Global antibiotic resistance in *Streptococcus pneumoniae*  

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The last two decades of the 20th century were marked by an increasing resistance rate among several bacteria. Threat of resistance is present in *Staphylococcus* spp., *Enterococcus* spp., *Pseudomonas* spp. and Enterobacteriaceae, which are the major pathogens in nosocomial infections. In the community, too, increasing resistance can be observed and is attributed mainly (but not exclusively) to *Streptococcus pneumoniae* and *Haemophilus influenzae*. To scrutinize this trend, resistance surveillance in the community was established about 10 years ago. One of the multinational, longitudinal surveillance programmes in place is the Alexander Project, which was established in 1992 to monitor the susceptibility of the major community-acquired lower respiratory tract pathogens to a range of antibacterial drugs. The Alexander Project has revealed a tendency towards increasing resistance of *S. pneumoniae* to penicillin and macrolide therapy. Within Europe, the prevalence of penicillin resistance among *S. pneumoniae* isolates is particularly high in France and Spain. Macrolide resistance in *S. pneumoniae* is also a growing problem in European countries such as France, Spain, Belgium and Italy, where the extent of macrolide resistance in *S. pneumoniae* now exceeds that of penicillin resistance.

Introduction

The emergence and spread of microbial resistance is a true global threat, affecting both industrialized and developing countries. Overuse of antibiotics in industrialized countries has contributed to an acceleration of the problem, as has underuse of efficacious antimicrobial drugs in developing countries as a result of poverty and the consequent lack of effective healthcare.¹

Misdiagnosis and defensive and unnecessary prescribing, as well as a lack of education about bacterial resistance, are important factors in the emergence of resistance. Even in industrialized countries, bacterial resistance is usually given limited coverage during medical training. In developing countries, the shortage of dispensing pharmacists, or their less than optimal training, is an important factor, given that in this setting most patients purchase antimicrobial drugs without first consulting a health worker or receiving adequate information.¹

An increase in the availability of counterfeit antibiotics compounds the problem. Between 1992 and 1994, more than 50% of counterfeit drugs detected by the WHO had no active ingredient; more than 70% of these cases occurred in developing countries. Only 4% of counterfeit drugs contained the same quantity and quality of medication as the corresponding authentic agents.¹ One other important reason for the resistance problem is the use of antibiotics in food production.¹

Until recently, the global problem of resistance was related mainly to *Staphylococcus* spp., enterobacteria and *Pseudomonas aeruginosa*. However, a major challenge for the future is the worrying tendency towards increased bacterial resistance among *Streptococcus pneumoniae* and *Haemophilus influenzae*, the key pathogens in community-acquired bacterial infection of the upper and lower respiratory tract. Empirical treatment of community-acquired respiratory tract infection must take account of the increasing prevalence of resistance among these major respiratory tract pathogens.

Surveillance has been highlighted by the WHO as a key strategy to combat the problem of bacterial resistance. Surveillance programmes should involve well-defined patient groups and organisms, and key antibiotics. Such programmes should use standardized, internationally recognized methods that are subject to rigorous quality control.² Information from well-conducted surveillance can be used to guide policies on antibiotic use and to help to control the development and spread of resistance.

In the context of resistance surveillance, the 1997 data from the Alexander Project, a surveillance project that focuses on
respiratory tract infection, will be described in this paper. Alexander Project data for some European countries from 1998 are also included as appropriate. To illustrate the resistance problem, this article will be restricted to the increasing resistance in *S. pneumoniae*.

### The Alexander Project

Resistance among common respiratory tract bacteria affects the treatment of respiratory tract infection, as reflected by decreasing clinical response rates. In response to a need to monitor resistance patterns, the Alexander Project was established in 1992 in Europe and the USA to examine the susceptibilities to antibiotics of the major pathogens in community-acquired lower respiratory tract infection. In 1996 and 1997, the project was extended to include centres in five continents. The project is ongoing; isolates derived from more than 20 countries are now collected each year. Minimum inhibitory concentrations are determined for frequently used antibiotics, including penicillin, amoxicillin, co-amoxiclav, cefuroxime, erythromycin and co-trimoxazole.

Breakpoint concentrations used to interpret MIC data qualitatively are based on those published by the NCCLS. The criteria for collection of isolates, their transportation, storage and re-identification, and the methods used to conduct broth microdilution for susceptibility testing have been described previously. The quality of the data from the Alexander Project is maintained by internal quality-control procedures at each test centre, as well as external checks by a quality-assurance panel. Data from the Alexander Project and from other surveillance programmes are used to plot local and national trends in resistance over time. In this way, resistance surveillance programmes, and especially large-scale national surveys, provide valuable information on local patterns of resistance among respiratory tract pathogens. This information can be used by physicians as a basis for selection of appropriate antimicrobial therapy, which in turn will reduce the emergence of antibiotic resistance both locally and globally.

### Streptococcus pneumoniae

*Streptococcus pneumoniae* is one of the major pathogens of community-acquired respiratory tract infection. Findings from the Alexander Project have confirmed an increasing prevalence of penicillin and macrolide resistance among *S. pneumoniae* isolates, both worldwide and within Europe.

#### Penicillin resistance in *S. pneumoniae*

Previous reports from the Alexander Project have indicated that penicillin resistance in *S. pneumoniae* is increasing in many parts of the world. In 1996 and 1997, 10.4 and 14.1%, respectively, of *S. pneumoniae* isolates were classified as resistant to penicillin (MIC ≥ 2 mg/L). In 1996 and 1997, 10.4 and 14.1%, respectively, of *S. pneumoniae* isolates were classified as resistant to penicillin (MIC ≥ 2 mg/L). In 1997, 14.1% of isolates in the USA (18.6%) (Figure 1). In Western Europe, the overall level of penicillin resistance in 1997 was 13.4%. (This figure excludes the Netherlands and Austria, for which data were not available.) There was, however, marked variability in the

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**Figure 1.** Global data from the Alexander Project (1997) for resistance to penicillin in *S. pneumoniae*. First values, intermediate isolates (MIC 0.12–1 mg/L); second values, resistant isolates (MIC ≥2 mg/L). Data for Eastern Europe were collected from the Czech Republic, Slovakia, Hungary (only 1996 data available) and Poland. No Scandinavian countries were included in Western Europe.
extent of resistance between different countries (Figure 2). Penicillin resistance was a particular problem in France and Spain, with 29.3 and 34.8% of \( S. pneumoniae \) isolates, respectively, found to be resistant. In the UK, the level of penicillin resistance was low but has been increasing. In 1996, 4.5% of isolates were classified as resistant, whereas in 1997, 6.3% of isolates were resistant (Figure 2). Data from 1998, however, reveal 14.9% of isolates to be resistant. In Italy and Germany, the level of penicillin resistance has remained consistently low (Figure 2). Similarly, countries such as the Netherlands, the Czech Republic and Austria are only marginally affected.

**Macrolide resistance in \( S. pneumoniae \).** Macrolides are generally regarded as the main alternative to \( \beta \)-lactam treatment of respiratory tract infection involving \( S. pneumoniae \). Data from the Alexander Project, however, indicate that macrolide resistance in \( S. pneumoniae \) is increasing. In some regions, the prevalence of erythromycin-resistant \( S. pneumoniae \) is two to five times higher than that of penicillin-resistant strains. In 1997, 21.9% of \( S. pneumoniae \) isolates were resistant to macrolides compared with 14.1% of isolates that were resistant to penicillin. Countries with high levels of penicillin resistance also tend to have correspondingly high levels of macrolide resistance. For example, in 1997, 77.8% of \( S. pneumoniae \) isolates in Hong Kong were resistant to macrolides (Figure 3).

Within Europe, there is cause for concern in France, Spain, Belgium and Italy, with macrolide resistance levels in 1997 of 45.9, 32.6, 31.1 and 29.8%, respectively (Figure 4). Data from 1998 for France, Belgium and Italy show a further increase, particularly in the case of Italy, with 42% resistance. Italy is perhaps unique among these countries, with high macrolide resistance but a low level of penicillin resistance (only 3.0% in 1998). It has been suggested that the increase in macrolide resistance in these countries may be attributable partly to increased prescribing of long-acting macrolides.

**Discussion**

Resistance surveillance programmes are necessary to monitor the susceptibility of bacteria to commonly used antibiotics. With continuous monitoring, physicians can be kept up to date about the development of resistance. Such information is important to assist them in their choice of appropriate antibiotics.

The value of global resistance surveillance programmes is to some extent limited. Whereas such programmes provide an overall estimation of bacterial resistance related to the different situations from country to country and continent to continent, quantitative analysis of the data depends not only on the variability of the resistance behaviour of the pathogens, but also on, amongst others, variations between the number of centres involved, their distribution nationally and numbers.
of strains tested. In particular, there is a degree of risk of over-
or underestimation of some local (national) results.

It is therefore necessary to conduct not only global but also national surveillance programmes, involving well-distributed local centres and sufficient numbers of pathogens; accurate national surveillance will provide physicians with reliable data for their own countries.

Figure 3. Global data from the Alexander Project (1997) for resistance to macrolides in all isolates of *S. pneumoniae*. Resistance is taken as erythromycin MIC \( \geq 0.5 \text{ mg/L} \). Data for Eastern Europe were collected from the Czech Republic, Slovakia, Hungary (only 1996 data available) and Poland. No Scandinavian countries were included in Western Europe.

Figure 4. European data from the Alexander Project (1997) for resistance to macrolides in all isolates of *S. pneumoniae*. Resistance is taken as erythromycin MIC \( \geq 0.5 \text{ mg/L} \).

References


Global resistance rates—*Streptococcus pneumoniae*


