The evolving threat of antibiotic resistance in Europe: new data from the Alexander Project

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The Alexander Project was established in 1992 to examine the antimicrobial susceptibility of community-acquired lower respiratory tract bacterial pathogens to a range of compounds. Since then it has expanded both geographically and in the number of antimicrobial agents tested. Within Europe, the most recent data have confirmed that the prevalence of penicillin resistance among isolates of *Streptococcus pneumoniae* is high in France and Spain, with both intermediate (MIC 0.12–1 mg/L) and resistant (MIC ≥ 2 mg/L) phenotypes, and combined resistance rates of >50%. Macrolide resistance is increasing generally both among penicillin-resistant and penicillin-susceptible isolates of *S. pneumoniae* and its prevalence now exceeds that of penicillin resistance, overall (16.5% and 10.4%, respectively, in 1996; 21.9% and 14.1% in 1997; 16.5% and 11.6% in 1998). β-Lactamase production was the principal mechanism of resistance observed among isolates of *Haemophilus influenzae* and *Moraxella catarrhalis*.

Introduction

*Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* are the most frequent pathogens causing community-acquired respiratory tract infections (RTIs), such as community-acquired pneumonia, acute exacerbation of chronic obstructive airways disease, otitis media and sinusitis. The so-called atypical pathogens, including *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Chlamydia pneumoniae*, are also found as causes of disease in a proportion of community-acquired RTIs.1–3

In 1992, the Alexander Project was established in Europe and the USA to examine the susceptibility of community-acquired RTI pathogens to a range of antimicrobial compounds. Since then the project has widened its scope both geographically, to cover five continents, and in the range of compounds it examines.

Findings have confirmed an increasing prevalence of resistance among isolates of the three major bacterial pathogens including β-lactamase production in *H. influenzae* and *M. catarrhalis*, and penicillin, macrolide and multiple resistance in *S. pneumoniae*.4 Different centres around the world experience different patterns and different prevalence of resistance, with causative organisms indifferent to political or geographical boundaries. Such resistance can contribute to therapeutic failure, increased cost and morbidity, and excess mortality.5,6 Alternative agents are urgently needed for the treatment of RTIs in this environment of increasing resistance to currently available antibiotics.

Materials and methods

*Alexander Project European collaborating centres*

The following European centres and investigators took part in the study in 1998: UK, London (D. Felmingham); Eire, Dublin (L. Fenelon, E. Smyth); France, Toulouse (J. Lemozy); Belgium, Leuven (J. Verhaegen); The Netherlands (one centre, co-ordinator A. J. de Neeling); Portugal (one centre, co-ordinator J. Melo Cristino); Italy, Genoa (G. C. Schito); Germany, Weingarten (H. Grimm); Austria, Vienna (U. Theuretzbacher); Czech Republic (one centre, co-ordinator P. Urbášková); Slovak Republic (one centre, co-ordinator P. Urbášková); Hungary, Budapest (M. Konkoly-Thege); Poland, Warsaw (K. Trzciński); Switzerland (seven centres, co-ordinator J. Bille).

*Bacterial isolates*

The pathogens collected for study were *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. The criteria for the collection of bacterial isolates, their transportation, storage and re-identification, and the microbroth dilution susceptibility
testing methods used have been described in detail previously.\textsuperscript{7,8} The antimicrobial agents and range of concentrations tested in the Alexander Project in 1998 were: penicillin, ampicillin and amoxycillin with or without clavulanic acid, 0.015–16 mg/L; cefaclor, cefprozil, loracarbef, erythromycin and clarithromycin, 0.004–64 mg/L; cefuroxime, 0.015–32 mg/L; cefixime, 0.008–16 mg/L; ceftriaxone and cefotaxime, 0.004–16 mg/L; azithromycin, 0.03–64 mg/L; doxycycline, 0.12–8 mg/L; chloramphenicol, 0.004–32 mg/L; ciprofloxacin and ofloxacin, 0.004–16 mg/L; and co-trimoxazole, 0.03–8 mg/L.

Breakpoint concentrations used to interpret MIC data qualitatively were based upon those published by the NCCLS\textsuperscript{9} and are indicated in the tables.

\section*{Results}

\subsection*{Streptococcus pneumoniae}

The evolution of penicillin and macrolide resistance in Europe, 1992–1998. The prevalence of penicillin and macrolide resistance for the isolates from countries included in 1998 is shown in Table I. The Figure shows the evolution of penicillin and macrolide resistance between 1992 and 1998 for the four countries (France, Italy, Germany and the UK) participating in the project throughout that period.

In France, the prevalence of penicillin-resistant \textit{S. pneumoniae} is high, with combined intermediate and resistant strains now accounting for 53.3% of submitted isolates. Spain, another region of established penicillin resistance, did not contribute strains in 1998, but had already achieved >50% combined intermediate and resistant strains by 1997. While comparatively low in 1998, penicillin resistance has been rising in the UK (London). Similar rates of intermediate resistance have been observed throughout the past 3 years (4.5% in 1996; 6.3% in 1997; 5% in 1998), but resistant rates increased (4.6% in 1996; 3.1% in 1997; 15% in 1998). No such increase was observed in Italy (Genoa), where penicillin resistance appears relatively stable, with intermediate-resistance rates of 4.2% (1996 and 1997) and 6% (1998), and resistance rates of 4.9% (1996) and 3.1% (1997 and 1998). Germany continues to have low resistance, but in 1998 the first strains (1.8%) exhibiting resistance to penicillin (\(\geq 2\) mg/L) were detected there.

A steady increase in macrolide resistance has been observed during the lifetime of the Alexander Project in four of the five original participating countries, namely France, Spain, UK and Italy. Different selection pressures appear to operate in each country. Resistance to the macrolides, doxycycline, chloramphenicol and co-trimoxazole was associated with penicillin resistance. The strongest association was between penicillin resistance (MIC \(\geq 2\) mg/L) and co-trimoxazole resistance, where approximately 90% cross-resistance was observed. Approximately half of all penicillin-resistant isolates were also resistant to macrolides, doxycycline and chloramphenicol.

\textbf{Italy}. In Italy, penicillin resistance in \textit{S. pneumoniae} has increased slowly during the last 3 years, with intermediate-

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|l|}
\hline
Country        & Total number of isolates & Pen-S & Pen-I & Pen-R & Ery-R  \\
&                      & no.  & %    & no.  & %    & no.  & %    \\
\hline
The Netherlands & 124                      & 120  & 96.8 & 4   & 3.2 & 0   & 0.0  \\
Germany       & 168                      & 156  & 92.9 & 9   & 5.4 & 3   & 1.8  \\
Belgium       & 100                      & 92   & 92.0 & 3   & 3.04 & 5   & 5.0  \\
Italy         & 100                      & 91   & 91.0 & 6   & 6.0 & 3   & 3.0  \\
Switzerland   & 138                      & 118  & 85.5 & 12  & 8.7 & 8   & 5.8  \\
UK            & 87                       & 70   & 80.5 & 4   & 4.6 & 13  & 14.9 \\
Poland        & 144                      & 131  & 91.0 & 8   & 5.5 & 5   & 3.5  \\
Austria       & 185                      & 162  & 87.6 & 14  & 7.6 & 9   & 4.8  \\
Portugal      & 129                      & 107  & 82.9 & 9   & 7.0 & 13  & 10.1 \\
Greece        & 171                      & 117  & 68.4 & 28  & 16.4 & 26  & 15.2 \\
France        & 167                      & 78   & 46.7 & 21  & 12.6 & 68  & 40.7 \\
Czech Republic & 99                       & 92   & 92.9 & 6   & 6.1 & 1   & 1    \\
Slovak Republic & 72                      & 35   & 48.6 & 15  & 20.8 & 22  & 30.6 \\
Eire           & 55                       & 37   & 67.3 & 4   & 7.3 & 14  & 25.5 \\
\hline
\end{tabular}
\caption{Penicillin and macrolide susceptibility of European isolates of \textit{Streptococcus pneumoniae}: Alexander Project 1998}
\end{table}

The Italian Epidemiological Observatory (IEO), a study stimulated by the Alexander Project, has reported antimicrobial resistance in RTI pathogens from 54 centres throughout the country.10 This study has confirmed the data from the Alexander Project, with penicillin resistance remaining stable between 1997 (14.3%) and 1998 (12.7%). It also shows the range of resistance levels encountered. For example, overall penicillin resistance (intermediate and resistant combined) in 1998 ranged from 0% in Cremona, Padua, Udine and Vicenza to 35% in Sassari, but only in Rome is there a significant proportion of resistant (MIC ≥ 2 mg/L) isolates (17.4%). The IEO study confirms that macrolide resistance is rampant in Italy. Erythromycin resistance increased from 29.1% in 1997 to 31.7% in 1998, and varied markedly in different parts of the country, with rates of 28.2% in northern Italy, 32.9% in southern Italy and 44.6% in central Italy. Between 1997 and 1998, erythromycin resistance rates did not increase in southern Italy, while annual increases of 3.6% and 5.8% were seen in northern and central Italy, respectively (Table II).

Comparative in vitro potency of fluoroquinolones. With regard to fluoroquinolone susceptibility, since 1994 there have been no significant changes in the MIC_{50}, MIC_{90}, modal MIC or the proportion of isolates with MICs ≥ 16 mg/L of ciprofloxacin or ofloxacin.11 Since the Alexander Project was initiated in 1992, only 33 isolates of S. pneumoniae with MICs of ≥16 mg/L of either ciprofloxacin or ofloxacin have been reported. In 1997, isolates with MICs ≥ 16 mg/L came from France (one), Spain (one), Germany (one), Poland (one), USA (two isolates, both from New York) and Hong Kong (five). In 1998, European isolates with MICs ≥ 16 mg/L came from Eire (one), France (four), Germany (one), Switzerland (two) and Poland (four).

For ciprofloxacin in 1998, the MIC_{50} was 1.0 mg/L at all centres except London, Weingarten and Genoa, where it was 2 mg/L. The MIC_{90} was 2.0 mg/L at all centres. For ofloxacin in 1998, the MIC_{50} was 2.0 mg/L at all centres and the MIC_{90} was 2.0 mg/L at all centres except London and the centres in the Czech Republic, where it was 4 mg/L.

Overall, against S. pneumoniae, the most active agents in previous years (in terms of potency and percentage susceptibility) were ceftriaxone and amoxycillin (with or without the addition of clavulanic acid). In 1998, when the range of antimicrobial agents tested was expanded, the most active agents were ceftriaxone and cefotaxime (MIC_{90} 1 mg/L).

**Haemophilus influenzae**


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**Figure.** Pencillin and macrolide resistance in S. pneumoniae between 1992 and 1998 in (a) Italy, (b) Germany, (c) UK and (d) France. □, Penicillin intermediate; □, penicillin resistant; ■, erythromycin resistant.
isolates of *H. influenzae* increased slightly between 1996 and 1998 (10.3%, 11.3% and 11.6% in 1996, 1997 and 1998, respectively) (Table III). High rates (>15%) of *β*-lactamase production were found in the UK, Eire, France, Belgium and Spain. The IOE study has shown the variability of *β*-lactamase prevalence within a single country (Italy). 10 Prevalence rates ranged from 4.5% (Veneto, Liguria) to 21.1% (Puglia), compared with an overall figure of 2.0% from the Alexander Project.

*β*-Lactamase-negative, ampicillin-resistant (MIC ≥ 4 mg/L) strains (BLNAR) were identified only rarely, with an overall prevalence of 0.2% in 1996, 0.3% in 1997 and 0.1% in 1998. In 1996, such strains were only found in Spain (four); in 1997 such strains were found in Eire (three), Portugal (one) and the Slovak Republic (two); and, in 1998, such strains were found in the UK (one) and The Netherlands (one).

### Table II. Distribution of penicillin and macrolide resistance of *Streptococcus pneumoniae* by centre in Italy in 1998

<table>
<thead>
<tr>
<th>Centre</th>
<th>Number of isolates</th>
<th>Penicillin resistance (%)</th>
<th>Macrolide resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>intermediate</td>
<td>resistant</td>
</tr>
<tr>
<td>Milan 1</td>
<td>32</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Milan 2</td>
<td>24</td>
<td>4.3</td>
<td>–</td>
</tr>
<tr>
<td>Genoa</td>
<td>60</td>
<td>1.7</td>
<td>5.0</td>
</tr>
<tr>
<td>Verona</td>
<td>26</td>
<td>3.8</td>
<td>–</td>
</tr>
<tr>
<td>Negar VR</td>
<td>22</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Rome 1</td>
<td>23</td>
<td>13.0</td>
<td>17.4</td>
</tr>
<tr>
<td>Rome 2</td>
<td>24</td>
<td>4.2</td>
<td>–</td>
</tr>
<tr>
<td>Sassari 1</td>
<td>20</td>
<td>35.0</td>
<td>–</td>
</tr>
<tr>
<td>Sassari 2</td>
<td>26</td>
<td>12.5</td>
<td>20.8</td>
</tr>
<tr>
<td>Catania</td>
<td>43</td>
<td>7.0</td>
<td>–</td>
</tr>
<tr>
<td>Ancona</td>
<td>27</td>
<td>14.8</td>
<td>–</td>
</tr>
<tr>
<td>Florence</td>
<td>25</td>
<td>12.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Padova</td>
<td>24</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Udine</td>
<td>25</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Vicenza</td>
<td>25</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rovereto</td>
<td>25</td>
<td>4.0</td>
<td>–</td>
</tr>
<tr>
<td>Cremona</td>
<td>40</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sondalo</td>
<td>52</td>
<td>11.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Bergamo</td>
<td>21</td>
<td>14.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Monza</td>
<td>27</td>
<td>3.7</td>
<td>3.7</td>
</tr>
<tr>
<td>Parma</td>
<td>28</td>
<td>7.1</td>
<td>10.7</td>
</tr>
</tbody>
</table>

*For Milan, Rome and Sassari, two centres in each city participated in the study.

**Moraxella catarrhalis**

The evolution of *β*-lactamase production in Europe, 1992–1998. *β*-Lactamase production was the only resistance mechanism of importance identified in the isolates of *M. catarrhalis* tested. Overall, 92.2% of 371 isolates collected in Europe in 1998 produced *β*-lactamase. The corresponding rates for 1996 and 1997 were 90.4% and 91.6%, respectively.

Macrolide (erythromycin) MICs did not vary between centres, but increased between 1997 and 1998. Similar changes were observed for clarithromycin and azithromycin (data not shown). With the exception of a single isolate from Poland, the MIC of erythromycin and clarithromycin for *M. catarrhalis* in 1998 was 0.5 mg/L.

**Discussion**

The Alexander Project has reported previously marked increases in resistance since 1992 and this situation continues in many countries in 1998. The number of centres involved in the Project has increased and the Alexander Project can now be considered truly ‘global’. For the first 2 years of the project, MIC distributions were published in
### Table III. Antimicrobial susceptibility of European isolates of *Haemophilus influenzae*—Alexander Project 1998

<table>
<thead>
<tr>
<th>Country</th>
<th>Total no. of isolates tested</th>
<th>(\beta)-lactamase positive</th>
<th>BLNAR(^a)</th>
<th>chloramphenicol(^b) -resistant</th>
<th>doxycycline(^c) -resistant</th>
<th>co-trimoxazole(^d) -resistant</th>
<th>ciprofloxacin/ofloxacin(^e) -resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>158</td>
<td>22.2</td>
<td>0</td>
<td>3.2</td>
<td>3.2</td>
<td>14.0</td>
<td>1.9</td>
</tr>
<tr>
<td>UK</td>
<td>100</td>
<td>18.0</td>
<td>1.0</td>
<td>4.0</td>
<td>0</td>
<td>7.0</td>
<td>0</td>
</tr>
<tr>
<td>Eire</td>
<td>111</td>
<td>17.1</td>
<td>0</td>
<td>1.8</td>
<td>0.9</td>
<td>13.5</td>
<td>0</td>
</tr>
<tr>
<td>Greece</td>
<td>50</td>
<td>16.0</td>
<td>0</td>
<td>0</td>
<td>0.9</td>
<td>20.0</td>
<td>0</td>
</tr>
<tr>
<td>Belgium</td>
<td>96</td>
<td>15.6</td>
<td>0</td>
<td>3.1</td>
<td>1.0</td>
<td>5.2</td>
<td>0</td>
</tr>
<tr>
<td>Portugal</td>
<td>213</td>
<td>11.7</td>
<td>0</td>
<td>1.4</td>
<td>2.8</td>
<td>13.6</td>
<td>0</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>98</td>
<td>14.3</td>
<td>0</td>
<td>1.0</td>
<td>0</td>
<td>15.3</td>
<td>0</td>
</tr>
<tr>
<td>Switzerland</td>
<td>105</td>
<td>10.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>21.9</td>
<td>0</td>
</tr>
<tr>
<td>Germany</td>
<td>193</td>
<td>6.7</td>
<td>0</td>
<td>0.5</td>
<td>0.5</td>
<td>27.5</td>
<td>0</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>141</td>
<td>6.4</td>
<td>0.7</td>
<td>1.4</td>
<td>0</td>
<td>11.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Poland</td>
<td>273</td>
<td>4.4</td>
<td>0</td>
<td>0.4</td>
<td>0.4</td>
<td>28.6</td>
<td>0</td>
</tr>
<tr>
<td>Austria</td>
<td>153</td>
<td>3.9</td>
<td>0</td>
<td>0</td>
<td>1.3</td>
<td>13.7</td>
<td>0</td>
</tr>
<tr>
<td>Italy</td>
<td>100</td>
<td>2.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11.0</td>
<td>0</td>
</tr>
<tr>
<td>Slovak Republic</td>
<td>99</td>
<td>8.1</td>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
<td>19.2</td>
<td>0</td>
</tr>
<tr>
<td>Combined</td>
<td>1890</td>
<td>11.6</td>
<td>0.1</td>
<td>1.2</td>
<td>1.0</td>
<td>18.7</td>
<td>0.2</td>
</tr>
</tbody>
</table>

\(^a\)\(\beta\)-Lactamase-negative, MIC of ampicillin \(\geq 4\) mg/L.

\(^b\)MIC of chloramphenicol \(\geq 4\) mg/L.

\(^c\)MIC of doxycycline \(\geq 4\) mg/L.

\(^d\)MIC of co-trimoxazole \(\geq 1/19\) mg/L.

\(^e\)MIC of ciprofloxacin/ofloxacin \(> 1\) mg/L; resistant to disc containing nalidixic acid 30 \(\mu\)g.
the Journal of Antimicrobial Chemotherapy. These and subsequent data (1992–1996) are now available online (at http://www.alexander-network.com). This report deals with results from European centres only.

For S. pneumoniae, previous reports of the Alexander Project have demonstrated an increasing prevalence of both intermediate (MIC 0.12–1 mg/L) and resistant (MIC ≥ 2 mg/L) penicillin phenotypes. Penicillin resistance is high, sustained or rapidly increasing in France, Spain, Greece, Eire, the UK and Portugal. For example, in the UK (London), penicillin resistance was low before 1995 but the proportion of resistant phenotypes had risen to 15% by 1998. Isolates from centres in Belfast (1992–1995) and Dublin (1997 and 1998) suggest that this increase is more advanced in the island of Ireland, as has been reported elsewhere.

Macrolides, including erythromycin, clarithromycin and azithromycin, are the principal alternative to β-lactams for the treatment of lower RTIs involving S. pneumoniae. Overall, rates of macrolide resistance (16.5% in 1996, 21.9% in 1997 and 16.5% in 1998) exceeded those of penicillin resistance (MIC ≥ 2 mg/L: 10.4% in 1996, 14.1% in 1997 and 11.6% in 1998). Resistance to this class of compounds has grown, not only among penicillin-resistant pneumococci but also among penicillin-susceptible strains.

Of the three centres showing the greatest macrolide resistance in 1998, France (47.9%), Belgium (34%) and Italy (42%), both Belgium and Italy had increasing macrolide resistance rates among penicillin-sensitive strains. In Italy, macrolide resistance has been increasing at an alarming rate and in a linear fashion throughout the lifetime of the Alexander Project. The UK is also showing signs of an impending crisis in macrolide resistance.

What are the alternatives? Earlier fluoroquinolones generally had poor activity against S. pneumoniae and this precluded their use as a class for empirical treatment of RTI. However, with the advent of increased resistance and the development of new fluoroquinolones with enhanced activity against pneumococci and more favourable pharmacokinetics, the debate has been re-opened.

Fluoroquinolone-resistant pneumococci (MIC of ciprofloxacin/ofloxacin ≥16 mg/L) have been found only rarely, and have not increased in prevalence during the period of the study (1992–1998), although an increase was noted between 1996 (0/2160 isolates) and 1997 (10/2036 isolates). Importantly, when clinical susceptibility is defined on the basis of NCCLS breakpoints for ofloxacin (susceptibility, ≤2 mg/L; intermediate resistance, 4 mg/L; resistance, ≥8 mg/L), there is no obvious association between reduced susceptibility (intermediate plus resistant isolates) and penicillin resistance, although multiresistant clones may exist. This favours the new fluoroquinolones as principal candidates as substitutes for β-lactams.

The most important mechanism of resistance expressed by isolates of H. influenzae remains β-lactamase production. Two enzymes have been identified, a TEM-1-type β-lactamase which is present in some 90% of positive strains and the less frequently found ROB-1 type. Both types of enzyme are inhibited by clavulanic acid. Non-β-lactamase-mediated resistance to ampicillin, defined by the NCCLS as strains requiring ≥4 mg/L for inhibition (BLNAR), occurs as a result of changes in the affinities of penicillin-binding proteins (PBPs), particularly PBP 3A and PBP 3B, for the β-lactams generally. However, the significance of these strains remains unclear.

Until 1997, susceptibility of H. influenzae to the three macrolides tested did not change, following a unimodal distribution of MIC in the rank order azithromycin > erythromycin > clarithromycin. However, in 1998, mode MIC values for erythromycin and clarithromycin became equivalent so that the rank order is currently azithromycin (mode MIC 2 mg/L) > erythromycin (mode MIC 8 mg/L) = clarithromycin (mode MIC 8 mg/L). Therefore, the use of arbitrary breakpoints in an attempt to distinguish between their clinical usefulness seems inappropriate. Considerably more pharmacodynamic and clinical trial data are necessary if useful breakpoints are to be established for these compounds, a point already well made.

Resistance in M. catarrhalis is associated with β-lactamase production; since first recognized in the late 1970s, β-lactamase-producing strains have increased and now account for >80% of clinical isolates. The Alexander Project confirms the importance of this resistance mechanism with prevalence rates among combined isolates of 75.7% in 1992, 93.3% in 1995, 90.4% in 1996, 91.6% in 1997 and 92.2% in 1998. With the exception of a single isolate, all M. catarrhalis isolates from all seven European centres participating in 1998 had MICs of erythromycin and clarithromycin of 0.05 mg/L, an MIC unrecorded 1 year previously. MICs of azithromycin also continue to increase. The situation needs to be monitored.

In conclusion, the Alexander Project is recording increasing resistance in many countries. If not halted, this resistance will render many current antimicrobial agents obsolete. In this situation, antimicrobial drugs covering the whole spectrum of community-acquired RTI pathogens and capable of overcoming resistance will need to be introduced for empirical use.

References
Antibiotic resistance in Europe


