Review

The use and resistance to antibiotics in the community

Milan Čizman *

University Medical Centre, Department of Infectious Diseases, Japljeva 2, 1525 Ljubljana, Slovenia

Abstract

The frequency of resistance to antibiotics among common community-acquired pathogens, and the number of drugs to which they are resistant have been increasing worldwide. The relationship between antibiotic usage and resistance is strongly supported by data from several studies. Countries with the highest per capita antibiotic consumption have the highest resistance. The emergence of penicillin-resistant Streptococcus pneumoniae is related to high consumption of antibiotics in general, as well as to increased use of aminopenicillins and/or probably to wider use of oral cephalosporins. Increased consumption of macrolides, especially the long-acting ones, correlates significantly with the level of macrolide resistance of group A streptococci and S. pneumoniae while increased use of oral cephalosporins might be associated with the increase of β-lactamase-producing strains of Moraxella catarrhalis. Trimethoprim/sulphamethoxazole resistance is strongly associated with resistance to penicillin. A rise in consumption of fluoroquinolones is consonant with a higher rate of resistance to quinolones of S. pneumoniae, Escherichia coli and other Gram-negative bacteria. Paediatric bacterial isolates are more often resistant to various antimicrobial agents than isolates from adult patients; this higher resistance rate may be due to more frequent antimicrobial treatments in children, and extensive child to child transmission. Reliable data on antimicrobial consumption and resistance should form a basis for national policies devised to reduce the resistance of microorganisms to antibiotics.

© 2003 Elsevier Science B.V. and the International Society of Chemotherapy. All rights reserved.

Keywords: Streptococcus pneumoniae; Moraxella catarrhalis; Escherichia coli

1. Introduction

Antibiotics are given to humans and animals for therapy and prophylaxis of infectious diseases. They are also used in animals for growth promotion and, to a lesser extent, in agriculture for plant protection and in industry [1]. In humans, 80–90% of antimicrobial drugs are used in outpatients and the rest in the hospitals [1–4]. It is estimated that 20–50% of all antibiotic use is questionable [1]. The consequences of antibiotic overuse and misuse include increased risk of adverse side effects, higher cost and higher rate of antimicrobial resistance of community pathogens. What distinguishes antimicrobial agents from other drugs, is that each antimicrobial agent used may have potential significant effect on, the world microbial ecology. Antibiotics affect both pathogens and the normal flora. In theory any antibiotic can select resistant strains as long as the local concentration of the drug exceeds the minimal inhibitory concentration (MIC) for the susceptible bacterial population but is below the MIC for the resistant clone. To what extent disturbances occur depend on the spectrum of the agent, dose, route of administration, pharmacokinetic and pharmacodynamic properties, and in vivo inactivation of the agent [5]. Incomplete absorption of orally administered drugs may influence the intestinal microflora, and secretion of an antimicrobial agent by the intestinal or vaginal mucosa, bile, salivary glands or eccrine or apocrine sweat glands may interfere with the normal flora at different habitats. As a consequence, antibiotic-resistant microorganisms may increase in numbers, and they also might serve as reservoirs for resistance genes. One antibiotic may select for resistance to one or more structurally unrelated antibiotics, because resistance may be genetically linked (via co-selection of multi-resistance plasmids and other resistance traits) [6]. Some antimicrobial agents are more selective for resistance than others [7]. Besides selective antibiotic pressure, transferable resistance (clonal spread or horizontal resistance gene transfer) is the
2. Total antimicrobial usage

Antibiotic usage and resistance rates vary from one country to another [2–4]. Cars et al. found that in 1997 the non-hospital usage of antibiotics between European Union countries varied more than fourfold (Table 2) [4]. Countries with the highest per capita antibiotic consumption have the highest resistance rates (Table 2). Table 2 indicates that in countries with the total outpatient antibiotic sales beyond 25 defined daily doses (DDD)/1000 inhabitants/day, the average resistance level of *Streptococcus pneumoniae* to penicillin was 35.05–42.1% (range 8–66%). In countries with consumption below 15 DDD/1000 inhabitants/day the average resistance of *S. pneumoniae* was 5.5%, (range 2–12%). Countries with high total outpatient antibiotic sales have a higher prevalence of *Haemophilus influenzae* β-lactamase positive strains, than those with low total usage. It is not only the amount of antibiotics used that selects for resistance, but also the number of individuals receiving the drug, and the population density [27]. Giving 1000 doses of an antibiotic to one individual will have considerably less ecological effect on resistance emergence than giving those same 1000 doses to 1000 individuals. Levy called this concept selection density [28]. A recent study suggests that a combination of antibiotic use and population density correlates more strongly with the prevalence of antibiotic resistance in a population than antibiotic use alone [21]. The data from Norway comparing the consumption of antibiotics and population density in Norway (13 inhabitants/km²) and Denmark (121 inhabitants/km²), did not confirm this hypothesis [21].

To study the relationship between antibiotic usage and bacterial resistance rate, several factors should be considered such as the types of specimens submitted to the laboratory, the area studied, representative isolates of those experiencing selection pressure, nosocomial strains, spread of resistant clones and duration of the study [29,30].

3. Class and group of antibiotics used

A study by Baquero et al. was one of the first to report a correlation between antibiotic use and bacterial resistance in the community [31]. The emergence of penicillin-resistant *S. pneumoniae* (PRSP) was linked to increased use of aminopenicillins in different geographical areas in Spain [31]. The lowest rates of PRSP occurred in countries with very low rates of β-lactam prescriptions [32] (Table 3).

In contrast, consumption is highest in Spain and France where penicillin resistance is also very high (Table 3). A recent Europe-wide, country specific study by Bronzaer et al. showed that in 11 European countries resistance of invasive isolates of *S. pneumoniae* to penicillin correlated with the use of β-lactam antibiotics as well [33]. Table 3 shows that in countries, with the consumption of broad-spectrum penicillins and cephalosporins is higher than 10 DDD/1000 inhabitants/day the average resistance level of *S. pneumoniae* to penicillin is between 31.3 and 34.2% (range 8–66%). In countries where the consumption of these two classes of antibiotics is between 5 and 10 DDD/1000 inhabitants/day and below 5 DDD/1000 inhabitants/day the prevalence of PRSP is approximately 20% (range 10.8–40%) and 5.2% (range 3–12%), respectively. In countries with the consumption of narrow-spectrum penicillins of ≥ 1.0 DDD/1000 inhabitants/day, the prevalence of resistance of pneumococci to penicillin is low [4]. Garcia-Rey et al. showed in their multivariate analysis that integrated consumption of both macrolides and β-lactams was strongly correlated with erythromycin ($R^2 = 0.7222, P = 0.002$) and penicillin ($R^2 = 0.706, P = 0.002$) resistance [34]. They found that macrolides were more important drivers for local differences in both erythromycin and penicillin resistance than β-lactams.

---

**Table 1**

<table>
<thead>
<tr>
<th>Key factors in the development of antimicrobial resistance [5]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total amount of antimicrobial usage</td>
</tr>
<tr>
<td>Drug used (class, group)</td>
</tr>
<tr>
<td>Dosage regimens (duration, dosage, route of administration, pharmacodynamics)</td>
</tr>
<tr>
<td>Frequency of cross-infection with resistant microorganisms (poor hygiene, nursing homes, day-care centres)</td>
</tr>
<tr>
<td>Public behaviour and social conditions (public expectation of receiving antibiotics for any infection, travel, overcrowding in long-term and day-care facilities, compliance)</td>
</tr>
</tbody>
</table>

---

major determinant of resistance development [8]. There are several ways to study the relationship between antibiotic usage and the incidence of bacterial resistance. Pharmacoepidemiology, mathematical modelling, pharmacokinetic and microbiological analysis of several body sites that normally harbour dense microbial flora are the methods used to study the evaluation and prediction of the ecological impact of antibiotics on the human microflora, as well as the use and the effects of drugs in human populations [9].

It is irrefutable that antibiotic use promotes resistance development. However, quantifying the specific contribution of antibiotic use to resistance poses some problems. Evidence is accumulating that social, economic and genetic factors also have impact on the establishment, maintenance and spread of resistance traits.

The likelihood of selecting resistance in the community depends on many factors. The key factors are shown in Table 1.
### Table 2
Total outpatient antibiotic sales (1997) and resistance of *Haemophilus influenzae* and *Streptococcus pneumoniae* (1997–1999) [4,10]

<table>
<thead>
<tr>
<th>Country</th>
<th>Total outpatient antibiotic sales in 1997 DDD/1000 inhabitants/day</th>
<th><em>H. influenzae</em>, β-lactamase positive (%)</th>
<th><em>S. pneumoniae</em>&lt;sup&gt;a&lt;/sup&gt; Penicillin intermediate and resistant (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>36.51</td>
<td>22.2–27.6</td>
<td>53.3–66.5</td>
<td>[11,12]</td>
</tr>
<tr>
<td>Spain</td>
<td>32.44</td>
<td>32.0</td>
<td>50.1–65.6</td>
<td>[12,13]</td>
</tr>
<tr>
<td>Slovak Republic</td>
<td>28.75&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12&lt;sup&gt;c&lt;/sup&gt;</td>
<td>51.4</td>
<td>[11]</td>
</tr>
<tr>
<td>Belgium</td>
<td>26.72</td>
<td>15.6</td>
<td>8.0–14.2</td>
<td>[11,14]</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>25.58</td>
<td>NA</td>
<td>30.4</td>
<td>[15]</td>
</tr>
<tr>
<td>Italy</td>
<td>23.99</td>
<td>2.0–7.7</td>
<td>9–16.8</td>
<td>[11,12]</td>
</tr>
<tr>
<td>Greece</td>
<td>22.69</td>
<td>16.0</td>
<td>31.6</td>
<td>[11]</td>
</tr>
<tr>
<td>Hungary</td>
<td>21.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15</td>
<td>40</td>
<td>[16]</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>19.96&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14.3</td>
<td>7.1</td>
<td>[11]</td>
</tr>
<tr>
<td>Finland</td>
<td>19.34</td>
<td>24</td>
<td>4.8</td>
<td>[17,18]</td>
</tr>
<tr>
<td>Ireland</td>
<td>18.34</td>
<td>17.1</td>
<td>32.8</td>
<td>[11]</td>
</tr>
<tr>
<td>UK</td>
<td>18.04</td>
<td>17.7</td>
<td>10.8–19.5</td>
<td>[11,12]</td>
</tr>
<tr>
<td>Slovenia</td>
<td>17.56</td>
<td>16</td>
<td>15</td>
<td>[19]</td>
</tr>
<tr>
<td>Norway</td>
<td>14.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3</td>
<td>[20,21]</td>
</tr>
<tr>
<td>Austria</td>
<td>13.80</td>
<td>3.9</td>
<td>12.4</td>
<td>[11]</td>
</tr>
<tr>
<td>Germany</td>
<td>13.58</td>
<td>5.7</td>
<td>7.2</td>
<td>[11,12]</td>
</tr>
<tr>
<td>Sweden</td>
<td>13.51</td>
<td>9.5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3</td>
<td>[22]</td>
</tr>
<tr>
<td>Denmark</td>
<td>11.35</td>
<td>10.4</td>
<td>2.4</td>
<td>[23,24]</td>
</tr>
<tr>
<td>Russia</td>
<td>11.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.3</td>
<td>7.5</td>
<td>[25,26]</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>8.96</td>
<td>6.4</td>
<td>3.2</td>
<td>[11]</td>
</tr>
</tbody>
</table>

<sup>a</sup> Intermediate and high resistance.
<sup>b</sup> 1998 Total use including hospital use.
<sup>c</sup> Liškava A, Krcmery V (personal communication).
<sup>d</sup> 1995, NA-not available.

### Table 3
Consumption of broad-spectrum penicillins and cephalosporins (1997 and 1998), and resistance of *S. pneumoniae* (1997–1999) [4,10]

<table>
<thead>
<tr>
<th>Country</th>
<th>Broad-spectrum penicillins DDD/1000 inhabitants/day</th>
<th>Cephalosporins DDD/1000 inhabitants/day</th>
<th><em>S. pneumoniae</em>&lt;sup&gt;a&lt;/sup&gt; Penicillin intermediate and resistant (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>18.97</td>
<td>3.75</td>
<td>53.3–66.5</td>
<td>[11,12]</td>
</tr>
<tr>
<td>Spain</td>
<td>18.01</td>
<td>2.48</td>
<td>50.1–65.6</td>
<td>[12,13]</td>
</tr>
<tr>
<td>Portugal</td>
<td>12.08</td>
<td>3.28</td>
<td>17.1–24.7</td>
<td>[11]</td>
</tr>
<tr>
<td>Italy</td>
<td>11.20</td>
<td>3.21</td>
<td>9–16.8</td>
<td>[11,12]</td>
</tr>
<tr>
<td>Slovak Republic</td>
<td>11.09&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>51.4</td>
<td>[11]</td>
</tr>
<tr>
<td>Belgium</td>
<td>10.96</td>
<td>2.85</td>
<td>8–14.2</td>
<td>[11,14]</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>10.58</td>
<td>2.86</td>
<td>30.4</td>
<td>[15]</td>
</tr>
<tr>
<td>Ireland</td>
<td>8.03</td>
<td>1.23</td>
<td>32.8</td>
<td>[11]</td>
</tr>
<tr>
<td>Greece</td>
<td>7.74</td>
<td>4.68</td>
<td>31.6</td>
<td>[11]</td>
</tr>
<tr>
<td>Slovenia</td>
<td>7.15</td>
<td>0.94</td>
<td>15</td>
<td>[18]</td>
</tr>
<tr>
<td>UK</td>
<td>6.93</td>
<td>0.98</td>
<td>10.8–19.5</td>
<td>[11,12]</td>
</tr>
<tr>
<td>Hungary</td>
<td>6.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>40</td>
<td>[16]</td>
</tr>
<tr>
<td>Austria</td>
<td>3.23</td>
<td>1.30</td>
<td>12.4</td>
<td>[11]</td>
</tr>
<tr>
<td>Finland</td>
<td>3.78</td>
<td>2.11</td>
<td>4.8</td>
<td>[17]</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>2.90</td>
<td>0.12</td>
<td>3.2</td>
<td>[11]</td>
</tr>
<tr>
<td>Germany</td>
<td>2.67</td>
<td>0.89</td>
<td>7.2</td>
<td>[11]</td>
</tr>
<tr>
<td>Denmark</td>
<td>2.39</td>
<td>0.02</td>
<td>2.4</td>
<td>[24]</td>
</tr>
<tr>
<td>Norway</td>
<td>≤ 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[20,21]</td>
</tr>
<tr>
<td>Sweden</td>
<td>1.36</td>
<td>0.59</td>
<td>3</td>
<td>[22]</td>
</tr>
<tr>
<td>Russia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.79&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.06&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>[26]</td>
</tr>
</tbody>
</table>

<sup>a</sup> Total use including hospital use in 1998.
<sup>b</sup> Resistance in 1995.
Cephalosporins were slightly more important penicillin resistance drivers thanaminopenicillins [34].

In a recent study conducted in Finland, no correlation was found between penicillin resistance of S. pneumoniae and cephalosporin use, although the consumption of these drugs in Finland is moderate compared with other European Union countries, and the resistance of S. pneumoniae to penicillin is low [18].

The frequency of β-lactamase production was analysed in a study of strains of Moraxella catarrhalis and H. influenzae isolated from middle-ear fluid of children <6 years of age in Tampere, Finland between 1978 and 1993 [35]. A bimodal increase was found in the proportion of strains of Moraxella catarrhalis producing β-lactamase that increased from 0% in 1978 to 60% in 1978 to 1983 and from 60% in 1988 to 80% in 1990. Concurrently with the second increase, the consumption of cephalosporins in the community increased substantially, from 0.21 to 2.70 DDD/1000 inhabitants/day (which might be linked). The frequency of β-lactamase-producing strains of H. influenzae did not increase during that period.

Resistance to pneumococcal antibiotics is increasing worldwide. The nasopharyngeal bacterial population is an important reservoir of infection, carriage and spread of pathogenic bacteria including antibiotic-resistant clones. Several randomised prospective studies have shown an association between the use of β-lactam antibiotics and the carriage of penicillin-resistant organisms [36–38]. The likelihood of carrying PRSP doubled in children who had used β-lactam antibiotics in the two months before testing [36]. Lipsitch reviewed 14 and 17 studies of the association between antibiotic use and carriage with PRSP, respectively [39]. He concluded that any recent antibiotic treatment makes it more likely that a patient who is carrying a pneumococcus has a resistant rather than a susceptible microorganism. This suggests that antibiotics, in particular β-lactam or cephalosporins exert an important effect at the community level by reducing the carriage of susceptible organism, and thereby indirectly promoting the transmission of resistant ones. In the setting of an outbreak of a resistant pneumococcus, antibiotic treatment puts a patient at a higher risk for colonization by the resistant strain. This presumably occurs because clearance of the patient’s own flora, makes new colonization more likely and exposes the patient substantially to the resistant strain. Outside the setting of a resistant outbreak there is little evidence that a patient on antibiotic treatment is more susceptible to carrying a resistant strain than an untreated patient. Indeed in some circumstances, at least in the short treatment term, treatment can clear a person of colonization with even a resistant strain, as has been shown in trials of amoxycillin–clavulanate [38].

In a cross-sectional and analytical prevalence study Arason et al. analysed the correlation of antimicrobial consumption and the carriage rate of penicillin-resistant and multiresistant pneumococci in children [40]. They found that both individual antibiotic use and total antimicrobial consumption in the community were strongly associated with nasopharyngeal carriage of penicillin-resistant pneumococci in children [40]. By univariate analysis, recent antimicrobial use (2–7 weeks) and the use of trimethoprim/sulphamethoxazole (TMP/SMX) were also significantly associated with the carriage of penicillin-resistant pneumococci [40].

Melander et al. also found that recent consumption of TMP/SMX emerged as an independent risk factor for PRP-carriage. The PRP-carriage rate in three day-care centres with high TMP/SMX consumption was higher (24%) than in other day-care centres (10%, P < 0.005) [41]. These data show the co-selection of PRP with the use of TMP/SMX.

Macrolide-resistant strains of Streptococcus pyogenes and S. pneumoniae have increased in many European countries and worldwide, paralleling the increasing use of macrolide antibiotics [34,42–50]. Countries with a higher macrolide consumption have a higher proportion of high-level macrolide resistance among S. pneumoniae isolates. Table 4 shows that in countries with macrolide consumption exceeding 4 DDD/1000 inhabitants/day, the resistance of S. pneumoniae to erythromycin is on average between 34.4–36.6% (range 18.1–58%) and in S. pyogenes 21% (range 12.9–38%), respectively. In countries with the consumption between 2 and 4 DDD/1000 inhabitants/day, the average resistance level in S. pneumoniae is 11.6–16.6% (range 4.2–27%) and in S. pyogenes 12.7–13.9% (range 3–36%), respectively. In countries with a consumption of ≤2 DDD/1000 inhabitants/day, the resistance of S. pneumoniae is on average 3.5% (range 2–3.6%) and of S. pyogenes 5.1% (range 2–12.4%), respectively.

A critical threshold of approximately 200 prescriptions/1000 inhabitants/year has been suggested to trigger the dispersion of erythromycin resistance [32]. In Slovenia the number of prescriptions/1000 inhabitants/year is <150, and resistance of S. pneumoniae is below 10% [38,45]. The twofold increase in macrolide consumption noted in Slovenia in a 6-year period was associated with a nearly linear increase in macrolide resistance, first in S. pyogenes then in upper respiratory S. pneumoniae isolates and lastly in invasive strains in S. pneumoniae [19,44,45].

Baquero examined the development of macrolide resistance in S. pneumoniae during the late 1980s and early 1990s, and found that the increasing resistance was due to reduced use of short-acting macrolides, such as erythromycin, and an wider use of the newer long-acting macrolides [58].
Preliminary analysis suggested that the threshold prescribing level for long-acting macrolide, which appears to link with resistance, is as low as 1.3 unit/1000 inhabitants/day. The association between long-acting macrolides and the selection of macrolide resistance may be explained by the concept of selective windows.

Antimicrobial agents with a low \( C_{\text{max}} \) and long half-lives will have a longer selective window, and thus the likelihood of selection of resistance is higher. Spiramycin, roxithromycin, clarithromycin and azithromycin have relatively long half-lives, which may facilitate the selection of resistance.

Granizo et al. reported that erythromycin resistance of \( S. \) pyogenes in Spain was highly correlated with the consumption of macrolides, especially those that are taken once or twice daily [46]. Also Goosens et al. found significant correlation between macrolide prescriptions and resistance of \( S. \) pyogenes [52]. Their data suggest that selective pressure is stronger with long-acting macrolides. Garcia-Rey et al. also recently, reported that consumption of once-a-day macrolides was a key factor for local erythromycin resistance variations in \( S. \) pneumoniae [34].

Nielsen et al. analysed the relationship between rates of infection with erythromycin-resistant \( S. \) pneumoniae and antimicrobial use at the county level in Denmark during the period 1995–2000 [48]. In the macrolide group erythromycin-resistant \( S. \) pneumoniae rates correlated with the use of azithromycin and erythromycin.

In the multivariate analysis only the use of azithromycin and erythromycin was independently related. Reinert et al. from Germany have also shown that erythromycin resistance of invasive pneumococcal isolates was highly correlated with the consumption of newer bd and od macrolides \( (R = 0.89, \ P < 0.01) \) [49]. All these studies show an unequivocal correlation between macrolide consumption, especially long-acting, with the development of resistance to macrolides.

Antimicrobial resistance rates are higher in paediatric populations in day-care centres and among isolates from the middle ear, nasopharynx or respiratory tract [59–62]. The higher resistance rate is possibly associated with a higher frequency of antibiotic treatment in children than in adults, and extensive child to child transmission in some settings, such as day-care centres and nursery schools.

The prevalence of \( S. \) pneumoniae with reduced susceptibility to fluoroquinolones increased in Canada. The reduced susceptibility increased from 0% in 1993 to 1.7% in 1998, and was probably a result of selective pressure of increased use of fluoroquinolones [63]. The number of fluoroquinolone prescriptions increased from 0.8 to 5.5/100 persons/year between 1988 and 1997/1998 \( (P = 0.01) \). Similarly in Barcelona, Spain, ciprofloxacin-resistant pneumococci increased from 0.9% in 1991/1992 to 3.0% in 1997/1998. The use of fluoroquinolones increased from 0.91 DDD/1000 inhabitants/day in 1985 to 2.22 DDD/1000 inhabitants/day in 1997 [64].

### Table 4

<table>
<thead>
<tr>
<th>Country</th>
<th>Use of macrolides and lincosamides</th>
<th>( S. ) pneumoniae Erythromycin resistance (%)</th>
<th>( S. ) pyogenes Erythromycin resistance (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>5.98</td>
<td>47.3–58</td>
<td>9.6</td>
<td>[11,15]</td>
</tr>
<tr>
<td>Spain</td>
<td>5.78</td>
<td>34.9</td>
<td>20.4</td>
<td>[13]</td>
</tr>
<tr>
<td>Italy</td>
<td>5.07</td>
<td>42.0–44.6</td>
<td>33.2</td>
<td>[11,15]</td>
</tr>
<tr>
<td>Greece</td>
<td>4.5</td>
<td>18.1</td>
<td>38</td>
<td>[11,51]</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>4.71</td>
<td>30.4</td>
<td>12.2</td>
<td>[24]</td>
</tr>
<tr>
<td>Belgium</td>
<td>4.06</td>
<td>34.0</td>
<td>12.9</td>
<td>[11,52]</td>
</tr>
<tr>
<td>Portugal</td>
<td>3.69</td>
<td>9.3</td>
<td>36</td>
<td>[11,53]</td>
</tr>
<tr>
<td>Austria</td>
<td>3.65</td>
<td>11.4</td>
<td>12–21.4</td>
<td>[11,54]</td>
</tr>
<tr>
<td>UK</td>
<td>3.22</td>
<td>18.4</td>
<td>10–11.6</td>
<td>[11,54]</td>
</tr>
<tr>
<td>Slovak Republic</td>
<td>3.2*</td>
<td>8.3–27</td>
<td>15</td>
<td>[11,55]</td>
</tr>
<tr>
<td>Poland</td>
<td>3.0*</td>
<td>6.2–22</td>
<td>12</td>
<td>[11,55]</td>
</tr>
<tr>
<td>Hungary</td>
<td>2.9*</td>
<td>29</td>
<td>3.3</td>
<td>[55]</td>
</tr>
<tr>
<td>Slovenia</td>
<td>2.85</td>
<td>5</td>
<td>10</td>
<td>[55]</td>
</tr>
<tr>
<td>Germany</td>
<td>2.54</td>
<td>4.2–15.3</td>
<td>13</td>
<td>[11,49,56]</td>
</tr>
<tr>
<td>Ireland</td>
<td>2.50</td>
<td>12.7</td>
<td>3</td>
<td>[11,54]</td>
</tr>
<tr>
<td>Norway</td>
<td>( \leq 2^a )</td>
<td>2(^b)</td>
<td>2</td>
<td>[20]</td>
</tr>
<tr>
<td>Denmark</td>
<td>1.97</td>
<td>2.8</td>
<td>2.4</td>
<td>[24]</td>
</tr>
<tr>
<td>Finland</td>
<td>1.86</td>
<td>5.3</td>
<td>9.6</td>
<td>[18,54]</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>1.24</td>
<td>2.4</td>
<td>2.0</td>
<td>[24]</td>
</tr>
<tr>
<td>Sweden</td>
<td>0.97</td>
<td>3.0</td>
<td>2.4</td>
<td>[22,41]</td>
</tr>
<tr>
<td>Russia</td>
<td>0.8*</td>
<td>3.6</td>
<td>12.4</td>
<td>[57]</td>
</tr>
</tbody>
</table>

\( a \) Total use including hospital use 1998.

\( b \) Data for 1995.
The correlation between antibiotic use and resistance in *Escherichia coli* was reported as well. Resistance to norfloxacin from five Dutch laboratories, covering approximately 14% of the Dutch population, increased from 1.3% in 1989 to 5.8% in 1998 [65]. The analysis of strata, classified by year, age and gender, demonstrated an association between the prescription of fluoroquinolones and resistance to norfloxacin in *E. coli* (*P* < 0.001).

In Slovenia, resistance of *E. coli* to ciprofloxacin in community isolates increased from 3.6 to 9.2% over 3 years, while the use of fluoroquinolones increased from 0.59 to 1.5 DDD/1000 inhabitants/day [66].

A rapid increase in the use of prophylactic TMP/SMX in HIV patients observed in San Francisco during the period 1998–1995 was associated with the increased resistance among all clinical isolates of *Staphylococcus aureus* and seven genera of Enterobacteriaceae; i.e. from 6.3% in 1988 to 53% in 1995 [67]. The largest increases in resistance were documented for *E. coli* (from 24% in 1988 to 53% in 1995) and *S. aureus* (from 0 to 48%).

4. Reversal of resistance

The first intervention to decrease bacterial resistance in the community occurred in Japan where decreased erythromycin consumption led to a decreased level of erythromycin-resistant *S. pyogenes* in the 1970s [68]. In Japan, 62% of *S. pyogenes* isolates were resistant to erythromycin in 1974, and macrolides accounted for 22% of all antibiotics used. By 1988, macrolides accounted for only 8% of antibiotic use and the proportion of *S. pyogenes* isolates resistant to erythromycin fell to 2%. Because of the increase of the macrolide resistance in *S. pyogenes*, in Finland a recommendation was made to decrease the use of macrolides in infections caused by group A streptococci. This recommendation nearly halved the usage of macrolides; from 2.44 DDD/1000 inhabitants/day to 1.38 and 1.44 DDD/1000 inhabitants/day in the year 1992 and 1996, respectively. During the follow-up period macrolide resistance of *S. pyogenes* decreased from 19 to 9% (*P* < 0.001) [69]. Similarly in Iceland the prevalence of penicillin-nonsusceptible pneumococcal carriage in children attending day-care centres dropped from 20 to 13% during the period 1993–1997 [70].

The use of antibacterial agents was the only known risk factor for resistance that had been reduced. Total national sale of antibacterial agents declined by approximately 10% and the sale of TMP/SMX and macrolides by approximately 30% [70].

The resistance rates in Finland and Iceland started declining approximately 3 years after the decrease in macrolide use in Finland and in overall antimicrobial sales in Iceland. This maximum lag time could have been even shorter if there had been a threshold level to be reached, and it was lower then the peak antimicrobial use [71]. Notable decrease in antibiotic prescribing does not necessarily reduce resistance within appropriate time period. The main reason seems to be the genetic linkage of the resistance index to other resistance determinants [72]. Despite a marked decrease in the number of sulphonamide prescriptions in England, which dropped from 320000/year in 1991–7000 in 1999 the rate of resistance of *E. coli* isolates in 1999 remained high compared with 1991 (46 vs 39.7%) [72].

5. Dosage regimens

Using antibiotics with poor activity or administering them at an inappropriate dosing level, dosing frequency, or for a prolonged duration increases the opportunity for selection of resistant strains. Guillemet et al. found that children treated with low daily doses of an oral β-lactam had an increased risk of PRSP carriage compared with children who did not [73]. Prolonged treatment (>5 days) with a β-lactam was associated with increased risk of PRSP carriage. The study by Nasrin et al. also showed higher penicillin resistance of *S. pneumoniae* in children who had taken β-lactam antibiotic for more than 14 days compared with a group taking no antibiotics or taking them for less than 7 days in the 6 months before nasal swabbing (26% vs 11–12%) [36]. Recently, Cohen et al. demonstrated an increase in the MIC of *S. pyogenes* in 8 of 79 children with streptococcal tonsillopharyngitis treated with azithromycin 10 mg/kg/day for 3 days, who were a bacteriological failure on day 14 in an intent-to-treat-assessable patients [74]. Before the treatment, the strains of *S. pyogenes* were susceptible to azithromycin. Their findings suggests that low dose antibiotic may promote the emergence of resistant strains, and it is the first time to author’s knowledge that macrolide resistance for *S. pyogenes* occurred in vivo, during antibiotic treatment. Further studies are required to confirm this finding and to determine optimal duration of treatment.

Marchese et al. showed that the use of injectable antibiotics to ensure higher and more persistent tissue and nasopharyngeal concentrations than orally administered drugs, can explain a relatively low incidence of bacterial resistance in Italy among pathogens responsible for community-acquired infections [75]. The study by Huchon et al. showed that in Italy 53% of outpatient lower respiratory tract infections are treated with parenteral antibiotics, compared with 10% in France, 8% in Spain, 1.2% in Germany and 0.2% in the UK [76].

A single intramuscular dose of ceftriaxone given to children with otitis media did not increase the risk for carriage of a PRSP 12–14 days after treatment, likewise
after a 10-day course of amoxycillin/clavulanate 80/10 mg/kg/day in three divided doses. Hence, the effect of a single dose of ceftriaxone on the emergence of resistance was not greater than that of a 10 day treatment with an oral antibiotic, which can clear also resistant strains of *S. pneumoniae* [38,77].

6. Pharmacokinetics/pharmacodynamics

The pharmacokinetic and pharmacodynamic properties of antibacterial agents also influence the development of resistance both in the pathogen under therapy and in the normal flora in the gut and elsewhere. Pharmacokinetic/pharmacodynamic parameters have been correlated with the drug's ability to prevent the emergence of resistant organisms. Several animal and in vitro studies have suggested that peak/MIC values of 8–10 or higher, and 24-h AUC/MIC ratios of 100 or greater can significantly reduce the emergence of resistant organism subpopulations during the treatment with fluoroquinolones and aminoglycosides in patients infected with Gram-negative bacilli, especially with *Pseudomonas aeruginosa* strains [78,79]. Lower ratios may be able to prevent the emergence of resistance with *S. pneumoniae* during exposure to fluoroquinolones [80]. High peak concentrations also appear to be capable of reducing the emergence of resistant Gram-negative bacilli with exposure to aminoglycosides. There is a paucity of information concerning other drug–organism combinations.

Dagan et al. recently, highlighted the impact of pharmacodynamics on the in vivo bacteriological efficacy of antibacterials. In a comparative study of the efficacy of azithromycin and amoxycillin–clavulanic acid in the treatment of acute otitis media, the investigators showed that the rates of *H. influenzae* eradication were significantly lower (*P = 0.0001*) in patients receiving azithromycin (13/33, 39%) compared with those treated with amoxycillin–clavulanic acid (26/30, 87%). It was believed that azithromycin concentrates within polymorphonuclear cells and, consequently its extracellular concentrations were insufficient to eradicate the extracellular pathogen *H. influenzae* [81]. Failure of an antibacterial to eradicate a bacterial pathogen can result in recolonization with resistant clones, which are then more likely to spread.

The mutant prevention concentration (MPC) has been proposed by Drlica et al. as a method to evaluate the propensity for emergence of resistance to antimicrobial agent [82]. MPC is defined as the lowest drug concentration in agar that prevents the growth of any colonies of resistant mutants from very large inocula (≈ 10^10 CFU). Resistant mutants are selected exclusively within a concentration range (mutant selection window) that extends from the point where growth inhibition begins, approximated by the MIC up to the MPC [83]. The initial data suggest that the MPC can vary for different organisms and for different drugs. For *S. pneumoniae* the MPC values ranged from 8 to 16 times the MIC [84]. In principle maintaining an antimicrobial at or above the MPC during the dosing interval should restrict the selection of mutants from a given population.

7. Cross-infections

Organisms can spread from person to person and between humans, animals, plants and other environments or by wide spread transfer of genetic material from the initial organisms to others [85]. Resistant strains vary in their propensity for spread according to the route of transmission of the species. Resistant strains of *Salmonella typhi* and *Shigella dysenteriae*, both widespread in many developing countries, pose little risk of widespread dissemination in developed countries provided that adequate standards of hygiene are observed. In contrast importation and subsequent dissemination in the local population of resistant strains of respiratory pathogens is well documented. Nasopharyngeal carriage in children is the major reservoir for perpetuation and dissemination of clones of antibiotic-resistant pneumococci. Crowding be observed in day-care centres, hospitals, or long-term care facilities, aids transmission. The pace of transmission is accelerated via selection pressure from antibiotic use. Any localised problem can be transported through international travel that brings isolates from one country to another. Isolates of *S. pneumoniae* serotype 23F, which is resistant to penicillin, chloramphenicol, tetracycline and TMP/SMX, and was found initially in Spain, were isolated from children who attended a day-care centre in Cleveland [86]. In Iceland, almost all of the multi-resistant pneumococci that appeared suddenly between 1989 and 1992 belonged to serotype 6B. They were indistinguishable from a subgroup of multiresistant pneumococci of serotype 6B, present with high incidence in Spain [87]. The molecular genetic studies have shown the spread of multidrug resistant *S. pneumoniae* through the world is clonal. Currently, most clinical isolates with high level resistance to β-lactam antibiotics belong to serogroups (6, 9, 14, 19 and 23), the resistance is mostly associated with serotypes 6B, 9V, 9A, 14, 19F and 23F [88,89]. For reasons not clearly understood, a majority of these clonal groups have also developed resistance to other drugs, including erythromycin, chloramphenicol, TMP/SMX and tetracycline. It is not yet clear why these molecular serotypes are more likely to contain antibiotic resistance determinants. It may be that these serotypes, which are commonly isolated from children, may be carried for longer periods of time, and thus are exposed
to increased antibiotic pressure. Recently, Richter et al. demonstrated that the spread of multidrug resistant \textit{S. pneumoniae} in the USA in the 1990s was also clonal. During the period 1994–2000, 8 distinct pulse-field-gel electrophoresis (PFGE) types accounted for approximately 70\% of all strains, and 4 of these had PFGE patterns similar to widespread- clones Spain 23F-1, approximately 70\% of all strains, and 4 of these had PFGE electrophoresis (PFGE) types accounted for approximately 70\% of all strains, and 4 of these had PFGE types. These observations support the hypothesis that the dominant factor in the emergence of PRSP in the USA in the 1990’s was human-to-human spread of relatively few clonal groups, harbouring resistance determinants to multiple classes of antibiotics. In addition, de novo emergence of new clones of PRSP occurred. Unexpected and marketed increase in erythromycin resistance in GAS isolates noted in many countries appears to be due to the sudden introduction and rapid spread of a single resistant clone [91].

Recently, Manges et al. presented surprising new findings concerning the epidemiology of uropathogenic \textit{E. coli} strains and of TMP/SMX resistance in these strains [92]. The authors described a previously unknown clonal group of uropathogenic \textit{E. coli} strains (clonal group A) that accounted for 38–51\% of strains resistant to TMP/SMX in three geographically diverse communities. This is yet another example of the ongoing global problem of antimicrobial resistance.

8. Patient compliance and public behaviour

Compliance is influenced by a number of factors. Many patients stop taking their medication once their symptoms have resolved yet before bacterial eradication is complete. This can lead to reinfection and selection of resistant strains. In the second type of noncompliance the patient reduces the number of daily doses. Missing one dose leads inevitably to lower serum/tissue area under the curve, and to shorter time of antibiotic concentrations over the MIC during the corresponding period. Such underdosing may promote the selection of resistance during therapy [80]. A recent international survey by Pechere reported that compliance is generally unsatisfactory. Overall, only 69\% (53–90\%) of respondents completed their most recent course of antibacterial treatment and 24\% (4–36\%) saved part of the course for future use [93]. Physicians overprescribe antibiotics either to meet patient’s expectations, instead of taking their time to explain to them why an antibiotic is not needed or for fear of misdiagnosing bacterial infections.

Excessive prescribing of antibacterial agents for trivial and non-bacterial infections in primary care partly reflects consumer pressure. Branthwaite and Pechere showed that the pressure on GPs to prescribe antibiotics was highlighted by over 50\% of interviewees, in five European Community countries and Turkey believing that they should be prescribed for most respiratory infections [94].

McFarlane et al. reviewed questionnaires completed by 787 of 1014 patients who had recently, presented to GPs with acute lower respiratory tract illness [95]. Of the 787 respondents 656 thought that an antibiotic would help; 564 wanted an antibiotic, 561 expected one, and 146 requested one. Patient pressure most commonly influenced the decision to prescribe when the doctor thought it to be unwarranted; patients who did not receive an antibiotic were prone to express dissatisfaction and were twice as likely to re-attend for the same episode, as satisfied patients.

In a survey of 915 paediatricians randomly chosen by the American Academy of Pediatrics analysed by Bauchner et al. 40\% of them responded that 10 or more times in the past month a parent had requested an antibiotic when the physician did not feel it was indicated [96]. Approximately one-third reported they occasionally or more frequently complied with these requests. Seventy-eight percent felt that educating parents should be the single most important programme for reducing inappropriate oral antibiotic use; 54\% indicated that parental pressure in contrast to concerns about legal liability (12\%) or need to be efficient in practice (19\%), contributed most to inappropriate use of oral antibiotics.

9. Conclusion

Antimicrobial agents were introduced into medical practice almost 60 years ago. Since then, the prevalence of antimicrobial resistance in community-acquired pathogens has increased worldwide. There is a complex relationship between the consumption of antimicrobial agents and the prevalence of drug resistance. Selective antibiotic pressure and spread of resistance both by spread of resistant bacteria, as well as by resistance genes transferred between bacteria are the major determinants of resistance. The influence of selective pressure, however, is specific for bacterial species and groups of antibiotics.

High consumption of antibacterials, particularly of broad-spectrum antibiotics, in the community should be avoided. The narrow-spectrum penicillins should be used whenever possible. Prospective long-term studies that record resistance and antibiotic use patterns are needed. Reliable data on antimicrobial consumption and resistance should form a basis for national policies designed to reduce the resistance of microorganisms to antibiotics.
Acknowledgements

I would like to thank Bojana Beovic and Marko Pokorn for his critical review and for his helping of the preparation of manuscript. I thank Andreja Sorman for her skilful technical assistance.

References

her skilful technical assistance.

Acknowledgements

I would like to thank Bojana Beovic and Marko Pokorn for his critical review and for his helping of the preparation of manuscript. I thank Andreja Sorman for her skilful technical assistance.

References

her skilful technical assistance.

Acknowledgements

I would like to thank Bojana Beovic and Marko Pokorn for his critical review and for his helping of the preparation of manuscript. I thank Andreja Sorman for her skilful technical assistance.

References

[10] Stratchounski L, Bedenk


