
Is antimicrobial resistance also subject to globalization?

G. C. Schito

Istituto di Microbiologia, Università di Genova, Genoa, Italy

In recent years one of the more alarming aspects of clinical microbiology has been the dramatic increase in the incidence of resistance to antibacterial agents among pathogens causing nosocomial as well as community-acquired infections. There are profound geographic differences in the incidence of resistance among pathogens of the respiratory tract, only some of which can be explained by the local use of antibiotics. A high percentage of *Moraxella catarrhalis* strains produce β -lactamase and are thus resistant to many β -lactam antibiotics. In contrast, β -lactamase production among strains of *Haemophilus influenzae* rarely reaches more than 30% around the world. Methicillin-resistance in *Staphylococcus aureus* is a common and increasing problem in hospitals but its extent varies both locally and nationally. Resistance is usually associated with the local spread of resistant strains. High standards of hygiene in hospitals can prevent the spread of such strains but once established they can be difficult to eradicate. Although *Streptococcus pyogenes* remains highly susceptible to penicillins, even after many decades of their use, resistance to macrolides has occurred. This resistance can rise and fall. Although the increase of macrolide resistance in *S. pyogenes* can often be associated with an increase in the use of these drugs, this is not always so. In some cases it has been shown to be caused by the spread of one or more resistant clones. Eradication of these clones can reduce the level of resistance markedly. Resistance to both macrolides and penicillins among strains of *Streptococcus pneumoniae* is seen world-wide but is highly variable from country to country. Local habits of drug usage may play a part. In Italy, for example, there is preference for the use of parenteral third-generation cephalosporins for some severe infections and there is a corresponding low level of penicillin-resistance among pneumococci.

INTRODUCTION

In recent years one of the more alarming aspects of clinical microbiology has been the dramatic increase in the incidence of antibacterial resistance among pathogens causing nosocomial as well as community-acquired infections. This increase in resistance is now a global problem, with no country remaining immune to its impact. All major bacterial pathogens have now acquired resistance to at least one drug and in some cases, they have become resistant to many drugs.

The situation regarding some important pathogens is discussed in this article. It will be noted that there is no uniform picture, in one country

resistance may be high in a particular pathogen to a particular drug, but not in that pathogen to another drug and not to that drug in all pathogens. The reasons for these variations are often not evident.

RESISTANCE VARIES GLOBALLY

Resistance to antimicrobial drugs is known to vary profoundly, depending on the geographic location, the pathogen and the drug. An additional contributing factor may be local variations in the use of antibacterial agents. A number of common community-acquired infections are caused by pathogens that are now frequently resistant to one or more antibacterial agents. These include the respiratory tract pathogens *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae*, as well as organisms causing a variety of other infections, such as *Escherichia coli*, *Neisseria gonorrhoeae*, *Salmonella* spp., *Staphylococcus aureus*

Corresponding author and reprint requests: Gian Carlo Schito, Istituto di Microbiologia, Università di Genova, Genoa, Italy

Tel: +39 01050 21 36

Fax: +39 01050 48 37

E-mail: schitogc@aleph.it

and *Mycobacterium tuberculosis*. Some pathogens are more commonly associated with hospital-acquired infections and many of these have also acquired resistance to one or more drugs. The species most commonly associated with resistance include *S. pneumoniae*, *S. aureus*, strains of *Pseudomonas*, *Enterococcus* and a wide range of enterobacteria.

Two species with a particularly high rate of resistance globally are *S. aureus* and *Moraxella catarrhalis*. Resistance to penicillin among strains of *S. aureus* has reached over 85% world-wide (see below) and over 90% of *M. catarrhalis* strains are resistant to all aminopenicillins. In contrast to these pathogens, β -lactamase production in strains of *H. influenzae* is spreading relatively slowly and it is rare to find more than 30% of strains resistant to the aminopenicillins [1]. Local differences can be identified, with a sharp increase in resistance to amoxicillin occurring in Italy, up from 5% in 1997 to 16% in 1999. Of note is the lack of resistance in *H. influenzae* to the other major groups of widely used β -lactam antibiotics, for example the third-generation cephalosporins, which do not have a recognized breakpoint for resistance (Figure 1).

It is interesting to speculate on the forces influencing these patterns of resistance. A factor influencing the high resistance among staphylococci and *Moraxella* could be the constant and ubiquitous selective pressure of the commonly used penicillins, but both *Haemophilus* and *S. pyogenes*

have been exposed to penicillins for many years without a uniform development of resistance. Invasive genetic elements may be a partial explanation.

STREPTOCOCCUS PYOGENES

The situation with *S. pyogenes* varies considerably, with resistance frequently being reported to macrolides but not to β -lactams. Despite the prolonged use of penicillins and other β -lactams over several decades, *S. pyogenes* remains highly susceptible to this class of antibiotics world-wide. In sharp contrast to this, resistance to macrolides is common but variable. In most countries it remains below 5% but major outbreaks of resistance to macrolides have occurred in some countries; often this can be linked to the spread of a particular clone or to high usage of macrolides.

Resistance to macrolides in *S. pyogenes* was first reported from the UK as long ago as 1959 and subsequently from many other countries. In some countries, high rates of resistance have been reported, including Australia, Finland, Sweden, Taiwan, Japan and Italy. The emergence of resistance can be surprisingly rapid [2,3].

Mechanisms of resistance to macrolides

There are two major mechanisms by which *S. pyogenes* develop resistance to macrolides and they result in three phenotypes [4]. In two of the

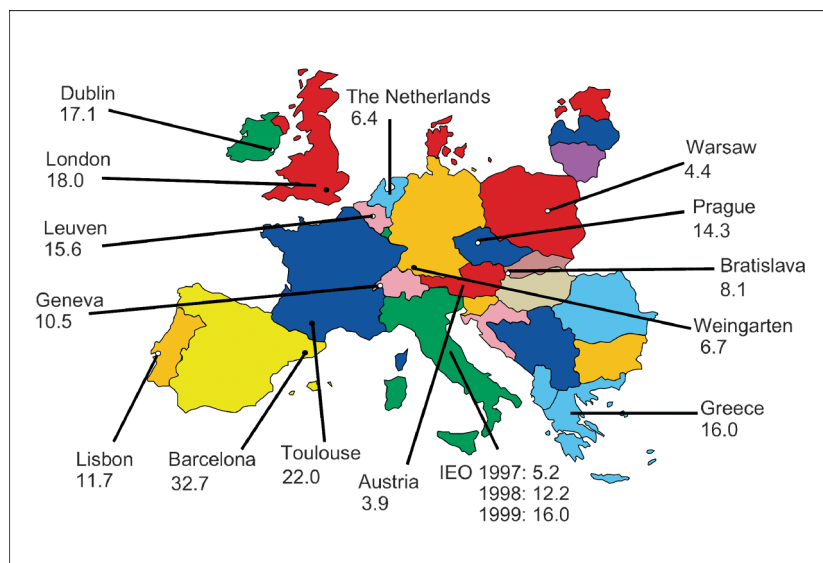


Figure 1 Prevalence of β -lactamase-producing strains of *Haemophilus influenzae*. Data adapted from Schito et al. [1] (Alexander Project 1998).

phenotypes the target site is modified and in the other phenotype the antibiotic is pumped out of the bacterial cell (efflux mechanism). The site of action of macrolides is on the ribosome, and if this is methylated the conformation is changed, leading to a reduction in binding of the antibiotic, which is thus rendered ineffective. This target alteration can be either a constitutive or an inducible characteristic. Strains with constitutive target modifications have high-level resistance to all macrolides and to the related lincosamides (including clindamycin) and streptogramin B (MLS_B compounds) and this is termed MLS_B resistance. If the resistance is inducible, then these strains are only resistant to the 14- and 15-membered ring macrolides and are still susceptible to other MLS compounds (including 16-membered ring macrolides and clindamycin). The resistance in these inducible phenotypes is more variable than with the constitutive phenotype. An alternative mechanism of resistance, an efflux pump, was first recognized by Seppala et al. [4]. The efflux mechanism is mediated by a *mef* gene and such strains (M phenotype) only have moderate resistance to 14- and 15-membered ring macrolides.

The fluctuations in resistance to macrolides in *S. pyogenes*

The fluctuations in the resistance to macrolides in *S. pyogenes* are a feature not seen with other species/drug combinations. In some cases this can be associated with a rise or a reduction in the consumption of macrolides, but this relationship is not always evident. There are several instances where an increase can be associated with the spread of a serotype or clone, often also enhanced by an increase in the use of macrolides.

In Japan, where macrolides were prescribed very heavily, resistance was unknown prior to 1970. During the next few years the increase was dramatic, the first isolates (8.5%) being reported in 1971 and the level rising to 20% in 1972. By 1974–5 the level of resistance had risen to 72.3% [5]. It was estimated in 1976 that nearly 160 tons of macrolides, including 50 tons of erythromycin, were used in Japan [6]. In a study published in 1979 [5], isolates were obtained from children and all were serotyped. There were 10 different serotypes among these isolates, five of which were resistant to various antibiotics, but all of the erythromycin-resistant isolates were of a single serotype; T12.

These strains were also resistant to lincomycin, tetracycline and chloramphenicol [5].

The authors of this study [5] commented that 'Erythromycin and other macrolides can no longer be considered as drug of choice in the management of streptococcal infections in Japan'. They suggested that regular surveillance should be carried out, however, there was no official intervention to reduce the use of macrolides and no reports are available on their consumption. Nevertheless, by the early 1980s resistance had fallen to 22% [7] and is currently below 5%. In this instance, the resistance, although influenced by the heavy use of the drugs, was clearly linked to the spread of a particular serotype.

A similar situation occurred in 1993 in Taiwan where a survey revealed a high incidence of resistance among isolates of *S. pyogenes* to erythromycin and azithromycin but not to β -lactams, vancomycin, or ofloxacin [8]. A total of 78 isolates were collected over a 2-year period, tested for susceptibility to a number of antibiotics and serotyped. The precise numbers of susceptible and resistant strains are not stated but erythromycin had poor activity, with a minimum 50% inhibitory concentration (MIC₅₀) of 16 mg/L and an MIC₉₀ of >128 mg/L. Clindamycin was also inactive against some of these strains, with an MIC₉₀ of >32 mg/L, indicating the presence of the constitutive MLS_B phenotype. There were 22 serotypes, with T12 being the most common (33 isolates); the next most common was T1 (nine isolates). All the resistant isolates belonged to these two serotypes, T1 or T12, with the majority of isolates from the throat being serotype T12 (21/24). The isolates of the T12 serotype were almost all (28/33) highly resistant to erythromycin (MIC >128 mg/L). Two of the isolates of the T1 serotype had lower resistance to erythromycin (MIC 32 mg/L).

A link is suggested by the authors between this high rate of resistance and the consumption of erythromycin in Taiwan, where apparently it is used commonly in primary-care clinics and is available over the counter. It is also used commonly in hospitals for the treatment of upper respiratory tract infections.

In Finland in the early 1990s macrolide resistance was found to be widespread but there was a marked variation in the incidence of resistance among the various health authorities, ranging from 2 to 44% [9]. Overall the levels of resistance

in *S. pyogenes* isolates from throat swabs showed a marked increase from 4% in 1989 to 13% in 1990. A highly significant association was found between the consumption of macrolides and the accompanying level of resistance to them in *S. pyogenes* in most health authority areas, but there were a few exceptions. Following this study, a deliberate program of intervention was undertaken [10]. Macrolide usage reduced from 2.40 to 1.38 defined daily doses per 1000 inhabitants per day between 1991 and 1992. The usage remained at approximately this level for the next 3 years and a concomitant reduction in the level of resistance was seen from a peak of 19% in 1993 to 8.6% in 1996.

Italy is another country where resistance to macrolides has risen markedly in the last decade. Until 1993, local rates of resistance to erythromycin were between 5 and 8% but from 1995 onwards various reports indicated a sharp rise in the incidence of resistance, which reached over 30% in some studies [2]. This is in contrast to the low rates of resistance to penicillins and macrolides seen in *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* in Italy.

Even in countries where the rate of resistance is not exceptionally high, clonal spread and/or an association with increased use has been reported. In Sweden, for example, 21 of 355 (5.9%) *S. pyogenes* isolates were resistant to erythromycin and 17 of these were found to be of the T12 protein type. The spread of these was noted within two families and a day-care center [11]. In contrast, in France, macrolide use has remained fairly constant for the last two decades and the level of resistance is low, a recent survey finding only 6.8% of strains to be resistant [12].

A survey of *S. pyogenes* isolates from adults and children in Madrid, Spain, showed a dramatic increase in resistance to macrolides from 2% in 1993 to 22.4% in 1996 [13]. Over 1300 isolates were collected over a 3-year period in Madrid and the overall level of resistance to erythromycin was 14.3%. Resistant strains were more frequently isolated from children (144/872) than from adults (44/434), a finding also noted by Seppala et al. [9]. A high proportion of the resistant isolates (>90%) were of the M phenotype and those examined carried the *mefA* gene. Clindamycin resistance was rare, occurring in only 18 strains, but tetracycline resistance was more common (8.5%). The authors also noted that the MIC of ofloxacin was 4 mg/L against 36 strains (2.7%).

Thus for macrolides and *S. pyogenes* a situation exists where in some cases the increase in resistance to macrolides can be linked to the spread of a small number of clones, whereas in others an association can be seen between increased consumption of macrolides and a rise in resistance. Such a simple explanation is not, however, always evident and in some cases it is not clear why resistance increases and may subsequently decline.

STAPHYLOCOCCUS AUREUS—THE PROBLEM OF MRSA

β -Lactamase production in *S. aureus* was evident within a few years of the introduction of the first penicillins, but it was some years before strains emerged with resistance to the new β -lactamase-stable penicillins (methicillin, cloxacillin, oxacillin). These methicillin-resistant *S. aureus* (MRSA) strains have spread to many countries but estimating their incidence is difficult since it varies markedly even within a country and can fluctuate from time to time [14]. A major study of European hospitals carried out between 1997 and 1999 reported varying levels of resistance from three different areas in Spain, ranging from 9 to 34% [15]. Results from four areas in France also reported varying levels of resistance (from 12 to 25%). Notwithstanding these problems, it is evident that the occurrence of MRSA is relatively low (less than 10%) in a number of countries, including Canada, Denmark, Finland, The Netherlands, Switzerland and Sweden [15–18]. In contrast, the rate of MRSA is higher (between 20 and 40% of hospital strains) in many other countries, including Belgium, France, Italy, Portugal, Spain, UK and USA [15,19,20]. In the Far East there are reports of an incidence as high as between 60 and 80% in Taiwan [21] and in India [22].

Resistance to methicillin is often accompanied by resistance to other antimicrobials; these can include aminoglycosides, macrolides, tetracyclines, cephalosporins, carbapenems, β -lactamase-inhibitor combinations, trimethoprim and sulfonamides [14].

The spread of MRSA strains

Methicillin-resistance is an acquired drug-resistance mechanism determined by the *mecA* gene. This gene is not believed to be native to *S. aureus*

but was probably acquired in the 1960s and has now become integrated into the staphylococcal DNA where it has diversified [23]. The *mecA* gene codes for the production of penicillin-binding protein 2a, which is altered in MRSA strains. A notable feature of MRSA is the presence of epidemic strains which have the ability to colonize and spread rapidly and are often the cause of major outbreaks. These strains are frequently multi-resistant, in contrast to non-epidemic or endemic strains most of which have a narrower spectrum of resistance and less ability to disseminate [17].

Many large hospitals, nursing homes and chronic-care facilities in a number of countries have a significant problem with MRSA, which is now endemic. Epidemic clones can disseminate rapidly and may even be transmitted across countries. Roman et al. [24] investigated an outbreak of MRSA in a tertiary-care teaching center in Canada and found that the outbreak was caused by a single strain. It was subsequently found that this strain was introduced into Canada by a patient from India and was then transmitted to two large hospitals within 6 weeks of the patient's entry into Canada. Similarly, an epidemic strain (type 1) was found to be widespread in Belgium and in various European countries. This strain was originally found in France and Belgium in the 1980s and has also been found in Germany and The Netherlands. Outbreaks in Dutch hospitals could be traced to patients from France carrying the strain [19].

Frequently a small number of epidemic MRSA strains accounts for the majority of isolates in a country, indicating the ability of these strains to spread and colonize. In the Belgian study [19] the epidemic strain type 1 accounted for 82% of the Belgian isolates and 51% of European isolates. In Taiwan, where the occurrence of MRSA is extremely high, over 50% of isolates were type C. The remaining isolates were of a range of other types [21]. In Canada, where the incidence of MRSA has increased between 1995 and 1999, 81% of the MRSA isolates belonged to one of four types [18].

Control of MRSA

Outbreaks of MRSA are difficult to control, especially those caused by epidemic strains, but as they can have significant morbidity and mortality, it is important that they are controlled or prevented.

Epidemic strains may be resistant to a wide range of antibacterial agents, with vancomycin often being the only antibiotic available to treat infections. Strict hospital hygiene is required to control such outbreaks as routine measures may have little impact. Rampling et al. [25] describe how normal hygiene, which included isolation of the affected patients, good hand hygiene to prevent person-to-person transmission and staggered closure and cleaning of the ward bays, was unable to prevent an epidemic strain (type 16) from infecting more patients and persisting in the hospital environment. The cleaning procedure was then changed to include increasing the domestic cleaning time dramatically and allocating responsibility for the routine cleaning of shared medical equipment. This intervention was successful in controlling the outbreak, removing it from the environment and reducing the numbers of patients colonized to only three [25].

The incidence of MRSA in Denmark and Sweden is particularly low and this is no doubt influenced by the strict control measures taken in hospitals in those countries, which prevent these strains becoming established. In Italy, however, control measures are generally insufficient and the incidence of MRSA is high (34.4%).

STREPTOCOCCUS PNEUMONIAE

The pneumococcus is the most common cause of community-acquired pneumonia and can also cause meningitis. Drug-resistant strains, many of them resistant to a range of antimicrobials, have spread world-wide. Resistance to penicillins is not caused by the production of β -lactamase but by changes to the cell wall and to the penicillin-binding proteins. Resistance to macrolides often accompanies resistance to β -lactams but it can occur in a penicillin-sensitive strain. As noted above for *S. pyogenes*, there are dramatic geographic differences in the incidence of resistance to the major antimicrobials, these are illustrated in Table 1.

In Europe the variability is particularly great, ranging from less than 5% macrolide and penicillin resistance in The Netherlands, to over 40% in France (see Table 2). The greatest resistance to macrolides is seen in France and Italy (over 40%) and the greatest overall resistance to penicillin occurs in France and the Slovak Republic (over 50%), with high levels also occurring in the

Table 1 Prevalence of penicillin resistance and macrolide resistance among *Streptococcus pneumoniae* isolates from various countries

Country	Percentage of strains resistant to		
	Penicillin (intermediate)	Penicillin (resistant)	Macrolide
Brazil	13.4	3.0	3.0
Hong Kong	3.6	71.4	81.0
Japan	20.2	30.9	71.3
Mexico	36.0	17.5	28.9
Russia	3.2	0.0	3.2
Singapore	12.2	32.7	46.9
Saudi Arabia	31.2	24.7	15.6
South Africa	36.3	15.4	18.7
USA	10.8	22.1	26.0

Alexander Project 2000, Data on file—GlaxoSmithKline; (manuscript in preparation).

Table 2 Prevalence of penicillin resistance and macrolide resistance among *Streptococcus pneumoniae* isolates from European countries

Country	Percentage of strains resistant to		
	Penicillin (intermediate)	Penicillin (resistant)	Macrolide
Austria	7.6	4.8	11.4
Belgium	3.0	5.0	34.0
Czech Republic	6.1	1.0	1.0
France	12.6	40.7	47.3
Germany	5.4	1.8	4.2
Greece	16.4	15.2	18.1
Irish Republic	7.3	25.5	12.7
Italy	6.0	3.0	42.0
The Netherlands	3.2	0.0	2.4
Poland	5.5	3.5	6.2
Portugal	7.0	10.1	9.3
Slovak Republic	20.8	30.6	8.3
Switzerland	8.7	5.8	18.8
UK	4.6	14.9	18.4

Data adapted from Schito et al. [1].

Republic of Ireland and Greece. An interesting feature of recent surveillance studies is that the high-level resistance to penicillins has increased and in many countries now exceeds the levels of intermediate resistance.

In Italy the incidence of penicillin-resistant pneumococci has been relatively low [2], with approximately 4% of strains having high-level resistance and 6–10% of strains having low-level resistance [26]. This is in sharp contrast to the situation with *S. pyogenes* described above. In a

detailed study of the types of penicillin-resistant pneumococcal isolates the majority were found to belong to three serotypes [27], serotype 23F (the Spanish/USA type), serotype 9V (French/Spanish type) and serotype 19. Two of these, 23F and 9V, are internationally widespread clones. Over half of these strains were also resistant to erythromycin and tetracycline, nearly 90% were resistant to cotrimoxazole and 41% were resistant to chloramphenicol. The strains with high-level resistance to erythromycin carried the *ermB* gene and the strains with low-level resistance to erythromycin carried the *mefE* gene.

Macrolide resistance is often linked to penicillin resistance (usually *erm/mef*) but can occur independently. In Italy macrolide resistance reaches 40%, whereas fluoroquinolone resistance is rare but increasing. While the problem has attained pandemic proportions, the prevalence of penicillin resistance and multiple resistance is highly variable depending on the site, e.g. The Netherlands and India <5%; Italy 5–15%; South Africa 30–40%; Spain and France 50%; Japan and Korea 70–80%.

What causes these differences?

It is not clear why there are such differences in the distribution and occurrence of penicillin-resistant strains of *S. pneumoniae*. The same predominant clones are present in Italy as are circulating in France, Spain, Japan and Korea, but their incidence is far lower in Italy. It is difficult to see any major differences in the hygienic measures taken in Italy, France and Spain. It is possible that the type of selective pressure could influence resistance. The use of less than adequate drugs such as cotrimoxazole and some third-generation oral cephalosporins may increase the possibility of resistance developing. Oral formulations, although preferred by both clinicians and patients, carry the risk of poor compliance, which can compromise the value of even the most active drug. This is especially so with some older agents which are dosed more than once daily.

It is of note in this context that resistance has not developed to ceftriaxone in pneumococci, despite 20 years of use. The drug is only available as a parenteral, not oral, formulation, which gives greater control over the dose given. Ceftriaxone has been widely used in Italy where acceptance of parenteral drugs for outpatient treatment is more

widespread than in certain other countries [28]. In Italy, 53% of lower respiratory tract infections in outpatients are treated with parenteral drugs, in contrast with only 0.2% in the UK, 8% in Spain and 10% in France.

Ceftriaxone has major pharmacokinetic and pharmacodynamic advantages, including a rapid bactericidal activity and a long serum half-life. A consequence of the long half-life is a sustained minimum bactericidal concentration present in many tissues throughout the body. A significant number of penicillin-resistant strains (those with intermediate resistance) are susceptible to ceftriaxone. This high degree of activity has been confirmed by the introduction of new breakpoints by the National Committee for Clinical Laboratory Standards for respiratory isolates of *S. pneumoniae* [29].

THE IMPACT OF RESISTANCE ON THERAPY

The effects of resistance on clinical response are not always easy to determine and can be controversial. There are, however, a few points on which most are agreed. Penicillin resistance (MIC ≥ 4 mg/L) in *S. pneumoniae* may not represent a threat in non-meningeal infections if only crude mortality rates are considered, but in meningeal infections, strains with high-level resistance are unlikely to respond to penicillin treatment and the drugs are contraindicated. On the contrary, fluoroquinolone resistance may lead to clinical failures in community-acquired pneumonia.

In a study by Varaldo et al. [30] the influence of macrolide resistance on outcome in children with pharyngitis caused by *S. pyogenes* was investigated. A significant difference in the rates of cure between children infected with erythromycin-resistant or erythromycin-susceptible strains was not evident, although there was a trend towards a lower rate of eradication (59.7% vs. 80.2%, respectively), see Table 3. The authors did not distinguish between patients infected with strains having a low resistance and those having a high-level resistance.

As noted above, MRSA infections generally fail to respond to β -lactams and when the strain is an epidemic multi-resistant one the choice of antibacterial agents becomes very restricted. There are strains now circulating against which vancomycin is the only drug that retains activity.

Table 3 Ability of macrolide therapy to eradicate *Streptococcus pyogenes* from children with pharyngitis correlated with susceptibility to erythromycin of the infecting strain

	No. of patients	Infecting strain eradicated	
		no. of patients	95% CI
Macrolide	321	230 (71.7%)	66.5–76.4
Erythromycin-S	187	150 (80.2%)	73.8–85.7
Erythromycin-R	134	80 (59.7%)	50.9–68.1

Adapted from Varaldo et al. [30].

CONCLUSIONS

Resistance to antimicrobial agents among the species discussed here is a global phenomenon, but with very wide variations seen both within and between countries. The spread of specific resistant clones can lead to high levels of resistance in some countries. In some instances a direct relationship can be seen between heavy consumption of a drug and consequent development of resistance. With some agents a reduction in the use of a specific group of drugs can result in a reduction in the incidence of resistance, for example macrolides and *S. pyogenes*. With other organisms, such as *S. aureus* and *M. catarrhalis*, a reversion to susceptibility is unlikely. Strict hygienic control methods in hospitals can limit the spread of resistant clones, for example of MRSA. The use of the most appropriate drugs at the appropriate dose and for an appropriate time is the best way to prevent the selection and spread of antibiotic resistance.

REFERENCES

- Schito GC, Debbia EA, Marchese A. The evolving threat of antibiotic resistance in Europe: new data from the Alexander Project. *J Antimicrob Chemother* 2000; 46(Suppl. T1): 3–9.
- Schito GC, Pesce A, Marchese A. The role of macrolides in *Streptococcus pyogenes* pharyngitis. *J Antimicrob Chemother* 1997; 39: 562–5.
- Stingemore N, Francis GR, Toohey M, McGeachie DB. The emergence of erythromycin resistance in *Streptococcus pyogenes*. in Fremantle, Western Australia *Medical J Aust* 1989; 150: 626–7; 630–1.
- Seppala H, Nissinen A, Yu Q, Huovinen P. Three different phenotypes of erythromycin-resistant *Streptococcus pyogenes* in Finland. *J Antimicrob Chemother* 1993; 32: 885–91.
- Maruyama S, Yoshioka H, Fujita K, Takimoto M, Satake Y. Sensitivity of group A streptococci to

- antibiotics. Prevalence of resistance to erythromycin in Japan. *Am J Dis Child* 1979; 133: 1143–5.
6. Fujii R. Present state of antibiotic consumption in Japan. *Saishuu-Igaku* 1977; 32: 1439–45.
 7. Fujita K, Murono K, Yoshikawa M, Murai T. Decline of erythromycin resistance of group A streptococci in Japan. *Pediatr Infect Dis J* 1994; 13: 1075–8.
 8. Hsueh PR, Chen HM, Huang AH, Wu JJ. Decreased activity of erythromycin against *Streptococcus pyogenes* in Taiwan. *Antimicrob Agents Chemother* 1995; 39: 2239–42.
 9. Seppala H, Klaukka T, Lehtonen R, Nenonen E, Huovinen P. Outpatient use of erythromycin: link to increased erythromycin resistance in group A streptococci. *Clin Infect Dis* 1995; 21: 1378–85.
 10. Seppala H, Klaukka T, Vuopio-Varkila J *et al.* The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. *N Engl J Med* 1997; 337: 441–6.
 11. Zackrisson G, Lind L, Roos K, Larsson P. Erythromycin-resistant beta-hemolytic streptococci group A in Goteborg, Sweden. *Scand J Infect Dis* 1988; 20: 419–20.
 12. Bingen E, Fitoussi F, Doit C *et al.* Resistance to macrolides in *Streptococcus pyogenes* in France in pediatric patients. *Antimicrob Agents Chemother* 2000; 44:1453–7.
 13. Orden B, Perez-Trallero E, Montes M, Martinez R. Erythromycin resistance of *Streptococcus pyogenes* in Madrid. *Pediatr Infect Dis* 1998; 17: 470–3.
 14. Baquero F. Gram-positive resistance. challenge for the development of new antibiotics. *J Antimicrob Chemother*, 1997; 39(Suppl. A): 1–6.
 15. Fluit AC, Wielders CL, Verhoef J, Schmitz FJ. Epidemiology and susceptibility of 3,051 *Staphylococcus aureus* isolates from 25 University hospitals participating in the European SENTRY study. *J Clin Microbiol* 2001; 39: 3727–32.
 16. Fleisch F, Zbinden R, Vanoli C, Ruef C. Epidemic spread of a single clone of methicillin-resistant *Staphylococcus aureus* among injection drug users in Zurich, Switzerland. *Clin Infect Dis* 2001; 32: 581–6.
 17. Salmenlinna S, Vuopio-Varkila J. Recognition of two groups of methicillin-resistant *Staphylococcus aureus* strains based on epidemiology, antimicrobial susceptibility, hypervariable-region type, and ribotype in Finland. *J Clin Microbiol* 2001; 39: 2243–7.
 18. Simor AE, Ofner-Agostini M, Bryce E *et al.* The evolution of methicillin-resistant *Staphylococcus aureus* in Canadian hospitals: 5 years of national surveillance. *Can Med Assoc J* 2001; 165: 21–6.
 19. Deplano A, Witte W, van Leeuwen WJ, Brun Y, Struelens MJ. Clonal dissemination of epidemic methicillin-resistant *Staphylococcus aureus*. in Belgium and neighboring countries. *Clin Microbiol Infect* 2000; 6: 239–45.
 20. Sa-Leao R, Sanches IS, Couto I, Alves CR, de Lencastre H. Low prevalence of methicillin-resistant strains among *Staphylococcus aureus* colonizing young and healthy members of the community in Portugal. *Microb Drug Resist* 2001; 7: 237–45.
 21. Wang JT, Chen YC, Yang TL, Chang SC. Molecular epidemiology and antimicrobial susceptibility of methicillin-resistant *Staphylococcus aureus* in Taiwan. *Diagn Microbiol Infect Dis* 2002; 42: 199–203.
 22. Verma S, Joshi S, Chitnis V, Hemwani N, Chitnis D. Growing problem of methicillin resistant staphylococci – Indian scenario. *Indian J Med Sci* 2000; 54: 535–40.
 23. Crisostomo MI, Westh H, Tomasz A, Chung M, Oliveira DC, de Lencastre H. The evolution of methicillin resistance in *Staphylococcus aureus*. Similarity of genetic backgrounds in historically early methicillin-susceptible and -resistant isolates and contemporary epidemic clones. *Proc Natl Acad Sci USA* 2001; 98: 9865–70.
 24. Roman RS, Smith J, Walker M *et al.* Rapid geographic spread of a methicillin-resistant *Staphylococcus aureus* strain. *Clin Infect Dis* 1997; 25: 698–705.
 25. Rampling A, Wiseman S, Davis L *et al.* Evidence that hospital hygiene is important in the control of methicillin-resistant *Staphylococcus aureus*. *J Hosp Infect* 2001; 49: 109–16.
 26. Marchese A, Mannelli S, Tonoli E, Gorlero F, Toni M, Schito GC. Prevalence of antimicrobial resistance in *Streptococcus pneumoniae* circulating in Italy: results of the Italian Epidemiological Observatory Survey (1997–1999). *Microb Drug Resist* 2001; 7: 277–87.
 27. Marchese A, Ramirez M, Schito GC, Tomasz A. Molecular epidemiology of penicillin-resistant *Streptococcus pneumoniae* isolates recovered in Italy from 1993 to 1996. *J Clin Microbiol* 1998; 36: 2944–9.
 28. Esposito S. Outpatient parenteral treatment of bacterial infections: the Italian model as an international trend? *J Antimicrob Chemother* 2000; 45: 724–7.
 29. National Committee for Clinical Laboratory Standards. *M100-S12 January 2002: NCCLS. Performance standards for antimicrobial susceptibility testing*, 12th Informational Supplement. Wayne PA: NCCLS.
 30. Valardo PE, Debbia EA, Nicoletti G *et al.* Nationwide survey in Italy of treatment of *Streptococcus pyogenes* pharyngitis in children: influence of macrolide resistance on clinical and microbiological outcomes. Artemis-Italy Study Group. *Clin Infect Dis* 1999; 29: 869–73.