES

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— Identification of factors associated with longer diagnostic times

CONCLUSIONS
Epidemiology is the study of the distribution and determinants of health-related states or events (including disease), and the application of these results to the control of diseases and other health problems.

Assumptions

- Health phenomena do not occur at random in the population;
- The unequal distribution of health phenomena is the product of the action of factors that distribute unequally in the population;
- Knowledge of the determinants of health phenomena allows the application of intervention actions.

Spatiotemporal epidemiology

Elliot e Watenberg, 2004

*Spatial epidemiology* is the description and analysis of geographically indexed health data with respect to demographic, environmental, behavioral, socioeconomic, genetic, and infectious risk factors.

AND TIME!!!!!!
Epidemic of cholera (John Snow, 1854)

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CONCLUSIONS
IDENTIFICATION OF AREAS OF RISK (methodological challenge)

There is a causal source (agent) or a risk factor that generates an excessive increase of cases in a region. Outbreaks: infectious agents, environmental contamination, fragile socio-economic conditions, ...;

Objective: to evaluate the spatial pattern of the data, verifying whether the variation in space and time is random or not, and to identify critical areas.

Types of approaches: global (Moran I), local (Spatial Scan Statistics, Lisa), ...

**Case study I**

**Spatial clusters**

Let $N(Z)$ – One variable that represents a count of a phenomenon occurring in $Z$.

For each location and for each window:

- **Spatial Scan Statistics**
  - $N(Z) \sim F(p)$
  - $N(Z^c) \sim F(q)$

- **Space-Time Scan Statistics**
  - $H_0: p = q$ vs $H_1: p > q$

(Kulldorf, 1997)
**Case study I**

**Spatial clusters**

**SPATIAL SCAN STATISTICS**

**Advantages:**
- can be adjusted by population density;
- can be adjusted by other variables;
- search all location and considering all dimensions;
- statistically robust: it uses the likelihood ratio and Monte Carlo simulations;
- easy to implement and interpret.

**Disadvantages:**
- rigid window shapes;
- results very sensitive to the parameters used;
- VALIDATION: there is no real / true. Innovation: Proposal of a validation process through geostatistical simulation.

**CLUSTERS: Windows shapes**

- Circular windows
- Eliptical windows (ratio = 1.5, 2, 3, 4, 5)
  Nº of angles (4, 6, 12, 15)
- Eliptical windows (semivariogram)
Spatial dependency occurs when the value of a variable at a point in space is related to its value at nearby points;

Semivariogram – to evaluate spatial dependency.

\[
\gamma(h) = \frac{1}{2} E \left\{ \left[ Z(x) - Z(x + h) \right]^2 \right\}
\]

\[
\gamma^*(h) = \frac{1}{2N(h)} \sum_{i=1}^{N(h)} \left[ Z(x_i) - Z(x_i + h) \right]^2
\]

Case study I

CLUSTERS: Windows shapes

GEOESTATISTICAL SIMULATION

Geostatistical simulation as an independent process of validating clusters:

\[
anisotropy \; ratio = \frac{143000}{89000} = 1.6
\]
### Case study I

**CLUSTERS: Windows shapes**

**Geoestatistical Validation**

<table>
<thead>
<tr>
<th>Model</th>
<th>Cluster</th>
<th>Angle Ratio</th>
<th>Time-period</th>
<th>Obs/Exp</th>
<th>Notified cases</th>
<th>Prob.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>0/1</td>
<td>2000-2004</td>
<td>1.54</td>
<td>5286</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>I</td>
<td>2</td>
<td>0/1</td>
<td>2000-2004</td>
<td>1.71</td>
<td>2686</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>I</td>
<td>3/5/8</td>
<td>0/1</td>
<td>2002</td>
<td>1.14</td>
<td>11262</td>
<td>0.45</td>
</tr>
<tr>
<td>II</td>
<td>4</td>
<td>84/5</td>
<td>2000-2004</td>
<td>1.27</td>
<td>14645</td>
<td>0.08</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>0/1.6</td>
<td>2000-2004</td>
<td>1.75</td>
<td>2780</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>III</td>
<td>7</td>
<td>90/1.6</td>
<td>2000-2004</td>
<td>1.68</td>
<td>5024</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>III</td>
<td>9</td>
<td>0/1</td>
<td>2003-2004</td>
<td>6.10</td>
<td>668</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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**Circular windows**

**Eliptical windows**

(ratio = 1.5, 2, 3, 4, 5)  
Nº of angles (4, 6, 12, 15)  

**Eliptical windows**

(semivariogram)
Case study II

Overcrowding
HIV/AIDS
Non-standard accommodation
Working-age individuals with no education level
Non-qualified workers
Unemployment
Prison population
Immigrants

Pulmonary tuberculosis and risk factors in Portugal: a spatial analysis
L. Couceiro, P. Santana, C. Nunes

Spatial clustering
Correlation

Validation (Logistic reg)
local intervention
Risk map

Ecological approach

Pulmonary TB
Literature Review
HIV/AIDS
Overcrowding
Non-standard accommodation
Working-age individuals with no education level
Non-qualified workers
Unemployment
Prison population
Immigrants
CLUSTERS: DETERMINANTS

VALIDATION:
Similar Areas (with Risk ≥ 3)
Nagelkerke $R^2 = 0.678$,
Sensitivity=81.8%,
Specificity= 96.9%,
ROC = 0.95
### RESULTS

<table>
<thead>
<tr>
<th>City</th>
<th>TB</th>
<th>HIV/AIDS</th>
<th>Overcrowding</th>
<th>Non-standard accom.</th>
<th>Unemployment</th>
<th>Prison population</th>
<th>Immigrants</th>
<th>“Risk”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porto</td>
<td>X</td>
<td>O</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>O</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Matosinhos</td>
<td>X</td>
<td>O</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Lisboa</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Loures</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Odívelas</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Amadora</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Oeiras</td>
<td>X</td>
<td>X</td>
<td>0</td>
<td>X</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lisboa</td>
<td>X</td>
<td>X</td>
<td>O</td>
<td>X</td>
<td>0</td>
<td>O</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Case study II

**IDENTIFICATION OF FACTORS ASSOCIATED WITH DEFAULT TREATMENT**

- Previous study based on individual factors but measured at ecological level
- In this study: considered individual factors and, after that, the presence (or not) of a significant spatial component

---

### Case study III

**IDENTIFICATION OF FACTORS ASSOCIATED WITH DEFAULT TREATMENT**

- Previous study based on individual factors but measured at ecological level
- In this study: considered individual factors and, after that, the presence (or not) of a significant spatial component

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**SHORT REPORT**

Who are the patients that default tuberculosis treatment? – space matters!

C. Nunes, R. Duarte, A. M. Veiga, and B. Taylor
**ESTUDO DE CASO**

**III**

**RESULTADOS**

- Study developed in the critical areas previously identified (Lisbon and Porto)
- In this study: individual factors
- Spatial survival analysis (R, Spatsurv)

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### Table: Odds ratio

<table>
<thead>
<tr>
<th>Variables (ref. class)</th>
<th>LR</th>
<th>Crude adjusted$^*$</th>
<th>GAM$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>Male</td>
<td>1.550</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age group (15-34) (ref.)</td>
<td>0-14</td>
<td>0.749</td>
<td>0.785</td>
</tr>
<tr>
<td>Alcohol (No)</td>
<td>Yes</td>
<td>2.402</td>
<td>1.635</td>
</tr>
<tr>
<td>Drugs (No)</td>
<td>Yes</td>
<td>5.166</td>
<td>2.761</td>
</tr>
<tr>
<td>Homeless (No)</td>
<td>Yes</td>
<td>5.459</td>
<td>0.664</td>
</tr>
<tr>
<td>HIV (No)</td>
<td>Yes</td>
<td>5.990</td>
<td>3.420</td>
</tr>
<tr>
<td>Migrant (PT)</td>
<td>Migrant</td>
<td>2.134</td>
<td>2.672</td>
</tr>
<tr>
<td>Imprisonment (No)</td>
<td>Yes</td>
<td>2.264</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*n.s.*, Not selected (stepwise method).

* Final model, using a stepwise selection method.

**Not statistically significant**

$p=0.047$, AIC: 5308 to 5296

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**Case study IV**

**Modelling the time to detection of urban tuberculosis in two big cities in Portugal: a spatial survival analysis**

C. Nunes, B. M. Taylor

- Centro de Investigação em Saúde Pública, Escola Nacional de Saúde Pública, Universidade NOVA de Lisboa, Lisboa, Portugal
- Faculty of Health and Medicine, Lancaster University, Lancaster, UK

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Fig. 1. Associations between individual risk characteristics and default treatment from both multiple regression models: Logistic regression (LR) and Generalized Additive Model (GAM). (a) Crude and adjusted odds ratio; (b) odds of failure over our study region, having adjusted for the other risk factors (spatial component of the GAM).
### Table 1
Descriptive statistics for Lisbon and Oporto areas

<table>
<thead>
<tr>
<th>Variables</th>
<th>Lisbon</th>
<th>Oporto</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1028 (38.0)</td>
<td>676 (35.9)</td>
</tr>
<tr>
<td>Male</td>
<td>1678 (62.0)</td>
<td>1207 (64.1)</td>
</tr>
<tr>
<td>Alcoholic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>322 (11.9)</td>
<td>253 (13.44)</td>
</tr>
<tr>
<td>No</td>
<td>2384 (88.1)</td>
<td>1630 (86.56)</td>
</tr>
<tr>
<td>Intravenous drug user</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>197 (7.3)</td>
<td>107 (5.7)</td>
</tr>
<tr>
<td>No</td>
<td>12509 (92.7)</td>
<td>776 (94.3)</td>
</tr>
<tr>
<td>Prison inmate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32 (1.7)</td>
<td>25 (1.3)</td>
</tr>
<tr>
<td>No</td>
<td>12674 (98.8)</td>
<td>858 (98.7)</td>
</tr>
<tr>
<td>Homeless</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>45 (1.7)</td>
<td>25 (1.3)</td>
</tr>
<tr>
<td>No</td>
<td>2661 (98.3)</td>
<td>1858 (98.7)</td>
</tr>
<tr>
<td>HIV positivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>495 (18.3)</td>
<td>175 (9.3)</td>
</tr>
<tr>
<td>No</td>
<td>2211 (81.7)</td>
<td>1708 (90.7)</td>
</tr>
<tr>
<td>Migrant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1972 (72.9)</td>
<td>1814 (96.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>794 (27.1)</td>
<td>65 (3.7)</td>
</tr>
</tbody>
</table>

HIV = human immunodeficiency virus.

### Table 2
Estimated RRs and 95% CIs for Lisbon and Oporto

<table>
<thead>
<tr>
<th></th>
<th>Lisbon</th>
<th>Oporto</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male(^t)</td>
<td>1.19 (1.09–1.29)</td>
</tr>
<tr>
<td></td>
<td>Female(^t)</td>
<td>1.03 (0.91–1.18)</td>
</tr>
<tr>
<td>Alcoholic</td>
<td>No(^t)</td>
<td>0.96 (0.82–1.16)</td>
</tr>
<tr>
<td>Intravenous</td>
<td>Drug user(^t)</td>
<td>1.13 (0.77–1.62)</td>
</tr>
<tr>
<td></td>
<td>Homeless(^t)</td>
<td>1.02 (0.75–1.43)</td>
</tr>
<tr>
<td></td>
<td>HIV(^t)</td>
<td>0.85 (0.76–0.95)</td>
</tr>
<tr>
<td></td>
<td>Migrant(^t)</td>
<td>0.87 (0.80–0.96)</td>
</tr>
<tr>
<td></td>
<td>(\sigma)</td>
<td>1.26 (1.19–1.39)</td>
</tr>
<tr>
<td></td>
<td>(\psi)</td>
<td>3490 (1618–7143)</td>
</tr>
</tbody>
</table>

* RRs > 1 are associated with shorter diagnostic delays; RRs < 1 are associated with longer delays. It should be noted that the effect of age is not indicated in this table (see Figure 2).

\(^t\) Class for each estimation is presented (all binary variables).

RR = relative risk; CI = credibility interval; HIV = human immunodeficiency virus.
Estimated baseline hazard

Plot of P[exp(Y) < 0.85] (the probability that the covariate-adjusted relative risk is less than 0.85);

- In both cities, sex and HIV are related to delays (Men and HIV + diagnosed faster)?
- There are different patterns in the two cities (mainly in relation to age and being emigrant)
- after the incorporation of these variables, there is still a significant spatial variation - new studies
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CONCLUSIONS

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TUBERCULOSIS

— In terms of incidence, relatively stable clusters in the study period (Lisbon and Porto), with Porto decreasing faster;
— Situations of anomalous magnitudes that are important to analyse in detail;
— Local determinants - the importance of local characteristics in high incidence rates areas - support for local action strategies;
— BUT: Importance of notification rate: incidence rate versus incidence rate notified and homogeneous (or not?) in space and time.
Spatiotemporal epidemiology

- It is an important tool in the epidemiological interpretation of health phenomena and, consequently, in the quality of decisions based on this evidence;
- Although these studies have methodological specificities with some complexity, they are powerful as a first approach on new risk factors (to be investigated later in individual studies) or to be developed based on determinants already solidly grounded in the literature;
- It allows greater precision and safety in decisions and intervention, leading to greater effectiveness in Public Health interventions.

CONCLUSIONS

Main published works (TB and space/time)

THANKS!

CARLA NUNES