Effect of social and climatological factors on antimicrobial use and *Streptococcus pneumoniae* resistance in different provinces in Spain

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**Objectives:** To investigate the association between geographical differences in antibiotic consumption and resistance of *Streptococcus pneumoniae* to penicillin and erythromycin in 15 provinces of Spain, taking into account the potential influence of a series of social and climatological factors.

**Methods:** Possible correlations between prevalence of resistance to penicillin and erythromycin of *S. pneumoniae*, as determined in the national reference laboratory, and antibiotic consumption, and socio-economic and climatological variables were investigated. Partial correlations and multivariate linear regression were performed to assess the relative importance of variables predicting resistance and to investigate explicative factors for antibiotic consumption, respectively.

**Results:** A correlation was found between resistance and educational level, the proportion of young people in the population and climate, but was explained by their effects on differences in antibiotic use, which appeared to be the basic and only force behind resistance patterns in different geographical areas. Antibiotic use was found to be determined by the interplay of adult illiteracy, rainfall and GDP per capita.

**Conclusions:** Interventions aimed at improving educational level and economic growth might therefore be followed by a noticeable reduction in overall antibiotic consumption, which might in turn be followed by a reduction in penicillin and erythromycin resistance in clinical isolates of *S. pneumoniae*.

Keywords: antibiotic consumption, resistance, *S. pneumoniae*

**Introduction**

The therapeutic use of antimicrobial agents has been accompanied by the development and spread of antibiotic resistance in Gram-positive cocci.¹ Resistance is pandemic among clinical isolates of *Streptococcus pneumoniae*.² This species is the most frequent isolate from clinical samples of respiratory tract infection, including paediatric acute otitis media, acute exacerbations of chronic bronchitis in the elderly and community-acquired pneumonia mainly in the elderly but also in younger people.³ On the other hand, the use of antibiotics in respiratory infections accounts for 80% of their overall use in the community.³ Bearing in mind that up to 85–90% of antibiotic consumption has a community origin,³ then the use of antibiotics to treat community respiratory infections is a major driver of resistance in *S. pneumoniae*.

However, the selective pressure exerted by antibiotics differs greatly in accordance with their patterns of use, which varies with geographical region and age population structure.⁴ All these factors, plus the frequency of respiratory infections, mean that any intervention aimed at prevention or adequate treatment will lead to a decrease in health expenditure.⁵

A number of studies have assessed the association between antibiotic use and the prevalence of resistance estimated at different time-points or locations.⁶-¹² All of them share a clear microbiological orientation. However, to our knowledge, there has not been any attempt to go further and explore other variables that are often beyond the grasp of microbiologists or clinicians, and that are likely to be involved in the complex interactions leading to resistance.

In theory, education of prescribers and patients should reduce the prevalence of resistance in a given region, although we must...
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not expect education to have the same effect in different regions, since many intertwined factors, including the age population pyramid, climate, economic, cultural and health resource determinants, are likely to influence the interface between bacteria and antibiotic exposure.

The objective of this study was to address the relationship of socio-economic, cultural and climatological factors with the consumption of antibiotics and/or resistance in S. pneumoniae, using the multidisciplinary approach of human geography applied to microbiology.

Material and methods

Bacteria

Bacterial isolates from clinical samples collected from 1 January to 31 December 2002 were received and processed by the National Pneumococcal Reference Laboratory at the Instituto de Salud Carlos III and the resultant data were grouped by province of origin. Both invasive and non-invasive isolates were included. Overall, 2726 isolates from 15 different provinces (at least 30 strains had to be provided by each province) were studied.

Determination of resistance

Penicillin and erythromycin were used as markers of the activity of their corresponding antibiotic class, β-lactams and macrolides, respectively. Resistance was determined by the agar dilution method, and was defined as an MIC of ≥ 0.5 mg/L of erythromycin and 0.12 mg/L of penicillin.\(^{13}\)

Demographic, cultural and socio-economic variables

A set of variables was tested to investigate their relationship with differences in antimicrobial use and prevalence of resistance. All the following data were obtained from the databases of the National Statistics System (NSS) (http://www.ine.es).

Official provincial population demographics as of January 2002; data on the proportions of the population > 65 and < 14 years of age dated to 1998; educational level as of 1998 expressed as the proportion of people over 16 years in the population who were illiterate or had not finished primary school; gross domestic product (GDP) of each province in 2000 in euros per capita; the agricultural Gross Added Value (GAV), that is, the percentage of the GDP in 1998 from agriculture, livestock, fishing, hunting and forestry economic activity, was used as a surrogate marker for the degree of ‘ruralization’ in a given province.

Climatological factors

These were obtained from meteorological observations made from 1979 to 1995 by the Spanish Institute of Meteorology (http://www.inm.es), using its network of surveillance sentinel stations across the country. In provinces with more than one station, the average values of all the stations were used. The variables included were the average annual temperature in Celsius and the precipitation in millimetres. The climatic Dantín–Revenga index, which takes into account these two simple variables, was used to integrate the information for each province.\(^{13}\) This index is better suited for Mediterranean climates and is calculated as follows: \(I_{DR} = (T \times 100)/R\), where \(T\) is the mean annual temperature and \(R\) is a measure of the annual precipitation in millimetres. The higher the index, the more arid the area, and a threshold value of 2 is the limit between arid and humid climates (0–1: very humid; 1–2: humid; 2–3: semi-arid; 3–6: arid; >6: subdesert).

Health resources

The numbers of physicians, odontologists, pharmacists and veterinarians who were members of their respective professional association (http://www.ine.es) per 100,000 inhabitants were calculated by province (data as of 31 December 2000).

Antibiotic consumption

Data of antibiotic sales in units from November 2001 to October 2002 were purchased from Intercontinental Marketing Services Health S.A. (IMS Health S.A.). This 2 month non-overlapping window was deemed as appropriate to account for the 12 month collection period from January to December 2003 in view of the possible delay of the antibiotics in any potential change in resistance.

Statistics

Univariate correlations were performed and the two-sided Spearman correlation coefficients calculated. Multivariate analyses were performed by the step method with those variables that were initially associated by the former univariate correlations. The adjusted determination coefficient \(R^2\) explains the variability observed in the dependent variable that can be explained by the model. The SPSS Windows Release 11.5 statistical package was used to carry out the analyses.

Results

Erythromycin and penicillin resistance data from the National Pneumococcal Reference Laboratory are shown in Table 1. This table also provides data on antibiotic consumption, socio-economic, educational and climatological factors, and the number of physicians plus odontologists per 100,000 persons.

Mean erythromycin resistance was 39.1% (range: 26.2–53.1%; 95% CI: 34.4–43.8%) whereas mean penicillin resistance was 43.1% (range: 28.9–56.2%; 95% CI: 38.9–47.4%). The prevalence of resistance to these two drugs varied in parallel by province, and thus a Spearman correlation coefficient of 0.843 \((P < 0.001)\) was obtained.

Antibiotic consumption by province was calculated in units/1000 inhabitants/year. The large difference in quantitative consumption between provinces is evident, with Almería (south-east Andalusia) nearly double that of Vizcaya (Basque Country, northern Spain). In qualitative terms, there were also differences between provinces, with minimum penicillin:cephalosporin ratios in Tenerife (Canary Islands), Murcia and Almería (south-east Spain), and maxima in the centre (Madrid), north (Santander, Asturias) and north-east (Barcelona and Tarragona) of Spain.

Total consumption was correlated inversely with the penicillin:cephalosporin ratio (Spearman correlation coefficient of \(-0.757; P<0.001\)), but not with the β-lactam:macrolide ratio. Total consumption by province correlated positively with both
### Table 1. Prevalence of resistance, antibiotic consumption, socio-demographic, economic and climatological variables

<table>
<thead>
<tr>
<th>Provinces</th>
<th>No. of isolates</th>
<th>Ery-R(^a) (%)</th>
<th>Pen-R(^b) (%)</th>
<th>Total antibiotic(^c)</th>
<th>β-lactams(^c)</th>
<th>Macrolides(^c)</th>
<th>Ratio P:C(^d)</th>
<th>GDP(^e)</th>
<th>Human health resources(^f)</th>
<th>GAV(^g) agric (%)</th>
<th>Young pop. (%)</th>
<th>Old pop. (%)</th>
<th>Low educational level (%)</th>
<th>Climate(^j)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vizcaya</td>
<td>149</td>
<td>29.5</td>
<td>28.9</td>
<td>1056.18</td>
<td>596.85</td>
<td>219.60</td>
<td>4.96</td>
<td>17945</td>
<td>521</td>
<td>1.4</td>
<td>12.1</td>
<td>18.4</td>
<td>4.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Navarra</td>
<td>225</td>
<td>39.1</td>
<td>36.4</td>
<td>1208.34</td>
<td>678.25</td>
<td>269.00</td>
<td>4.04</td>
<td>18412</td>
<td>551</td>
<td>4.7</td>
<td>13.7</td>
<td>17.7</td>
<td>7.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Madrid</td>
<td>677</td>
<td>38.1</td>
<td>45.9</td>
<td>1241.01</td>
<td>677.69</td>
<td>268.23</td>
<td>6.00</td>
<td>18986</td>
<td>585</td>
<td>0.2</td>
<td>15.0</td>
<td>14.3</td>
<td>7.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Santander</td>
<td>31</td>
<td>29.0</td>
<td>32.3</td>
<td>1262.60</td>
<td>702.06</td>
<td>255.75</td>
<td>5.41</td>
<td>14491</td>
<td>504</td>
<td>4.8</td>
<td>13.5</td>
<td>18.9</td>
<td>8.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Asturias</td>
<td>210</td>
<td>26.2</td>
<td>38.1</td>
<td>1284.48</td>
<td>684.74</td>
<td>304.69</td>
<td>5.54</td>
<td>12876</td>
<td>546</td>
<td>2.5</td>
<td>11.7</td>
<td>21.7</td>
<td>11.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Pontevedra</td>
<td>54</td>
<td>35.2</td>
<td>40.7</td>
<td>1328.38</td>
<td>676.90</td>
<td>298.79</td>
<td>2.97</td>
<td>11643</td>
<td>406</td>
<td>7.6</td>
<td>14.7</td>
<td>17.2</td>
<td>16.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Barcelona</td>
<td>755</td>
<td>31.3</td>
<td>39.6</td>
<td>1420.58</td>
<td>804.06</td>
<td>282.53</td>
<td>5.01</td>
<td>17425</td>
<td>514</td>
<td>0.6</td>
<td>14.0</td>
<td>16.7</td>
<td>16.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Zaragoza</td>
<td>199</td>
<td>51.3</td>
<td>48.2</td>
<td>1441.92</td>
<td>729.00</td>
<td>355.72</td>
<td>3.57</td>
<td>15926</td>
<td>631</td>
<td>3.8</td>
<td>13.1</td>
<td>19.8</td>
<td>10.3</td>
<td>4.7</td>
</tr>
<tr>
<td>León</td>
<td>43</td>
<td>39.5</td>
<td>51.2</td>
<td>1472.99</td>
<td>792.57</td>
<td>338.68</td>
<td>3.53</td>
<td>13150</td>
<td>448</td>
<td>5.8</td>
<td>12.7</td>
<td>24.1</td>
<td>10.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Tarragona</td>
<td>128</td>
<td>48.4</td>
<td>48.4</td>
<td>1473.56</td>
<td>847.02</td>
<td>282.99</td>
<td>5.24</td>
<td>18326</td>
<td>386</td>
<td>3.4</td>
<td>14.8</td>
<td>17.2</td>
<td>18.2</td>
<td>3.2</td>
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<tr>
<td>Zamora</td>
<td>40</td>
<td>32.5</td>
<td>40.0</td>
<td>1552.13</td>
<td>860.61</td>
<td>322.60</td>
<td>2.63</td>
<td>11457</td>
<td>420</td>
<td>10.1</td>
<td>12.5</td>
<td>27.9</td>
<td>10.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Tenerife</td>
<td>45</td>
<td>42.2</td>
<td>42.2</td>
<td>1653.99</td>
<td>812.13</td>
<td>365.53</td>
<td>1.94</td>
<td>12714</td>
<td>383</td>
<td>3.3</td>
<td>17.2</td>
<td>12.0</td>
<td>20.6</td>
<td>7.2</td>
</tr>
<tr>
<td>Las Palmas</td>
<td>33</td>
<td>42.4</td>
<td>45.5</td>
<td>1712.03</td>
<td>830.36</td>
<td>351.66</td>
<td>2.94</td>
<td>13578</td>
<td>380</td>
<td>2.7</td>
<td>18.5</td>
<td>10.2</td>
<td>17.9</td>
<td>17.8</td>
</tr>
<tr>
<td>Murcia</td>
<td>105</td>
<td>48.6</td>
<td>56.2</td>
<td>1740.03</td>
<td>912.94</td>
<td>418.87</td>
<td>2.31</td>
<td>11668</td>
<td>391</td>
<td>8.2</td>
<td>18.7</td>
<td>14.0</td>
<td>23.8</td>
<td>5.5</td>
</tr>
<tr>
<td>Almería</td>
<td>32</td>
<td>53.1</td>
<td>53.1</td>
<td>1986.51</td>
<td>1140.64</td>
<td>357.71</td>
<td>2.28</td>
<td>12535</td>
<td>333</td>
<td>15.4</td>
<td>19.7</td>
<td>13.3</td>
<td>29.7</td>
<td>9.5</td>
</tr>
</tbody>
</table>

\(^a\)Prevalence of erythromycin resistance (MIC ≥ 0.5 mg/L).
\(^b\)Prevalence of penicillin resistance (MIC ≥ 0.12 mg/L).
\(^c\)Expressed in units per 1000 inhabitants per year.
\(^d\)Ratio of penicillin consumption to cephalosporin consumption.
\(^e\)Gross domestic product in euros per inhabitant.
\(^f\)Number of physicians plus odontologists per 100000 inhabitants.
\(^g\)Proportion of the GDP due to agricultural, livestock, fishing, hunting and forestry economical activities.
\(^h\)Proportion of the population ≥ 14 years.
\(^i\)Proportion of the population ≥ 16 years.
\(^j\)Thermopluviometric Dantín–Revenga index, the higher, the more arid (a value < 2 corresponds to a humid climate).
erythromycin \((R=0.696; P=0.004)\) and penicillin resistance \((R=0.736; P=0.002)\) rates. When looking more specifically at consumption, then \(\beta\)-lactam and macrolide consumption was associated with penicillin resistance, with correlation coefficients of 0.629 \((P=0.012)\) and 0.711 \((P=0.003)\), and with erythromycin resistance, with coefficients of 0.600 \((P=0.018)\) and 0.700 \((P=0.004)\). The association between penicillin resistance and consumption of penicillins was 0.543 \((P=0.004)\), whereas it was 0.600 \((P=0.018)\) for cephalosporins. The penicillin:cephalosporin ratio correlated inversely with resistance to erythromycin \((R=-0.571; P=0.026)\), but, although close, failed to show statistical significance with penicillin resistance \((R=-0.432; P=0.108)\).

In addition to antibiotic consumption, the proportion of young people \((\leq 14\) years) in the population, low educational level in adults and the Dantin–Revenga aridity index also showed statistical correlations \((P<0.05)\) with both erythromycin resistance \((R=0.675, 0.514\) and 0.796, respectively\) and penicillin resistance \((R=0.607, 0.536\) and 0.671, respectively\).

Total consumption correlated inversely with GDP per capita \((R=-0.607; P=0.016)\) and the number of health professionals per 100\,000 inhabitants \((R=-0.629; P=0.012)\). Interestingly, only the number of physicians \((R=-0.789; P<0.001)\) and odontologists per 100\,000 \((R=-0.729; P=0.002)\) correlated negatively with differences in antibiotic consumption, but not those of pharmacists and veterinarians. Consumption was, however, directly correlated with the proportion of young population \((R=0.611; P=0.016)\), of adult population with low educational level \((R=0.850; P<0.001)\), the Dantin–Revenga index \((R=0.814; P<0.001)\) and the agricultural GAV \((R=0.504; P=0.056)\).

Since the proportion of young people in the population, low educational level and the Dantin–Revenga index also showed a positive correlation with both erythromycin and penicillin resistance, partial correlations were performed between erythromycin and penicillin resistance and consumption but leaving fixed the Dantin–Revenga index, young population and illiteracy. After having adjusted for the potential combined effect of these three variables we found that correlation continued to be seen between both traits of resistance \((R=0.707; P=0.005)\), and, more importantly, that total antibiotic consumption was still linked to resistance to both erythromycin \((R=0.455; P=0.069)\) and penicillin \((R=0.631; P=0.014)\). In order to ascertain the importance that these three ‘non-consumption’ variables might have on the different resistance rates, we adjusted for antibiotic consumption and then found that none of these three variables (proportion of young population, low educational level and climatologic index) retained their previous associations with resistance.

Given that consumption was also independently correlated with the provincial GDP per capita, the number of physicians plus odontologists, the proportion of population under the age of 14, the proportion of adult population with low educational level and the climatological Dantin–Revenga index, a multiple linear regression analysis by the step method was performed (Tables 2 and 3). Only the proportion of low educational level population and the climatological Dantin–Revenga index fitted the model \((R=0.931; R^2=0.867; P<0.001)\), whereas the other three variables, namely GDP, the number of physicians/odontologists and the proportion of younger population, were excluded. Non-standardized \(B\) coefficients were 1025.6 \((P<0.001; 95\% \text{ CI: 898.5–1152.7})\) for the constant, 25.6 \((P<0.001; 95\% \text{ CI: 15.8–35.5})\) for the proportion of illiterate population and 16.6 for the agricultural GAV \((P=0.032; 95\% \text{ CI: 1.7–31.5})\). The standardized coefficients were 0.72 and 0.31 for these two variables, and therefore illiteracy was more than twice as important as climate when accounting for provincial differences in antibiotic use.

### Table 2. Model summary of multivariate analyses of consumption

<table>
<thead>
<tr>
<th>Model</th>
<th>(R)</th>
<th>(R^2)</th>
<th>Adjusted (R^2)</th>
<th>(F) value</th>
<th>Sig. ((P))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^a)</td>
<td>0.895</td>
<td>0.802</td>
<td>0.787</td>
<td>52.591</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2(^b)</td>
<td>0.931</td>
<td>0.867</td>
<td>0.845</td>
<td>39.171</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3(^c)</td>
<td>0.967</td>
<td>0.935</td>
<td>0.924</td>
<td>86.045</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4(^d)</td>
<td>0.985</td>
<td>0.970</td>
<td>0.962</td>
<td>118.180</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Dependent variable: Antibiotic consumption.
\(^a\)Independent variables: Constant and Education.
\(^b\)Independent variables: Constant, Education, Rain and Dantin–Revenga index.
\(^c\)Independent variables: Constant, Education and Rain.
\(^d\)Independent variables: Constant, Education, Rain and GDP.

### Table 3. Coefficients of multivariate analyses of consumption

<table>
<thead>
<tr>
<th>Model</th>
<th>Non-adjusted coefficients</th>
<th>Adjusted coefficients</th>
<th>95% CI for B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(B) standard error</td>
<td>beta</td>
<td>(t)</td>
</tr>
<tr>
<td>1 (Constant)</td>
<td>1009.520</td>
<td>68.020</td>
<td>0.895</td>
</tr>
<tr>
<td>Education</td>
<td>31.760</td>
<td>4.380</td>
<td>0.723</td>
</tr>
<tr>
<td>2 (Constant)</td>
<td>1025.591</td>
<td>58.335</td>
<td>0.308</td>
</tr>
<tr>
<td>Education</td>
<td>25.646</td>
<td>4.501</td>
<td>0.733</td>
</tr>
<tr>
<td>Rainfall</td>
<td>16.588</td>
<td>6.826</td>
<td>-0.399</td>
</tr>
<tr>
<td>3 (Constant)</td>
<td>1229.603</td>
<td>60.221</td>
<td>-0.206</td>
</tr>
<tr>
<td>Rainfall</td>
<td>1602.022</td>
<td>112.421</td>
<td>0.959</td>
</tr>
<tr>
<td>GDP</td>
<td>21.112</td>
<td>2.445</td>
<td>0.595</td>
</tr>
<tr>
<td>4 (Constant)</td>
<td>-0.227</td>
<td>0.030</td>
<td>-0.226</td>
</tr>
</tbody>
</table>
Drug use and resistance in *S. pneumoniae*

Since the Dantin–Revenga index is ultimately a mere function of the average temperature and precipitation, we repeated the analysis but breaking this index into its two components, thus including up to six potential explicative variables. On this occasion we found a model that fitted three variables, namely low educational level, precipitation and GDP, with an $R = 0.985$ ($R^2 = 0.970$; adjusted $R^2 = 0.962$; $F = 118.18$; $P < 0.001$). Details of this model are also provided in Table 2. The three variables, low educational level, rainfall and per capita GDP, each had a very high statistical power, and their corresponding standardized $B$ coefficients were 0.595, -0.440 and -0.226. It seemed therefore that average temperature was masking the effect of GDP on provincial differences in antibiotic use. Hence, low educational level and precipitation would have an almost equivalent, although inverse, weight on differences in antibiotic use, whereas the GDP was half as important as precipitation as a ‘protection factor’ for drug consumption.

**Discussion**

Differences in estimated rates of resistance varied as much as two-fold from one province to another (for erythromycin, Asturias had a resistance rate of 26.2%, while Almería had a resistance rate of 53.1%; for penicillin, Vizcaya had a resistance rate of 28.9% versus 56.2% in Murcia). Mean provincial erythromycin resistance was 39.1% (95% CI: 34.4–43.8%), which confirms the steady upward trend already reported. However, mean provincial penicillin resistance was 43.1% (95% CI: 38.9–47.4%), and this result is also in line with the steady or even downward trend observed.

The parallel variation between resistance to erythromycin and to penicillin between provinces ($R = 0.843$; $P < 0.001$) stresses the importance of the selection of co-resistance and its potential implications in terms of either cross-selection of one antibiotic resistance trait by a non-structurally related drug, or spread of specific multi-resistant clones, or both. The recent work by McCormick et al. highlights the extremely important role of differences in antibiotic use as the main force driving differences in resistance to penicillin and to erythromycin, and at the same time rules out the theory that the population structure of serotypes has a determinant weight on final resistance rates. Hence, antibiotic use would be the predominant factor for selecting resistance. Whether selection of resistance occurs in a previously de novo susceptible population, or facilitates dissemination of clones particularly well-suited to cope with the environmental multiplicity of antibiotics, could be only two different extremes of the same evolutionary process, with shades of grey in between.

In our study we documented an ample variation in quantitative consumption of antibiotics by province, with seemed to have a north–south gradient, as reported by other authors. Moreover, we also documented qualitative differences expressed as the penicillin:cephalosporin ratio. Some authors have reported that the higher this index, the lower the resistance. Interestingly, there was an inverse correlation between total antibiotic use and the penicillin:cephalosporin ratio ($R = -0.757$; $P < 0.001$) and therefore the lower the consumption, the higher the relative contribution of penicillin to it.

Total antibiotic consumption correlated directly with both erythromycin ($R = 0.696$; $P = 0.004$) and penicillin resistance ($R = 0.736$; $P = 0.002$). After the breaking down of consumption into different drug families, correlations remained. Therefore, statistically, consumption of either group is likely to lead to resistance to erythromycin and/or penicillin. The fact that the penicillin:cephalosporin ratio was inversely associated with erythromycin resistance and almost associated with penicillin resistance might have important implications regarding the qualitative interactions involved. The proven higher capability of selection of resistance *in vitro* for cephalosporins compared with penicillins might account for these epidemiological findings.

Several variables were found to be associated with provincial differences in antibiotic use, and of those explored the proportion of adult low educational level, the climate and the proportion of the population ≤14 years were directly correlated, whereas the per capita GDP and the number of health professionals per 100,000 correlated inversely. Agricultural GAV was very close to having a positive association with antibiotic use. In contrast to common statements in the literature blaming the elderly population for a presumed increase in antibiotic consumption, we did not find any relationship between these two variables ($P = 0.184$).

Partial correlations controlling for differences in consumption unmasked the confounding interaction among the remaining variables accounting for measured resistance rates, and unveiled that neither climate, young population nor low educational level remained associated with differences of resistance, although, as expected both erythromycin and penicillin resistance traits continued to be linked ($R = 0.630$; $P = 0.008$). Moreover, when the combined effects of climate, young population and low educational level were removed, then antibiotic consumption still appeared associated with resistance to erythromycin ($R = 0.455$; $P = 0.069$) and to penicillin ($R = 0.631$; $P = 0.014$), and association of both resistance traits did not disappear, either ($R = 0.707$; $P = 0.005$). Therefore, in our study, differences in antibiotic consumption emerge as the most important driving force for geographical differences in resistance.

Assuming this to be true, it would be vital to investigate the factors likely to influence these differences in antibiotic use. To this end the linear multivariate approach was used, and we found that illiteracy and climate were enough to explain up to 88% of the observed variability in antibiotic use, and the two variables were highly significant as parameters of the resultant multiple equation. Low educational level weight in this model ($B = 0.72$) was more than twice that of climate ($B = 0.31$).

A more detailed analysis considering the two climatological components of the Dantin–Revenga index separately along with the remaining variables, ended up fitting another model able to explain 97% of the observed variation in antibiotic consumption using low educational level, rainfall and per capita GDP as dependent variables. On this occasion, both precipitation and per capita GDP were negative, and therefore they could somehow be considered as ‘protection factors’ versus illiteracy as a ‘risk factor’ for increased consumption.

We acknowledge that our study would have benefited from having more provincial observations but unfortunately data on resistance were only available for 15 provinces which provided at least 30 isolates. However, we think that there are enough provinces to consider the results meaningful. Likewise, because the isolates were sent to the reference laboratory in a passive surveillance fashion, estimates of resistance rates might be less accurate than if data from an active surveillance had been obtained.
Our data on consumption of antibiotics were obtained from IMS and this source of information is nowadays deemed to be the most precise means to assess this variable. Other authors have used other sources such as the Spanish prescription database of the Ministry of Health, which accounts for all the prescriptions written under the different regional health systems, but unfortunately do not record the $\sim 15-20\%$ of private and over-the-counter antibiotic prescriptions, and therefore these data underestimate the reality. On the other hand, given that IMS provides information on sales, it is likely to slightly overestimate real consumption since not all the antibiotics sold are consumed. Besides, we have not used data of consumption transformed in defined daily doses, because for this kind of study it probably would not be necessary. The same presentations are available for the whole country throughout the $1$ year study period and therefore we would not have introduced any bias, as might be possible if these data were used to compare between different countries (which have different antibiotic presentations) or even over a given time period of several years during which new antibiotics can be authorized for sale, or presentations can vary.

The use of the thermopluviometric Dantin–Revenga index was considered the most appropriate given the unique characteristics of Spain, since other climatological indexes have not been tested in our country. Although temperature did not ultimately enter the last multivariate analysis, ideally it should be tested with more observation points than just $15$ provinces.

Ecological studies on exposure and outcome are valid if differences in exposure at the population level can be assumed to be an accurate reflection of differences in exposure to all of the individuals within populations. However, we have used aggregate data (on prescribing, resistance, GDP, educational level) and for instance, with respect to prescribing, large variations in the average consumption of drugs by populations are the product of much greater variation in exposure within the population. Therefore, ecological studies of exposure and outcome must be interpreted with caution. Ideally, the results of this study should be confirmed by information at the individual level, since it is likely that the strong association found with educational level, climate and GDP is confounded by other variables that have not been able to be explored because of the lack of individual data about exposure and outcome.

With the above in mind, the importance of these findings lies, first, in the confirmation that differences in consumption are able to explain on their own differences in resistance, and that any other variable initially associated with resistance can be explained as its ultimate effect on consumption. Secondly, we have been able to find a pattern to explain the wide differences in antibiotic use found between provinces based on a number of social and climatological factors that had not been explored previously. Educational level and per capita GDP are modifiable variables that hopefully can both be improved in an attempt to decrease antibiotic use and therefore optimize our struggle against pneumococcal resistance.

Although the influence of climate should not be ignored, its effects cannot be changed. However, modification of educational level and per capita GDP themselves will not only benefit all society (since it should always be desirable to increase the literacy and the GDP per head of a country), but it would also amount to a considerable economic saving, allowing for a better redistribution of wealth. Educational and economic inequalities are known to be responsible for many differences in human behaviour, and now they have also been shown to account for differences in antibiotic consumption. Addressing these inequalities therefore should be a top priority, and may, in turn, have an ecological impact on society as a whole.

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References

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