**Streptococcus pneumoniae** in community-acquired respiratory tract infections in Spain: the impact of serotype and geographical, seasonal and clinical factors on its susceptibility to the most commonly prescribed antibiotics

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Resistance of *Streptococcus pneumoniae* to antimicrobial agents shows geographical variation and also depends on serotype, patient age and sample origin. Factors affecting antibiotic resistance in *S. pneumoniae* were studied from results of a multicentre susceptibility study of 12 antimicrobial agents, carried out in 14 Spanish hospitals between May 1996 and April 1997. The most frequent serotypes were serotypes 6 (14.8%), 19 (11.8%), 23 (10.5%), 3 (9.9%), 9 (8.0%), 14 (8.0%), 15 (3.9%) and 11 (3.2%); 9.6% of isolates were not typeable. The remaining 25 serotypes constituted 20.2% of strains. Penicillin resistance was more prevalent in serotypes 14 (88%), 23 (66%), 9 (62%) and 6 (57%), whereas erythromycin resistance was more prevalent in serotypes 6 (68.5%), 15 (61.4%), 14 (49.5%), 19 (42.7%) and 23 (39.3%). Serotypes 6 and 19 were the serotypes most commonly isolated from both children and adults, although with different proportions (24.0% and 19.2% of isolates from children were serotype 6 and 19, respectively, with the corresponding figures for isolates from adults being 13.6% and 11.5%, respectively). The rates of resistance of pneumococcal strains to penicillin and cefuroxime were significantly higher in strains from children than in those from adults (resistance to penicillin, 50.4% in children and 37.0% in adults; resistance to cefuroxime, 62.4% in children and 45.6% in adults). There was significantly more resistance to erythromycin in middle ear isolates (48.9%) than in blood isolates (27%). The prevalence of resistance to β-lactams showed a seasonal pattern, with higher rates in summer and winter, proportional to the magnitude of resistance. Susceptibility to macrolides did not vary seasonally. Our results stress the relative importance that geographical, temporal (seasonality), patient (sample type, origin, age group) and bacterium-related (serotype) factors have on the variations in susceptibility observed among different pneumococcal clinical isolates.

**Introduction**

Not only is *Streptococcus pneumoniae* becoming increasingly non-susceptible to penicillin in many areas of the world, but the prevalence of highly resistant strains is also growing rapidly. This increase in penicillin non-susceptibility is usually associated with resistance to other antibiotics and poses a well-demonstrated risk of therapeutic failure for pneumococcal meningeval infections as well as a potential danger for respiratory tract infections.\textsuperscript{1} In Spain, the prevalence of non-susceptibility to penicillin increased from 6% in 1979 to 44% in 1989 with many strains showing high-level (15%) and multidrug resistance (7%);\textsuperscript{2} there was then a plateau during 1990–1996, when 49% of strains were non-susceptible.\textsuperscript{3} As clinical decisions often have to be made empirically, factors influencing resistance, such as geo-
graphical variations, serotype, sample origin and patient age, must be considered.4–12

We carried out a 1 year multicentre prospective study in order to assess the impact that geographical site, serotype, season of isolation and patient age might have on the antimicrobial susceptibility pattern of *S. pneumoniae* isolated from patients suffering from community-acquired respiratory infections in Spain.13

**Materials and methods**

**Microorganisms**

Between May 1996 and April 1997, all consecutive *S. pneumoniae* isolates obtained from patients suffering from upper or lower community-acquired respiratory tract infections (only one isolate from each patient) in 14 Spanish hospitals were collected.13

Each centre kept isolates at −70°C until used. Isolates were plated on enriched medium, incubated overnight at 35–37°C and sent to a central laboratory (Instituto Valenciano de Microbiología, Valencia, Spain) along with epidemiological data such as age group of the patient (paediatric or adult), date of the sample, hospital, origin and source of the sample. Samples processed included middle ear exudate, pleural fluid, blood, sputum and bronchoscopy specimens.

Isolates were serotyped at the Instituto Valenciano de Microbiología and in the Servicio de Microbiología del Centro Nacional de Microbiología del Instituto de Salud Carlos III de Majadahonda (Madrid, Spain) using Quellung (Staten Seruminstitut, Copenhagen, Denmark) and dot blot analyses, respectively.14,15

**Antibiotics used and antibiotic susceptibility studies**

MICs were determined by a semiautomatic microdilution test (Sensititre, West Sussex, UK) following the recommended NCCLS guidelines,16 with the antibiotics most frequently used as empirical treatment for respiratory tract infections in Spain, namely penicillin, amoxycillin, amoxycillin–clavulanic acid, cefixime, cefaclor, cefuroxime, cefotaxime, ceftriaxone, erythromycin, clarithromycin, azithromycin and ciprofloxacin. Wide antibiotic concentration ranges were chosen including a two-fold dilution higher and lower than the breakpoints of resistance and susceptibility to the antibiotics tested. The control strains used were *Streptococcus pneumoniae* ATCC 49619 and *Staphylococcus aureus* ATCC 29213.

The breakpoints used to calculate rates of resistance were ≥2 mg/L for penicillin, amoxycillin, amoxycillin–clavulanic acid, cefotaxime, ceftriaxone, cefuroxime and azithromycin and ≥1 mg/L for clarithromycin and erythromycin.

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Number of isolates (%)</th>
<th>Penicillin MIC&lt;sub&gt;50&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)</th>
<th>Penicillin resistance (%)</th>
<th>Penicillin MIC&lt;sub&gt;50&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>165 (148)</td>
<td>2/4</td>
<td>0.125/2</td>
<td>Micafungin MIC&lt;sub&gt;50&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt; (%)</td>
</tr>
<tr>
<td>Non-typeable</td>
<td>107 (96)</td>
<td>0.03/0.06</td>
<td>0.015/0.125</td>
<td>Micafungin MIC&lt;sub&gt;50&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt; (%)</td>
</tr>
<tr>
<td>Others</td>
<td>225 (202)</td>
<td>0.03/0.25</td>
<td>0.015/0.125</td>
<td>Micafungin MIC&lt;sub&gt;50&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt; (%)</td>
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**Table 1.** MIC<sub>50</sub>/MIC<sub>90</sub> and prevalence of resistance (%) for the most common serotypes isolated from patients suffering from community-acquired respiratory infections in Spain.

<table>
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<tr>
<th>Serotype</th>
<th>Number of isolates (%)</th>
<th>Amoxycillin–clavulanate MIC&lt;sub&gt;50&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)</th>
<th>Amoxycillin–clavulanate resistance (%)</th>
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</tbody>
</table>

<table>
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<tr>
<th>Serotype</th>
<th>Number of isolates (%)</th>
<th>Cefuroxime MIC&lt;sub&gt;50&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)</th>
<th>Cefuroxime resistance (%)</th>
<th>Cefuroxime MIC&lt;sub&gt;50&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt; (%)</th>
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**Table 1.** MIC<sub>50</sub>/MIC<sub>90</sub> and prevalence of resistance (%) for the most common serotypes isolated from patients suffering from community-acquired respiratory infections in Spain.
Antibiotic resistance in Spanish *S. pneumoniae*

**Statistical methods**

To compare the proportions obtained, a $\chi^2$ test was used with Yates–Bonferroni adjustments (multiple comparisons) when necessary. Calculations were carried out with the software EpiInfo 6.02 (CDC, Atlanta, GA, USA).

**Results**

During the year of the study, we obtained 1113 non-duplicate strains of *S. pneumoniae*, each originating from a different patient.13 Table I shows the overall distribution of serotypes obtained, their MIC$_{50}$, MIC$_{90}$ and prevalence of resistance to penicillin, amoxycillin–clavulanate, cefuroxime and erythromycin. The susceptibility to clarithromycin and azithromycin was almost equalled that to erythromycin, while susceptibility to amoxycillin was only slightly worse than that for amoxycillin–clavulanate. High-level resistance to parenteral third-generation cephalosporins was 10%.

The most common serotypes were serotypes 6 (14.8%), 19 (11.8%), 23 (10.5%), 3 (9.9%), 9 (8.0%), 14 (8.0%), 15 (3.9%) and 11 (3.2%). One hundred and seven isolates (9.6%) were non-typeable. The remaining 225 pneumococci (20.2%) were made up of 25 different serotypes, each representing <2% of the total.

Serotype 3 was, as expected, the most susceptible to antibiotics, in terms of both MIC$_{90}$s (≤0.25 mg/L) and rates of resistance (<5%). Serotype 14 showed the highest rates of resistance (>50%) (Table I). The prevalence of resistance to macrolides was ≥35% for all the main serotypes except serotypes 3, 9 and 11.

The non-typeable pneumococci showed penicillin and erythromycin resistance rates of 37.4% and 48.6%, respectively (Table I). In the 225 pneumococci of the less frequent serotypes, rates of resistance to penicillin and erythromycin were low (1.8% and 8.5%, respectively). The patterns of distribution of penicillin and erythromycin MICs differed among serotypes (Figures 1 and 2).

Tables II and III show the proportion of resistant isolates by age group and by sample origin, respectively. The distribution of penicillin and erythromycin MICs by sample are depicted in Figures 3 and 4.

In the 125 paediatric samples, serotypes 6 (24.0%) and 19 (19.2%) were most common and the proportion of non-typeable strains approached 8.0%. In samples from adults (admitted to internal medicine wards), these two serotypes were also the most common, although their proportions differed (13.6% and 11.5% for serotypes 6 and 19, respectively), and 11.9% of the strains were non-typeable.

In paediatric isolates resistance to penicillin and cefuroxime was statistically significantly more prevalent than that from adults in internal medicine wards (50% and 37%, respectively, for penicillin; 62.4% and 45.6%, respectively, for cefuroxime; $P < 0.05$). There was no statistically significant difference between paediatric and adult isolates in terms of resistance to amoxycillin, amoxycillin–clavulanic acid, third generation cephalosporins or macrolides (Table II).

Ninety (8%) of the samples came from the middle ear;

### Table II. Comparison of the antibiotic resistance of *S. pneumoniae* strains from children and adults (internal medicine wards)

<table>
<thead>
<tr>
<th>Source of sample</th>
<th>Total number (%) of strains</th>
<th>Number (%) of resistant isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>546</td>
<td>penicillin 202 (37.0) amoxycillin–clavulanate$^b$ 144 (26.4) cefuroxime 249 (45.6) erythromycin 194 (35.5)</td>
</tr>
<tr>
<td>Children</td>
<td>125</td>
<td>penicillin 63 (50.4) amoxycillin–clavulanate$^b$ 41 (32.8) cefuroxime 78 (62.4) erythromycin 54 (43.2)</td>
</tr>
</tbody>
</table>

*A breakpoint of ≥2 mg/L was used for amoxycillin–clavulanate and cefuroxime resistance.

$^b$Only the amoxycillin component is listed.

### Table III. Comparison of antibiotic resistance in *S. pneumoniae* by origin of sample

<table>
<thead>
<tr>
<th>Source of sample</th>
<th>Total number (%) of strains</th>
<th>Number (%) of resistant isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory tract</td>
<td>849 (76)</td>
<td>penicillin 309 (36.4) amoxycillin–clavulanate$^b$ 219 (25.8) cefuroxime 383 (45.1) erythromycin 284 (33.5)</td>
</tr>
<tr>
<td>Blood culture</td>
<td>174 (16)</td>
<td>penicillin 55 (31.6) amoxycillin–clavulanate$^b$ 38 (21.8) cefuroxime 73 (42.0) erythromycin 47 (27.0)</td>
</tr>
<tr>
<td>Middle ear</td>
<td>90 (8)</td>
<td>penicillin 42 (46.7) amoxycillin–clavulanate$^b$ 27 (30.0) cefuroxime 55 (61.1) erythromycin 44 (48.9)</td>
</tr>
</tbody>
</table>

*A breakpoint of ≥2 mg/L was used for amoxycillin–clavulanate and cefuroxime resistance.

$^b$Only the amoxycillin component is listed.
of these, 69% were from children. The most frequent serotypes found in middle ear samples were again serotypes 6 (24.4%) and 19 (25.6%). In respiratory samples, ‘other’ serotypes, serotype 6 and non-typeable isolates were most frequently found. Serotypes belonging to the category ‘other’ and serotype 3 were the most common from blood cultures, accounting for up to 31% and 12.6% of the isolates, respectively. Serotype 11 (which is very similar to

Figure 1. Distribution of penicillin MICs for *S. pneumoniae* strains by serotype.

Figure 2. Distribution of erythromycin MICs for *S. pneumoniae* strains by serotype.
Antibiotic resistance in Spanish *S. pneumoniae* serotype 3 in its penicillin and erythromycin susceptibilities represented 3.5% of blood pneumococci, so almost 50% of the blood isolates were in the susceptible category. Pneumococci isolated from middle ear fluids (*n*/*H11005* 90) showed the highest prevalence of resistance, and those from blood cultures (*n*/*H11005* 175) the lowest, with a statistical significance only for macrolides (*P* < 0.05) and not for β-lactams.

Geographical variations in the susceptibility to penicillin or erythromycin are shown in Table IV. Strains from the Hospital Insular de Las Palmas (Canary Islands) and those from the Hospital Xeral de Santiago de Compostela (Galicia) were more susceptible to antibiotics (≤31% of strains showing high resistance to any antibiotic). Strains from the Hospital Santa Creu i Sant Pau de Barcelona and from the Hospital Basurto de Bilbao exhibited the highest rates of resistance.

Seasonal variation in numbers of isolates is shown in Figure 5. The number of isolates and proportion of resistant isolates found in each season was as follows: spring 1996, 113 (10.2%); summer 1996, 150 (13.5%); autumn 1996, 286 (25.7%); winter 1996, 357 (32.1%); and spring 1997, 207 (18.6%). Resistance to all the β-lactams showed a statistically significant (*P* < 0.05) seasonal variation, peaking in summer and winter. The magnitude of the seasonal effect was proportional to the rate of resistance to each β-lactam drug, being much more evident for cefuroxime (to which there is a high rate of resistance) than for aminopenicillins or parenteral cephalosporins. For macrolides there was no seasonal effect, resistance rates remaining stable during the study period (30–35%).

### Table IV. *S. pneumoniae* isolates and rates of resistancea by hospital

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Total number of strains (%</th>
<th>Number (%) of highly resistant isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>penicillin</td>
</tr>
<tr>
<td>Hospital Insular, Las Palmas</td>
<td>65 (5.8)</td>
<td>15 (23.1)</td>
</tr>
<tr>
<td>Hospital Virgen de la Macarena, Sevilla</td>
<td>46 (4.2)</td>
<td>15 (32.6)</td>
</tr>
<tr>
<td>Hospital Reina Sofia, Córdoba</td>
<td>35 (3.1)</td>
<td>14 (40.0)</td>
</tr>
<tr>
<td>Hospital Virgen de las Nieves, Granada</td>
<td>73 (6.5)</td>
<td>33 (45.2)</td>
</tr>
<tr>
<td>Hospital Infanta Cristina, Badajoz</td>
<td>12 (1.1)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Hospital Gregorio Marañón, Madrid</td>
<td>197 (17.7)</td>
<td>69 (35.0)</td>
</tr>
<tr>
<td>Hospital La Paz, Madrid</td>
<td>73 (6.55)</td>
<td>32 (43.8)</td>
</tr>
<tr>
<td>Hospital La Fe, Valencia</td>
<td>81 (7.3)</td>
<td>30 (37.0)</td>
</tr>
<tr>
<td>Hospital Sta. Creu i S. Pau, Barcelona</td>
<td>44 (3.9)</td>
<td>21 (47.7)</td>
</tr>
<tr>
<td>Hospital Clinic Universitari, Barcelona</td>
<td>217 (19.5)</td>
<td>77 (35.5)</td>
</tr>
<tr>
<td>Hospital Basurto, Bilbao</td>
<td>27 (2.4)</td>
<td>17 (63.0)</td>
</tr>
<tr>
<td>Hospital Clínico, Zaragoza</td>
<td>93 (8.3)</td>
<td>38 (40.9)</td>
</tr>
<tr>
<td>Hospital Clínico, Salamanca</td>
<td>75 (6.7)</td>
<td>26 (34.7)</td>
</tr>
<tr>
<td>Hospital Xeral da Galiza, Santiago</td>
<td>75 (6.7)</td>
<td>15 (20.0)</td>
</tr>
<tr>
<td>Total</td>
<td>1113 (100)</td>
<td>406 (36.5)</td>
</tr>
</tbody>
</table>

*a* A breakpoint of ≥2 mg/L was used for amoxycillin–clavulanate and cefuroxime resistance.

*b* Only the amoxycillin component is listed.
amoxycillin–clavulanate; (strains to cephalosporins.18 Our isolates were obtained before cur-
edged in the newly published NCCLS breakpoints for the different geographical provenance of the samples in the
intermediately resistant to penicillin.17 This is acknowl-
ance is the same whether the strains are susceptible or
meningeal isolates influences choice of appropriate break-
strains isolated from normally sterile sites, such as blood,
cerebrospinal fluid and so on (hereafter refer to as ‘inva-
Discussion
Seasonal variation in the susceptibility of S. pneu-
Figure 5. Seasonal variation in the susceptibility of S. pneu-
serotypes with clavulanate) and 34.86% for oral cefuroxime are
serotypes 6, 19 and 23 were the most common in both
groups, although with different prevalence rates (13.6%,
11.5% and 9.9%, respectively, for adults, and 24.0%, 19.2%
and 13.6%, respectively, for children). No single serotype
showed a clear predominance in adults, but three serotypes
made up ≥55% of the total in children, in agreement with a
previous report.3
The association between the resistance to penicillin and
serotype is well known. In this study, serotype 3 was particu-
larly susceptible, as expected, to all the antibiotics tested,
with resistance rates of <5%. The rates of resistance among
the other more prevalent serotypes were higher, although
without a homogeneous pattern: serotypes 6 and
9 both had penicillin resistance rates of >50%, but differed
in their resistance to erythromycin (68% and 12%, respect-
ively). In serotype 19, the rate of resistance to penicillin and
erythromycin was 33% and 42%, respectively. Serotypes
14 and 23 both showed a high prevalence of resistance to
oral β-lactams and macrolides (above 40%). In the light of
these results, it seems that the widely held opinion that
resistance to penicillin is associated with resistance to other
antibiotics may require modification, as our data suggest
that this may only be true for some serotypes (serotypes 9
and 15).
The differences between participating hospitals in the
prevalence of resistance might result from differences in
the populations studied, as the proportion of paediatric
samples differed between centres, and to environmental
factors, such as local differences in consumption of anti-
biotics. Nevertheless, the huge sample size together with
the large number of hospitals involved and the short period
of time (1 year) during which the study was conducted
might be expected to have outweighed bias. The wide
range in the number of isolates submitted from each
hospital should also be noted; obviously, the fewer isolates
per centre the higher the potential bias in reporting resist-
ance.

Although statistically significant seasonality has already
been reported for penicillin resistance,13 this has not been
reported for oral or parenteral β-lactams. One of the most
interesting findings in this study is the existence of a sea-
sonal pattern of resistance to oral β-lactams, and, to a much
lesser extent, parenteral third generation cephalosporins.
This phenomenon may be a result of the seasonal variabil-
ity of isolation of serotypes over the 12 months of study.
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This phenomenon may be a result of the seasonal variabil-
ity of isolation of serotypes over the 12 months of study.
Our population MIC data for the different serotypes show
the existence of different pneumococcal subpopula-
tions on the basis of their susceptibility to penicillin and
erythromycin. This adds to the multifactorial complexity of
penicillin or erythromycin resistance in S. pneumoniae.

Whether penicillin susceptibility is of clinical import-
ance in the treatment of respiratory infections is contro-
versial, but it seems that at least for pneumococcal strains
with a penicillin MIC ≤ 2 mg/L, penicillin can be safely
used in treating pneumonia. Nevertheless, clinical resist-
ance is not the same as loss of susceptibility. It is the slow
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and progressive shift in MIC for a given bacterial population (loss of susceptibility) that allows clinically susceptible strains to accumulate progressive mutations that would ultimately render them clinically resistant.

If practical and rational antibiotic policies are to be developed with the aim of helping doctors to prescribe more suitable empirical antibiotics, then national multicentre surveillance studies that take into account and integrate regional data seem more useful than multinational studies that can only evaluate nationally collected raw data, which may differ between countries. Evidently, regional studies would be even more accurate than national surveillance, but results would also be more difficult to generalize (accuracy does not mean usefulness). Given the disparity between the extreme accuracy of local studies and the extreme generalization of results in multinational studies, intermediate surveillance studies such as national multicentre projects seem mandatory if relevant susceptibility results are sought for the empirical antibiotic treatment of any infectious condition.

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