Trends of penicillin and erythromycin resistance among invasive *Streptococcus pneumoniae* in Europe

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on behalf of EARSS participants

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Received 3 June 2004; returned 15 July 2004; revised 7 September 2004; accepted 12 September 2004

**Objectives:** To forecast trends in resistance to penicillin and erythromycin among *S. pneumoniae* in Europe.

**Methods:** Since 1999, the European Antimicrobial Resistance Surveillance System (EARSS) has collected routine antimicrobial susceptibility test results of *S. pneumoniae*. To observe and predict changes of reduced susceptibility over time, we used a multinomial logistic regression model.

**Results:** Large variations in penicillin and erythromycin non-susceptibility were observed between countries, and reduced susceptibility to erythromycin (17%) has become more frequent than reduced susceptibility to penicillin (10%) in Europe overall. An overall decrease in single penicillin non-susceptibility, but an increase in dual non-susceptibility was observed, indicating a shift of single penicillin to combined non-susceptibility with erythromycin. By 2006, the proportion of single erythromycin and dual non-susceptibility could increase to as much as 20.4% and 8.9%, respectively.

**Conclusions:** Our results indicate that appropriately dosed β-lactams for empirical therapy are still the treatment of choice, and that macrolides should be used with prudence.

Keywords: public health, antimicrobial resistance, antimicrobial use

**Introduction**

*Streptococcus pneumoniae* is the single most important cause of community-acquired pneumonia and acute otitis media, and one of the most important pathogens leading to bloodstream infections and meningitis in children and adults. Increasing prevalence of resistant strains in the past 15 years is now threatening the successful treatment of these infections. The frequent prescription of antibiotics is associated with the increase in resistance and emphasizes the importance of judicious antibiotic use and the possible need for alternative control strategies such as vaccination.

In 1999, the European Antimicrobial Resistance Surveillance System (EARSS), recognized by the EU council recommendations, began monitoring the prevalence of antimicrobial resistance of invasive *S. pneumoniae* infections. This network connects national surveillance systems and provides comparable and validated results of routine antimicrobial susceptibility tests (ASTs) using standardized protocols from a representative set of laboratories per country, annually validated through external quality assurance (EQA) exercises. Therefore, the EARSS database allows identification of trends in different European countries in a consistent manner and provides the means to assess the effectiveness of interventions.
In the present study, we describe the resistance trends for penicillin and erythromycin among invasive *S. pneumoniae* isolates and forecast resistance trends in Europe.

### Materials and methods

#### Data collection

EARSS collects routine AST results of primary invasive *S. pneumoniae* isolates from blood or CSF. According to the standard EARSS protocol (www.earss.rivm.nl), participating laboratories screen for penicillin non-susceptibility by using an oxacillin disc diffusion test. Isolates with inhibition zones of <20 mm or 26 mm for disc loads of 1 mg or 5 mg oxacillin, respectively, are subject to MIC determination to confirm penicillin non-susceptibility.

All participating laboratories performed antimicrobial susceptibility tests and interpreted their penicillin and erythromycin susceptibility results according to national or international guidelines as S (susceptible), I (intermediately resistant) or R (resistant). The majority of laboratories participating in EARSS use the NCCLS guidelines (61%).

AST results (S, I or R) together with laboratory code, date of sample collection, patient ID or month and year of birth, are collected quarterly, and only the primary isolate (per patient) per year is recorded.

Annually, EQA exercises are performed by the laboratories participating in EARSS, to assess the comparability of susceptibility test results between countries. The overall concordance of the EQA exercise in 2000 for the detection of penicillin non-susceptible *S. pneumoniae* (PNSP) was 97%, and ranged from 96% to 99% for the three strains tested. Erythromycin resistance was detected correctly by 99% of the participants for all three control strains.

#### Data analysis

Data analysis was carried out using SAS software (release 8.02; SAS Institute Inc., Cary, NC, USA) and SPSS (release 11.0.1; SPSS Inc., Chicago, IL, USA). In the subsequent analysis, the susceptibility test results I and R were grouped together and referred to as non-susceptible, for both penicillin and erythromycin. To predict changes of resistance over time, a multinomial logistic regression model was used as described by Lipsitch, and McCormick et al. The seven European countries that reported more than 100 isolates per year with penicillin and erythromycin susceptibility data for the entire observation period (1999–2002) were included in the logistic regression model. The proportion of resistance in the logistic model was described as the percentage of isolates with single non-susceptibility to penicillin, or erythromycin, or dual non-susceptibility to penicillin.

### Table 1. Changes in the proportion of single and dual non-susceptibility to penicillin and erythromycin in invasive *S. pneumoniae* isolates over time, by country

<table>
<thead>
<tr>
<th>Country (total no. of isolates)</th>
<th>1999</th>
<th>2002</th>
<th>Rate of increase (rank)</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>lower bound</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>upper bound</td>
</tr>
<tr>
<td>Proportion single penicillin non-susceptibility (rank)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium (4058)</td>
<td>6.7(3)</td>
<td>5.9(3)</td>
<td>0.885(5)</td>
<td>0.768</td>
</tr>
<tr>
<td>Finland (1231)</td>
<td>3.5(5)</td>
<td>2.9(5)</td>
<td>0.998(3)</td>
<td>0.747</td>
</tr>
<tr>
<td>Germany (790)</td>
<td>0.4(7)</td>
<td>0.0(7)</td>
<td>1.015(2)</td>
<td>0.548</td>
</tr>
<tr>
<td>Ireland (679)</td>
<td>17.6(1)</td>
<td>11.2(1)</td>
<td>0.864(6)</td>
<td>0.692</td>
</tr>
<tr>
<td>Italy (643)</td>
<td>6.3(4)</td>
<td>6.5(2)</td>
<td>0.966(4)</td>
<td>0.711</td>
</tr>
<tr>
<td>Sweden (2514)</td>
<td>1.4(6)</td>
<td>1.7(6)</td>
<td>1.068(1)</td>
<td>0.823</td>
</tr>
<tr>
<td>UK (1074)</td>
<td>8.7(2)</td>
<td>5.0(4)</td>
<td>0.787(7)</td>
<td>0.618</td>
</tr>
<tr>
<td>Proportion single erythromycin non-susceptibility (rank)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>25.5(1)</td>
<td>27.9(2)</td>
<td>1.033(4)</td>
<td>0.967</td>
</tr>
<tr>
<td>Finland</td>
<td>4.9(7)</td>
<td>11.0(5)</td>
<td>1.378(1)</td>
<td>1.109</td>
</tr>
<tr>
<td>Germany</td>
<td>6.9(5)</td>
<td>13.7(3)</td>
<td>1.304(2)</td>
<td>1.083</td>
</tr>
<tr>
<td>Ireland</td>
<td>12.5(4)</td>
<td>11.6(4)</td>
<td>1.015(5)</td>
<td>0.803</td>
</tr>
<tr>
<td>Italy</td>
<td>23.4(2)</td>
<td>28.5(1)</td>
<td>1.100(3)</td>
<td>0.948</td>
</tr>
<tr>
<td>Sweden</td>
<td>5.5(6)</td>
<td>5.1(7)</td>
<td>1.012(6)</td>
<td>0.850</td>
</tr>
<tr>
<td>UK</td>
<td>13.4(3)</td>
<td>10.4(6)</td>
<td>0.858(7)</td>
<td>0.718</td>
</tr>
<tr>
<td>Proportion dual non-susceptibility (rank)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>12.1(1)</td>
<td>14.2(1)</td>
<td>1.054(4)</td>
<td>0.959</td>
</tr>
<tr>
<td>Finland</td>
<td>1.5(5)</td>
<td>4.5(3)</td>
<td>1.339(2)</td>
<td>0.978</td>
</tr>
<tr>
<td>Germany</td>
<td>0.0(7)</td>
<td>0.6(7)</td>
<td>2.688(1)</td>
<td>0.545</td>
</tr>
<tr>
<td>Ireland</td>
<td>5.6(3)</td>
<td>3.3(5)</td>
<td>0.790(7)</td>
<td>0.529</td>
</tr>
<tr>
<td>Italy</td>
<td>11.3(2)</td>
<td>10.2(2)</td>
<td>0.989(6)</td>
<td>0.775</td>
</tr>
<tr>
<td>Sweden</td>
<td>0.4(6)</td>
<td>0.6(6)</td>
<td>1.231(3)</td>
<td>0.725</td>
</tr>
<tr>
<td>UK</td>
<td>3.3(4)</td>
<td>3.8(4)</td>
<td>1.011(5)</td>
<td>0.716</td>
</tr>
</tbody>
</table>

aOnly the countries with a minimum of 100 isolates per year for the whole observation period (1999–2002) are displayed.

bRank of 1 = highest proportion of non-susceptible or largest rate of increase.

cHigh rate of increase due to starting point (1999) of 0%.
and erythromycin compared with the susceptible group of isolates (see Table 1). The multinomial coefficients extracted from the logistic regression model describe the rate of increase/decrease per year.

**Results**

**Isolate characteristics**

Between 1999 and 2002, 561 laboratories from 26 countries reported susceptibility results from 22,277 invasive *S. pneumoniae* isolates to EARSS. Ninety-three per cent of the isolates were recovered from blood and 7% from CSF cultures. Fifty-five per cent were from male patients. Thirteen per cent of the isolates were from patients under 5 years of age, 4% were from the age group 5–19 years, 38% were from 20–64 year olds and 44% of the patients were 65 years or older. Thus, the highest relative number of *S. pneumoniae* isolates was reported for the age band <5 years (n = 2786). AST results for erythromycin were reported for 17,938 of the 22,277 *S. pneumoniae* isolates (81%).

**Streptococcus pneumoniae resistance**

For the entire observation period, overall, 10% of the *S. pneumoniae* isolates were penicillin non-susceptible, 17% were erythromycin non-susceptible and 6% were co-resistant (non-susceptible to penicillin and erythromycin). MICs of penicillin were available for 2090 of 2220 penicillin non-susceptible isolates (94%). No significant difference in the proportion of penicillin non-susceptible *S. pneumoniae* (PNSP) and erythromycin non-susceptible *S. pneumoniae* (ENSP) was observed between men and women. The highest proportion of PNSP (20%) and ENSP (33%) was reported for the age group <5 years of age. Seventy-eight per cent of the PNSP isolates showed intermediate resistance to penicillin, whereas nearly all isolates (97%) with reduced susceptibility to erythromycin were fully resistant.

**Distribution of resistance in Europe**

The proportions of PNSP and ENSP are displayed by country for the 4 year observation period in Figures 1 and 2. For both agents the highest proportions of resistance were observed among the Mediterranean countries (Figures 1 and 2). Co-resistance (non-susceptibility to penicillin and erythromycin) was highest in Spain (18%), followed by Luxembourg with 12%, and Belgium, Israel and Croatia with 10%. Figure 3 shows the proportion of penicillin non-susceptible, divided into intermediate and full resistance per country and it shows that the highest proportions of fully resistant strains were found in Bulgaria (11%), Spain (11%), Israel (6%) and Luxembourg (6%).

**Resistance trends**

An overall rate of decrease in the proportion of single penicillin non-susceptibility, for the countries included in the regression model, was observed (−5.3% per year). A consistent increase in single erythromycin non-susceptibility was observed in all countries, except for the United Kingdom, which resulted in an overall rate of increase of 5.9% per year. An overall trend of increase with a rate of 7.6% per year was also observed for the proportion of isolates with dual non-susceptibility (Figure 4).

When analysed by country, we found that none of the countries showed a significant trend in the proportions of single penicillin non-susceptibility. However, countries with the lowest proportions of erythromycin and dual non-susceptibility in 1999 showed the highest rates of increase (Table 1). Finland is a good example of a country with one of the lowest overall proportions in 1999 and the fastest rates of increase for single erythromycin and dual non-susceptibility (Table 1 and Figure 5).
Extrapolating the regression model from 1999 to 2006, showed that overall (i) single penicillin non-susceptibility is predicted to decrease from 4.8% to 3.6%, (ii) single erythromycin non-susceptibility is predicted to increase from 14.6% to 20.4%, and (iii) dual non-susceptibility is predicted to increase from 5.4% to 8.9% (Figure 4).

**Discussion**

EARSS is an international network of national surveillance systems that has been collecting AST data of invasive *S. pneumoniae* isolates since 1999. The results are consistent with data from other antibiotic resistance surveillance projects, mutually corroborating the reliability of the data. The annual EQA exercises performed by the laboratories participating in EARSS, and the high adherence to the EARSS protocol requesting that penicillin resistance is confirmed by MIC method also provides reassurance that, overall, AST data are of good quality.

The highest proportions of penicillin non-susceptibility were demonstrated in southern European countries and exceeded 30% in France, Israel and Spain (Figure 1). Even though a large proportion of the PNSP isolates reported to EARSS (78%) are intermediate resistant, full penicillin resistance is not rare (>10%) in Bulgaria and Spain (Figure 3). Erythromycin resistance displays the same north–south gradient and has become more frequent (17%) than penicillin non-susceptibility (10%) in Europe overall (Figure 2). Indeed, a trend of increase in the proportion of resistance to erythromycin was observed from 1999 to 2002 for six of the seven European countries included in the regression model. The most pronounced rate of increase was observed among strains with dual non-susceptibility (7.6% per year), but strains with single erythromycin non-susceptibility also showed a considerable increase (5.9% per year).

Among the countries (included in the model), with the lowest proportions of resistance, we observed the highest rate of increase in single erythromycin and/or dual non-susceptibility. This indicates that low proportions of resistance now are no guarantee for low resistance proportions in the future. A considerably increase in single erythromycin and dual non-susceptibility was observed in Finland (Figure 5). This observation is in line with the reports from the national surveillance system FINRES, where an increase in erythromycin resistance in *S. pneumoniae* had already been observed from 1995 onwards.

Consistently, countries that reached a certain level of resistance showed smaller rates of increase than those that had low levels of baseline resistance. This might be explained by changed prescribing habits towards alternative agents in countries with high resistance levels.

Extrapolation from the regression model showed that by 2006 dual non-susceptibility and single erythromycin non-susceptibility overall may reach 8.9% and 20.4% respectively, for these seven countries. On the other hand, the rate of change for isolates with single penicillin non-susceptibility was ~5.3% per year, which would return the overall resistance proportion to 3.6% by 2006, indicating a shift from single penicillin non-susceptibility to co-resistance with erythromycin (Figure 4). Only time can tell whether these predictions will actually prevail, and might be influenced by the model assumptions that (i) the ecological forces (like antibiotic use) that drive resistance...
remain stable over time, and (ii) herd immunity and fitness cost do not impinge on the carrying capacity of resistant pneumococci in the population. However, one can hardly deny the increasing trend of reduced susceptibility from 1999 to 2002, which is destined to continue if no intervention measures are taken.

In this study the same approach was used as in a study performed by McCormick et al. in the United States, although our findings differed from theirs. In Europe the actual and predicted proportion of single erythromycin non-susceptibility was highest, whereas in the United States the actual and predicted proportion of dual non-susceptibility was most pronounced (15.5% in 1996 to 40.1% in 2004). Assuming that both studies generated valid and representative results, the differences may well be explained by distinct patterns of antibiotic use. In a study comparing Germany with the USA antibiotic overuse for doubtful indications such as colds, upper respiratory tract infections and acute bronchitis was much higher in the USA. In addition, the low-level dosage of oral β-lactam antibiotics may also have contributed to the higher base-line proportion of penicillin non-susceptibility in the USA (27% in 1999). The high resistance levels found in the USA are alarming. To prevent the increase in resistance in the range forecasted by our model, reconsideration of antibiotic policies should not be delayed.

The rise in erythromycin resistance might be the result of the increased prescription for children under the age of 5 years. Because resistance to erythromycin, unlike penicillin reduced susceptibility, tends to be solid and clinically relevant, it is more likely to lead to treatment failures and subsequent dissemination of resistant strains. Although generally considered a good alternative for β-lactam antibiotics, increasing numbers of clinical treatment failures have been reported for macrolides. Moreover, it has been shown that macrolides select for co-resistance more frequently than β-lactams. This would also explain the increasing proportions of dual non-susceptibility to erythromycin and penicillin in countries where macrolides are the favored paediatric treatment options. We conclude that prudent use of macrolides is especially important in situations where penicillin and erythromycin resistance is common.

Next to prudent antimicrobial use, the pneumococcal conjugate vaccine may be another effective tool for preventing infections caused by drug-resistant strains. Whether vaccine use will slow the expansion of resistant pneumococci, or whether resistant strains not covered by the vaccine will replace vaccine serotypes, remains to be seen. As indicated in the present study, the paediatric age group is a reservoir for antibiotic-resistant pneumococci and lends support to the decision to vaccinate this age group, most vulnerable to pneumococcal infections. In a recent US study it was found that the use of pneumococcal conjugate vaccine is preventing pneumococcal disease in young children. Moreover, besides preventing disease, vaccine-induced immunity also reduces the opportunity for transmission by preventing carriage, and subsequently may contain the spread of resistant strains.

The predictions from the regression model show that the increased proportion of erythromycin resistance in 2006, whether or not in combination with reduced susceptibility to penicillin, calls for timely intervention, and that appropriately dosed β-lactams should be the preferred empirical treatment. Vaccination, especially of young children, may offer an alternative in controlling antibiotic resistance in pneumococcal disease in Europe.

Acknowledgements

We gratefully thank all national representatives, data managers and the EARSS advisory board for contributing to the success of the network during the past 5 years. We are indebted to all EARSS participants for allowing us to use their data for the present study. The EARSS national representatives for 2002 were H. Mittermayer, W. Koller (Austria), H. Goossens, E. Hendrickx (Belgium), B. Markova (Bulgaria), S. Kalecnic, A. Tambic-Andracevic (Croatia), P. Urbaskova (Czech Republic), D. Monnet (Denmark), P. Naaber (Estonia), O. Lyytikäinen, A. Nissinen (Finland), H. Aubry-Damon, P. Courvalin (France), U. Buchholz, W. Witte (Germany), N. Legakis, G. Vatopoulos (Greece), M. Füzi (Hungary), K. Kristinsson (Iceland), D. O’Flanagan, O. Murphy (Ireland), R. Raz, H. Edelstein (Israel), G. Cornaglia, P. D’Ancona (Italy), R. Hemmer (Luxembourg), M. Borg (Malta), A. de Neeling, E. Tiemersma (The Netherlands), A. Hoiby, E. Bjørøw (Norway), W. Hryniewicz (Poland), M. Canica (Portugal), I. Codita (Romania), M. Gubina, J. Kolman (Slovenia), L. Langsadl (Slovakia), F. Bajquero, J. Campos (Spain), B. Liljequist (Sweden), A. Johnson, M. Wale (UK). We thank John Stelling for designing and maintaining the WHONET data-entering program, which is used by many EARSS participants. We thank Dr Nico Nagelkerke for his statistical advice. The EARSS is funded by the European Commission under SI2.324194 (2001CVG4-011) and the Dutch Ministry of Health, Welfare and Sports. This work was performed at the National Institute for Public Health and the Environment, Bilthoven, The Netherlands.

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