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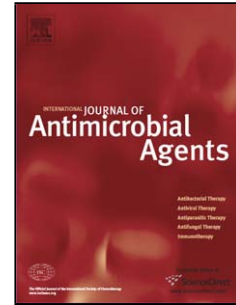
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Antimicrobial resistance of *Streptococcus pneumoniae* in Southeast Austria, 1997–2008 [☆]

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ABSTRACT

Antibiotic resistance in *Streptococcus pneumoniae* has increased worldwide but varies within geographical regions. We conducted a retrospective analysis of resistance in *S. pneumoniae* over a 12-year period to assess local and temporal trends in antibacterial resistance. From 1997 to 2008, a total of 1814 non-duplicate *S. pneumoniae* isolates were identified at the Institute of Hygiene, Microbiology and Environmental Medicine, Medical University of Graz, Austria. Antibiotic resistance was determined by the Clinical and Laboratory Standards Institute (CLSI) disk diffusion test. For penicillin, the minimum inhibitory concentration was determined by Etest. Susceptibility was defined according to CLSI interpretive criteria. For penicillin, resistance rates were consistently low at 0.2% over the 12-year study period. An increase in resistance was remarkable for erythromycin (3.5% in 1997; 14.7% in 2008), clindamycin (1.8% in 1997; 10.6% in 2008) and tetracycline (1.8% in 2000; 11.0% in 2008). For trimethoprim/sulfamethoxazole, resistance increased slightly to 9.2% in 2008. Quinolones showed a low resistance rate of 0.2% that persisted over the whole study period. In contrast to previously published national data, resistance to penicillin was observed to remain at a remarkably low and constant level. Although international surveillance programmes have set up sustainable and interlinked data networks, our results suggest that regional surveillance may still be needed as decision support for appropriate empirical antibiotic therapy in the local health setting.

1. Introduction

Streptococcus pneumoniae continues to be a significant cause of morbidity and mortality in humans [1]. It is a common causative organism of respiratory tract infections, including acute otitis media, acute bacterial sinusitis and community-acquired pneumonia [2,3]. Early initiation of appropriate empirical antibiotic therapy is decisive for the outcome of pneumococcal infection, with antibiotic regimens primarily consisting of penicillin, macrolides and quinolones [4]. The challenge of choosing an effective empirical antibiotic therapy has recently been complicated by two developments. First, rates of resistance to antibiotics widely used for the therapy of pneumococcal infections have increased significantly in recent years [2,5,6]. Second, rates of resistance vary not only between continents but also between European countries, as shown by the European Antimicrobial Resistance Surveillance System (EARSS). In particular, resistance to penicillin and erythromycin has spread rapidly but varies within European countries from 1–39% and 1–25%, respectively [2].

The aim of this study was to assess whether regional resistance patterns from Southeast Austria reflect the national patterns reported previously and to what extent resistance varies within national borders. In this study, we present results of antibiotic susceptibility testing for pneumococci over a 12-year period in Southeast Austria and link the results to national and international resistance reports.

2. Patients and methods

2.1. Patients and bacterial isolates

From 1997 to 2008, 1814 non-duplicate isolates of *S. pneumoniae* were identified at the Institute of Hygiene, Microbiology and Environmental Hygiene, Medical University of Graz, Austria. Numbers of *S. pneumoniae* isolates per year are shown in Table 1. There were 943 male patients (52%) and 871 female patients (48%). Patient age ranged from <1 year to >90 years. Of the 1814 *S. pneumoniae*, 892 (49.2%) were isolated in children under 10 years of age. Sources of the obtained isolates included the upper respiratory tract (1409; 77.7%), lower respiratory tract (257, 14.2%) and others (148; 8.2%). Moreover, 1150 (63.4%) of the *S. pneumoniae* isolates were obtained from outpatients and 664 (36.6%) were from hospitalised patients.

2.2. Identification and antimicrobial susceptibility testing

Identification of *S. pneumoniae* was based on susceptibility to optochin, bile solubility, API 20 Strep test (bioMérieux Vitek, Inc., Hazelwood, MO) or the GPC card on the VITEK II instrument (bioMérieux, Marcy l'Etoile, France) [7,8]. Susceptibility testing was performed by disk diffusion. Resistance was determined according to relevant testing conditions and the new susceptibility interpretation standards proposed by the Clinical and Laboratory Standards Institute [9]. Minimum inhibitory concentrations (MICs) for penicillin were determined by the Etest method (AB BIODISK, Solna, Sweden). Macrolide resistance phenotypes were determined by the double-disk method [10].

Isolates that were non-susceptible to penicillin and to two or more other antibiotics from erythromycin, tetracycline, trimethoprim/sulfamethoxazole (SXT) and quinolones were

classified as multidrug-resistant pneumococci (MDRP). Following identification, all *S. pneumoniae* isolates were stored at $-70\text{ }^{\circ}\text{C}$.

3. Results

3.1. Penicillin resistance

Streptococcus pneumoniae isolates with resistance to penicillin were found only sporadically and did not increase over the study period; 3/1814 isolates (0.2%) showed resistance and 46 (2.5%) showed intermediate susceptibility to penicillin. The distribution of MIC values as well as MIC values for 50% and 90% of the organisms (MIC₅₀ and MIC₉₀, respectively) are shown in Table 2.

3.2. Erythromycin resistance

Resistance to erythromycin was found to have increased steadily from 3.5% in 1997 to 14.7% in 2008. The overall resistance rate was 9.3% (169/1814 isolates). Resistance rates to clindamycin increased from 1.8% in 1997, reaching 10.6% in 2008. The M-phenotype was found in 45% (76/169) and the MLS_B phenotype in 55% (93/169) of the erythromycin-resistant isolates (Table 1). An increase in the MLS_B phenotype compared with the M-phenotype was noted over the study period.

3.3. Susceptibility to other antibiotics

Tetracycline resistance increased steadily over the study period. Whereas 1.8% of *S. pneumoniae* isolates showed resistance to tetracycline in 1997, the rate increased to

11.0% in 2008. For SXT, resistance rates increased from 7.1% in 1997 to 9.2% of *S. pneumoniae* isolates in 2008 (Table 1).

Rates of resistance to quinolones (represented by ciprofloxacin and moxifloxacin) remained very low, with no more than one *S. pneumoniae* isolate per year being resistant (4/1814; 0.2%) (Table 1).

3.4. Multidrug-resistant pneumococci

MDRP were found in 36/1814 (2.0%) of *S. pneumoniae* isolates (0.9% in 1997, 0.7% in 1998, 3.5% in 1999, 1.8% in 2000, 0% in 2001, 1.7% in 2002, 3.3% in 2003, 2.8% in 2004, 0% in 2005, 1% in 2006, 5.7% in 2007 and 2.8% in 2008).

4. Discussion

The antibiotic susceptibility of *S. pneumoniae* over a 12-year period was assessed and very low rates of penicillin resistance were found, whereas resistance to other antibiotic classes developed in accordance with national and international trends.

Since the first description of an *S. pneumoniae* strain with reduced susceptibility to penicillin in 1967, resistance to penicillin among pneumococci has increased and spread worldwide. The steady increase of penicillin-resistant clones in the last two decades has been associated with the extensive use of penicillin for infections caused by pneumococci [2].

High rates of penicillin-resistant pneumococcal isolates were reported from the USA (21%), Mexico, Brazil, South Africa, Japan and South Korea [12–14]. Within European countries, the frequency of penicillin-resistant pneumococcal isolates varies widely. Resistance rates of >15% were found in Turkey, Bulgaria and Romania and rates of 5–10% in Spain, Ireland, Croatia and France, whilst resistance rates of <1% were found in most northern European countries, Germany and the Czech Republic [2]. In several countries (including Turkey, Hungary, Croatia and Ireland), penicillin resistance has increased dramatically over recent years [2,15,16]. Overall, an increase in penicillin resistance from 5.7% in 2007 to 6.3% in 2008 was reported in invasive isolates in Europe [16].

For the northern part of Austria, Buxbaum et al. [17] found a slight increase in penicillin-resistant pneumococcal isolates from 2% in 1996 to 2.2% in 2002. For invasive *S. pneumoniae* isolates, an overall 6-year resistance rate of 0.9%, reaching 1.6% in 2007, was reported from Austria [16,18]. However, we found constant 5- to 12-fold lower rates of penicillin-resistant *S. pneumoniae* isolates in Southeast Austria (0.17% over the 12-year study period and no resistant isolate since 2006).

These data may indicate the importance of regional surveillance in addition to international surveillance programmes such as EARSS as decision support for appropriate empirical antibiotic therapy in the local health setting. However, two possible limitations must be considered when comparing these data with previously published Austrian data. First, different inclusion criteria may have influenced divergent results compared with the study of Buxbaum et al. [17]. Whilst patients below 18 years of age were excluded in their study, this group of patients accounted for the majority of patients in the current study. Second,

inclusion of all detected non-duplicate *S. pneumoniae* isolates in this study and not only of invasive isolates may have strengthened results differing from EARSS data for Austria. However, the low rate of penicillin resistance in our study would then be contrary to results by García-Suárez et al. [19] and Lambertsen et al. [20] who both showed that resistance rates in non-invasive isolates were higher than resistance rates in invasive *S. pneumoniae* isolates.

Spread of penicillin-resistant pneumococci has led to more extensive use of macrolides for infections caused by *S. pneumoniae* [21]. However, increasing use of macrolides has been associated with an increase in pneumococcal resistance to these agents, and macrolide-resistant *S. pneumoniae* are now more common than penicillin-resistant *S. pneumoniae* in many parts of the world [21].

High rates of erythromycin-resistant pneumococci were found in Asian countries (e.g. 80% in Japan and Korea), South Africa (52%) and the USA (35%) [12–14]. Erythromycin resistance rates between 10% and 25% were reported from most European countries. Highest resistance rates were reported from France (31%), Hungary (31%), Turkey (27%) and Italy (25%); resistance rates <5% were only observed in the Czech Republic, Bulgaria and Baltic countries [15,16]. A remarkable increase in resistance to erythromycin over the last years was observed in several European countries (Finland from 6% in 1999 to 24% in 2008, and Turkey from 7% in 2003 to 27% in 2008) [2,15,16]. An overall European resistance rate of 16.4% was reported in invasive isolates in 2008 [16].

As published previously, resistance of *S. pneumoniae* to erythromycin in Austria increased from 3.2% in 1996 to 12.8% in 2007 and 9.8% in 2008 [16–18]. In our study, rates of

erythromycin-resistant *S. pneumoniae* isolates increased in accordance with national and international trends from 3.5% in 1997 to 18.2% in 2004 and 14.7% in 2008. Over the study period, 9.3% of *S. pneumoniae* isolates from Southeast Austria were found to be resistant to erythromycin.

Erythromycin-resistant pneumococci often show co-resistance to tetracycline. More than 60% of isolates in the USA and more than 80% in Spain and Italy showed this resistance pattern [22–24]. In Europe, resistance rates for tetracycline vary between 1% (Denmark) and 41% (France) [25]. In Austria, 8.5% of pneumococci were reported to be resistant to tetracycline in 1996 [26]. We found increasing resistance rates to tetracycline, ranging from 1.8% in 1997 to 11% in 2008.

For SXT, reported resistance ranges from 7% in Denmark to 48% in Poland [25]. In this study we found varying rates of resistance to SXT, from 7.1% in 1997 to 9.2% in 2008.

During the last decade, a worldwide increase of resistance to quinolones in *S. pneumoniae* has been reported. Notable resistance rates were observed in Hong Kong (14.3%), South Korea (2.9%) and the USA (1.8%) [27,28]. In Canada, the rate of ciprofloxacin resistance in *S. pneumoniae* increased from <1% in 1997 to 4.2% in 2005 [29]. In a study by Reinert et al. [30] assessing *S. pneumoniae* isolates from eight European countries, resistance to quinolones ranged from 0% (Austria) to 1.3% (Italy). For Ireland, resistance rates have reached 15.2%, as reported by Goldsmith et al. [31]. Quinolone resistance is observed almost exclusively among isolates from adults [28,32]. In our study, where most isolates were derived from children, the percentage of resistance against quinolones remained low (0.2%), with no more than one *S. pneumoniae* isolate per year being resistant.

In conclusion, the presented data cover resistance in pneumococci over a 12-year period in Southeast Austria. International surveillance programmes for antibiotic resistance have set up sustainable and interlinked data networks [5]. However, owing to varying resistance rates even within national borders, as we have shown for penicillin resistance in *S. pneumoniae*, regional surveillance is still needed as decision support for appropriate empirical antibiotic therapy in the local health setting.

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Competing interests

None declared.

Ethical approval

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Table 1

Percentage resistance to erythromycin, clindamycin, tetracycline, trimethoprim/sulfamethoxazole (SXT) and quinolones in 1814

Streptococcus pneumoniae isolates collected in 1997–2008 in Southeast Austria

Year	No. of isolates	% resistant				
		Erythromycin	Clindamycin	Tetracycline	SXT	Quinolones
1997	113	3.5	1.8	1.8	7.1	0.9
1998	140	2.1	0	0.7	1.4	0.0
1999	115	3.5	0.9	0.0	2.6	0.0
2000	110	5.4	1.8	4.5	2.7	0.0
2001	203	6.4	2.9	3.4	3.5	0.5
2002	179	9.5	5.6	7.9	7.8	0.0
2003	122	10.6	7.4	7.3	6.5	0.0
2004	143	18.2	6.3	9.8	14.5	0.0
2005	166	7.8	5.4	6.6	9.0	0.0
2006	148	12.2	5.4	8.8	9.5	0.7
2007	157	13.4	8.9	8.9	7.3	0.0
2008	218	14.7	10.6	11.0	9.2	0.5

Table 2

Distribution of minimum inhibitory concentrations (MICs) as well as MIC₅₀ and MIC₉₀ values and percent susceptibility for penicillin in 1814 *Streptococcus pneumoniae* collected in 1997–2008 in Southeast Austria

Standard	n	No. of isolates inhibited at MIC (mg/L):												MIC (mg/L)		% susceptibility	
		<0.016	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	>4	MIC ₅₀	MIC ₉₀	%I	%R	
Former ^a	1814	1419	242	60	25	27	26	7	4	3	1	0	<0.016	0.016	3.5	0.22	
New ^b															2.5	0.17	
Meningitis, i.v.	25	17	7				1						<0.016	0.016	–	4.0	
Non-meningitis, i.v.	505	386	69	21	9	6	8	2	2	1	1		<0.016	0.016	0.2	0	
Non-meningitis, oral	1284	1016	166	39	16	21	17	5	2	2			<0.016	0.016	3.5	0.2	

MIC_{50/90}, MIC of an antimicrobial agent inhibiting 50% or 90% of isolates, respectively; I, intermediate susceptible; R, resistant; i.v., intravenous.

^a Resistance defined as an MIC \geq 2 mg/L and intermediate susceptibility as an MIC of 0.125–1.0 mg/L [11].

^b Resistance defined according to Clinical and Laboratory Standards Institute (CLSI) 2008 guidelines [9]. Meningitis and i.v.

penicillin: resistance MIC \geq 0.125 mg/L, no intermediate susceptibility; non-meningitis and i.v. penicillin: resistance MIC \geq 8 mg/L

and intermediate susceptibility MIC = 4 mg/L; non-meningitis and oral penicillin: resistance MIC \geq 2 mg/L, intermediate susceptibility

MIC = 0.125–1.0 mg/L.