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Macrolide-Resistant *Streptococcus pneumoniae* and *Streptococcus pyogenes* in the Pediatric Population in Germany during 2000-2001

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In a nationwide study in Germany covering 13 clinical microbiology laboratories, a total of 307 *Streptococcus pyogenes* (mainly pharyngitis) and 333 *Streptococcus pneumoniae* (respiratory tract infections) strains were collected from outpatients less than 16 years of age. The MICs of penicillin G, amoxicillin, cefotaxime, erythromycin A, clindamycin, levofloxacin, and telithromycin were determined by the microdilution method. In *S. pyogenes* isolates, resistance rates were as follows: penicillin, 0%; erythromycin A, 13.7%; and levofloxacin, 0%. Telithromycin showed good activity against *S. pyogenes* isolates (MIC_{90} = 0.25 μg/ml; MIC range, 0.016 to 16 μg/ml). Three strains were found to be telithromycin-resistant (MIC ≥ 4 μg/ml). Erythromycin-resistant strains were characterized for the underlying resistance genotype, with 40.5% having the efflux type *mef*(A), 38.1% having the *erm*(A), and 9.5% having the *erm*(B) genotypes. *emm* typing of macrolide-resistant *S. pyogenes* isolates showed *emm* types 4 (45.2%), 77 (26.2%), and 12 (11.9%) to be predominant. In *S. pneumoniae*, resistance rates were as follows: penicillin intermediate, 7.5%; penicillin resistant, 0%; erythromycin A, 17.4%; and levofloxacin, 0%. Telithromycin was highly active against pneumococcal isolates (MIC_{90} ≤ 0.016 μg/ml; range, 0.016 to 0.5 μg/ml). The overall resistance profile of streptococcal respiratory tract isolates is still favorable, but macrolide resistance is of growing concern in Germany.

Streptococcus pyogenes is responsible for the majority of cases of pharyngitis in children and adolescents and can also cause severe life-threatening diseases, such as necrotizing fasciitis and toxic shock syndrome (6). *Streptococcus pneumoniae* continues to be a significant cause of morbidity and mortality in humans and is responsible for respiratory tract infections and otitis media (15).

Macrolide resistance in *S. pneumoniae* is usually caused by the presence of the *erm*(B) or *mefE* [renamed *mef*(A)] resistance determinants. The *erm*(B) protein encodes a 23S rRNA methylase, and most pneumococcal strains that harbor the gene are resistant to 14-, 15-, and 16-membered-ring macrolides, lincosamides, and streptogramin B (MLS_B phenotype). The *mef*(A) protein encodes an efflux pump that leads to resistance to only 14- and 15-membered-ring macrolides (24). Other mechanisms of macrolide resistance have only been described in a few clinical isolates of *S. pneumoniae*, and changes were clustered in a highly conserved sequence of L4 and in the nucleotide residues of domain V of 23S rRNA, which have a key role in macrolide binding (5, 7, 26).

Macrolide resistance has also been increasingly detected in *S. pyogenes* in Europe and other parts of the world and is mediated by *erm*(A), *mef*(A) and, less commonly, by *erm*(B) mechanisms.

Telithromycin (HMR 3647) is the first of a novel family of antimicrobials, the ketolides, developed specifically for the treatment of community-acquired respiratory tract infections. The ketolides are a new addition to the MLS group of antimicrobials. Ketolides are characterized by a ketone group, which replaces the cladinose sugar at position 3 of the macrolactone ring.

The aims of the present study were (i) to evaluate the prevalence of antibiotic resistance in *S. pyogenes* and *S. pneumoniae* isolates in Germany, (ii) to compare the in vitro activity of the new ketolide telithromycin with those of other antibiotics used for the treatment of respiratory tract infections, and (iii) to identify the predominant macrolide resistance mechanisms and macrolide-resistant serotypes and *emm* types.

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MATERIALS AND METHODS

Consecutive clinical isolates collected between November 2000 and March 2001 from patients with community-acquired respiratory infections (acute pharyngitis caused by *S. pyogenes* and acute otitis media, acute exacerbations of chronic bronchitis, and pneumonia caused by *S. pneumoniae*) were collected. Only strains from children less than 16 years of age were included.

Strains were shipped to a central laboratory (National Reference Center for Streptococci, Aachen, Germany), where compliance of the isolates with the criteria for inclusion in the study was checked. Confirmation of the identification of isolates was provided by positive bile solubility and inhibition by optochin for *S. pneumoniae. S. pyogenes* isolates were identified by their hemolysis on sheep blood agar, Lancefield grouping, by using a commercially available agglutination technique (Slidex, Streptokit; BioMérieux, Marcy l'Etoile, France), and by the pyrrolidonyl-arylamidase test.

MIC testing was performed by using the broth microdilution method as recommended by the National Committee for Clinical Laboratory Standards (NCCLS) (17). Commercially manufactured microtiter plates (Micronaut-S; Merlin Diagnostics, Bornheim, Germany) containing penicillin G, cefotaxime, amoxicillin, erythromycin A, clindamycin, levofloxacin, and telithromycin and cation-adjusted Mueller-Hinton broth (Oxoid, Wesel, Germany), plus 5% lysed horse

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blood (Oxoid), were used. The final inoculum was 5×10^5 CFU/ml. MICs were determined after incubation at 35°C for 24 h in ambient air. *S. pneumoniae* ATCC 49619 was used as a control strain. Current NCCLS interpretive criteria were used to define antimicrobial resistance. For telithromycin, breakpoints of ≤1 and ≥4 μg/ml were used for sensitivity and resistance, respectively. Isolates were stored at −70°C on porous beads (Microbank; Mast Diagnostics, Rheinfeld, Germany).

For the detection of *erm*(B) and *mef*(A) in pneumococcal strains, we used primers described by Trieu-Cuot et al. (27) and Tait-Kamradt et al. (25). For *erm*(B) we selected 5′-CGA GTG AAA AAG TAC TCA ACC-3′ (positions 362 to 382) and 5′-GGC GTG TTT CAT TGC TTG ATG-3′ (positions 978 to 958), and for *mef*(A) we selected 5′-AGT ATC ATT AAT CAC TAG TGC-3′ (positions 57 to 77) and 5′-GTA ATA GAT GCA ATC ACA GC-3′ (positions 551 to 532).

Macrolide-resistant *S. pyogenes* strains were tested by PCR for the presence of *erm*(A), *erm*(B), or *mef*(A). The following primer pairs were used: 5′-TTA TAA CCG GCA AGG AGA-3′ and 5′-GCT TCA GCA CCT GTC TTA ATT GAT-3′ for *erm*(A), 5′-AAA (C/T)TG ATT TTT (A/T)GT AAA-3′ and 5′-AGG TAA AGG GCA TTT-3′ for *erm*(B), and 5′-CTA TGA CAG CCT CAA TGC G-3′ and 5′-ACC GAT TCT ATC AGC AAA G-3′ for *mef*(A) (4). Nucleotide sequences for 23S rRNA and L4 and L22 ribosomal proteins in *Escherichia coli* and *S. pneumoniae* were obtained from the Institute for Genome Research website (http://www.tigr.org/.). Specific oligonucleotide primers were designed from these sequences. Primer sequences and conditions for PCR amplifications were those described by Canu et al. (5). The following primers were used: for *rplV* (L22), 5′-GCAGACGACAAGAAAACACG-3′ and 5′-GCCGACACGCA TACCAATTG-3′; for *rplD* (L4), (i) 5′-AAAGGTAACGTACCAGGTGC-3′ and 5′-GCGTGGTGGTGGTGTTG-3′ and (ii) 5′-CACGAGTGTCAACTTCA AATAC-3′ and 5′-GAGCGTCTACAGCTACG-3′; for *rrl* (23S rRNA domain II), 5′-CGGCGAGTTACGATTATGATGC-3′ and 5′-CTCTAATGTCGACG CTAGCC-3′; and for *rrl* (23S rRNA domain V), (i) 5′-CTGTCTCAACGAGA GACTC-3′ and 5′-CTTAGACTCCTACCTATCC-3′ and (ii) 5′-GTATAAGG GAGCTTGACTG-3′ and 5′-GGGTTTCACACTTAGATG-3′.

emm typing of *S. pyogenes* isolates was performed according to the method of Podbielski et al. (20). Similarity searching was performed by using the *N*-terminal hypervariable region of the M gene based on the latest information of the Centers for Disease Control website (http://www.cdc.gov/ncidod/-biotech/strep/strains/emmtypes.html). *S. pyogenes* CS101 (M type 49) was used as a reference strain. Pneumococcal strains were serotyped by using Neufeld's Quellung reaction, with type and factor sera provided by the Statens Serum Institut, Copenhagen, Denmark. *S. pneumoniae* ATCC 700669 (serotype 23F), *S. pneumoniae* ATCC 700670 (serotype 6B), *S. pneumoniae* ATCC 700671 (serotype 9V), and *S. pneumoniae* ATCC 700672 (serogroup 14) were used as reference strains.

Multilocus sequence typing was performed according to the method of Enright et al. (8). In brief, internal fragments of the glucose kinase (*gki*), glutamine transporter protein (*gtr*), glutamate racemase (*murI*), DNA mismatch repair protein (*mutS*), transketolase (*recP*), xanthine phosphoribosyl transferase (*xpt*), and acetyl coenzyme A acetyltransferase (*yqiL*) genes were amplified by PCR by using the following primer pairs: *gki*-up (5′-GGC ATT GGA ATG GGA TCA CC-3′) and *gki*-dn (5′-TCT CCT GCT GCT GAC AC-3′), *gtr*-up (5′-GAG GTT GTG GTG ATT ATT GG-3′) and *gtr*-dn (5′-GCA AAG CCC ATT TCA TGA GTC-3′), *murI*-up (5′-TGC TGA CTC AAA ATG TTA AAA TGA TTG-3′) and *murI*-dn (5′-GAT GAT AAT TCA CCG TTA ATG TCA AAA TAG-3′), *mutS*-up (5′-GAA GAG TCA TCT AGT TTA GAA TAC GAT-3′) and *mutS*-dn (5′-AGA GAG TTG TCA CTT GCG CGT TTG ATT GCT-3′), *recP*-up (5′-GCA AAT TCT GGA CAC CCA GG-3′) and *recP*-dn (5′-CTT TCA CAA GGA TAT GTT GCC-3′), *xpt*-up (5′-TTA CTT GAA GAA CGC ATC TTA-3′) and *xpt*-dn (5′-ATG AGG TCA CTT CAA TGC CC-3′), and *yqiL*-up (5′-TGC AAC AGT ATG GAC TGA CCA GAG AAC AAG ATG C-3′) and *yqiL*-dn (5′-CAA GGT CTC GTG AAA CCG CTA AAG CCT GAG-3′). For each locus, every different sequence was assigned a distinct allele number, and each isolate was defined by a series of seven integers (the allelic profile) corresponding to the alleles at the seven loci, in the order (alphabetical) of *gki*, *gtr*, *murI*, *mutS*, *recP*, *xpt*, and *yqiL*. Isolates with an identical allelic profile were assigned to the same sequence type (ST).

RESULTS

In all, 640 isolates comprising 307 *S. pyogenes* and 333 *S. pneumoniae* isolates were collected by 13 centers. Pneumococcal strains were isolated from the following sources: nasopharynx ($n = 184$ [55.3%]), ear swabs ($n = 87$ [26.1%]), eye swabs ($n = 40$ [12.0%]), sputum ($n = 5$ [1.5%]), paracentesis ($n = 8$ [2.4%]), and other sources ($n = 9$ [2.7%]). *S. pyogenes* isolates were mainly isolated from the throat ($n = 222$ [72.3%]), 46 (15.0%) strains were isolated from other respiratory sources, and 39 (12.7%) strains were isolated from wound infections.

Pneumococci were predominantly isolated from infants and young children ≤5 years of age ($n = 221$, 66.4% of cases), followed by the children in the 5- to 10-year age group ($n = 90$, 27.0% of cases). *S. pyogenes* infections were mainly seen among children 5 to 10 years of age ($n = 255$, 46.6% of cases).

Among pneumococcal strains, 92.5% of isolates were found to be susceptible to penicillin G (MIC ≤ 0.06 μg/ml) and 7.5% were found to be penicillin intermediate (MIC = 0.1 to 1 μg/ml). Isolates highly resistant to penicillin G (MIC ≥ 2 μg/ml) were not detected. Totals of 58 (17.4%) and 29 (8.7%) strains were resistant to erythromycin A and clindamycin, respectively. Amoxicillin ($MIC_{50} \leq 0.016$ μg/ml; $MIC_{90} = 0.03$ μg/ml; all strains were susceptible) and cefotaxime ($MIC_{50} \leq 0.016$ μg/ml; $MIC_{90} < 0.03$ μg/ml; 1.5% intermediate) showed good activity against penicillin-susceptible and penicillin-intermediate isolates. All strains were levofloxacin and telithromycin susceptible.

S. pyogenes strains were susceptible to β-lactams. Resistance to erythromycin A was detected in 42 (13.7%) strains. All strains were levofloxacin susceptible, and three strains were resistant to telithromycin.

Erythromycin-resistant strains ($n = 100$ [58 *S. pneumoniae* and 42 *S. pyogenes*]) were analyzed for the underlying resistance determinants. A total of 29 (50%) of the pneumococcal strains showed the *erm*(B) type of resistance, and 29 (50%) showed the *mef*(A) type of resistance.

S. pyogenes strains belonged to the following resistance genotypes: *mef*(A) ($n = 22$, 42.5%), *erm*(A) ($n = 16$, 38.0%), and *erm*(B) ($n = 4$, 9.5%).

The antimicrobial susceptibility results for macrolide-resistant strains are presented in Table 1. *Mef*(A)-positive pneumococcal strains showed slightly elevated telithromycin MICs (MIC_{90} 0.25 μg/ml). All erythromycin-resistant pneumococcal strains [*erm*(B) and *mef*(A)-positive strains] remained telithromycin susceptible. Clindamycin was only active against *mef*(A)-positive strains. Erythromycin-resistant pneumococcal strains showed reduced sensitivity to β-lactams. Penicillin G-intermediate strains were more often found among *erm*(B)-positive strains (31%) compared to *mef*(A)-positive strains (10.3%) (Table 1).

All *erm*(A)- and 88.2% of *mef*(A)-positive erythromycin-resistant *S. pyogenes* remained telithromycin susceptible. All ($n = 4$) *erm*(B)-positive *S. pyogenes* strains were telithromycin intermediate ($n = 1$) or resistant ($n = 3$).

The three telithromycin-resistant strains were screened for mutations in 23S rRNA and ribosomal proteins L4 and L22. Since better discrimination between mutated alleles was obtained for denatured DNA fragments between 150 and 500 bp, portions of the *rrl* gene (domains II and V of 23S rRNA), the entire *rplV* gene and two overlapping fragments of the L4 gene (*rplD*) were amplified. The three fragments amplified from *rrl*, two for domain V and one for domain II, included bases critical for erythromycin resistance: G2057, A2058, A2062, G2505, C2611, and A752 (5). All three strains showed the wild type for L4, L22, and the *erm* gene, but a new mutation in the

TABLE 1. Antimicrobial susceptibility of macrolide-resistant *S. pneumoniae* and *S. pyogenes* isolates with different resistance genotypes

Organism (*n*)	Antibiotic	MIC (μg/ml)		No. (%) of strains that were[a]:		
		50%	90%	Susceptible	Intermediate	Resistant
S. pneumoniae mef(E) positive (29)	Penicillin G	≤0.016	0.125	26 (89.7)	3 (10.3)	0 (0)
	Cefotaxime	≤0.016	0.06	29 (100)	0 (0)	0 (0)
	Amoxicillin	≤0.016	0.25	29 (100)	0 (0)	0 (0)
	Erythromycin A	4.0	4.0	0 (0)	0 (0)	29 (100)
	Clindamycin	0.06	0.06	29 (100)	0 (0)	0 (0)
	Telithromycin	0.03	0.25	29 (100)	0 (0)	0 (0)
S. pneumoniae erm(B) positive (29)	Penicillin G	0.03	0.5	20 (69.0)	9 (31.0)	0 (0)
	Cefotaxime	0.03	0.5	27 (93.1)	2 (6.9)	0 (0)
	Amoxicillin	≤0.016	0.25	29 (100)	0 (0)	0 (0)
	Erythromycin A	≥32	≥32	0 (0)	0 (0)	29 (100)
	Clindamycin	≥32	≥32	0 (0)	0 (0)	29 (100)
	Telithromycin	≤0.016	0.06	29 (100)	0 (0)	0 (0)
S. pyogenes mef(A) positive (17)	Penicillin G	≤0.016	≤0.016	17 (100)	0 (0)	0 (0)
	Cefotaxime	≤0.016	≤0.016	17 (100)	0 (0)	0 (0)
	Amoxicillin	≤0.016	≤0.016	17 (100)	0 (0)	0 (0)
	Erythromycin	8.0	8.0	0 (0)	0 (0)	17 (100)
	Clindamycin	0.06	0.06	17 (100)	0 (0)	0 (0)
	Telithromycin	0.5	2.0	15 (88.2)	2 (11.8)	0 (0)
S. pyogenes erm(A) positive (16)	Penicillin G	≤0.016	≤0.016	16 (100)	0 (0)	0 (0)
	Cefotaxime	≤0.016	≤0.016	16 (100)	0 (0)	0 (0)
	Amoxicillin	≤0.016	≤0.016	16 (100)	0 (0)	0 (0)
	Erythromycin	≥32	≥32	0 (0)	0 (0)	16 (100)
	Clindamycin	≥32	≥32	0 (0)	0 (0)	16 (100)
	Telithromycin	≤0.016	0.25	16 (100)	0 (0)	0 (0)
S. pyogenes erm(B) positive (4)	Penicillin G	≤0.016	≤0.016	4 (100)	0 (0)	0 (0)
	Cefotaxime	≤0.016	≤0.016	4 (100)	0 (0)	0 (0)
	Amoxicillin	≤0.016	≤0.016	4 (100)	0 (0)	0 (0)
	Erythromycin A	≥32	≥32	0 (0)	0 (0)	4 (100)
	Clindamycin	1	≥32	1 (25)	0 (0)	3 (75)
	Telithromycin	4	16	0 (0)	1 (25)	3 (75)

[a] Breakpoints (intermediate and resistant, respectively) according to the NCCLS: penicillin G, 0.1 to 1 and ≥2 μg/ml; amoxicillin, 4 and ≥8 μg/ml; cefotaxime, 1 and ≥2 μg/ml; erythromycin A, 0.5 and ≥1 μg/ml; clindamycin, 0.5 and ≥1 μg/ml; levofloxacin, 4 and ≥8 μg/ml. The telithromycin breakpoints are not NCCLS approved. Breakpoints of ≤1 and ≥4 μg/ml were used.

23S rRNA was detected (T2166C). In addition, all strains showed an identical MLS type (ST 52) and *emm* type (*emm* 28), indicating the clonal relatedness of the strains. Strains were isolated in different federal states in Germany (Table 2).

Erythromycin-resistant pneumococcal strains were serotyped; serotypes 14 (n = 13, 22.4%), 19F (n = 11, 19.0%), 19A (n = 8, 13.8%), and 23F (n = 7, 12.1%) were predominant. Most erythromycin-resistant serotype 14 (10 of 13 strains) and 23F (6 of 7 strains) strains were *mef*(A) positive, whereas the MLS_B type of resistance was mainly seen among serogroup 19 (18 of 19 strains).

emm typing of erythromycin-resistant *S. pyogenes* isolates (n = 42) showed that strains of *emm* type 4 (n = 19, 45.2%) and 77 (n = 11, 26.2%) accounted primarily for macrolide resistance, whereas *emm* type 12 (n = 5, 11.9%) and *emm* type 28 (n = 4, 9.5%) were only rarely represented among resistant isolates.

Most (16 of 19 strains) of the *emm* type 4 and all of the *emm* type 12 erythromycin-resistant *S. pyogenes* strains were *mef*(A) positive. All *emm* type 77 strains were *erm*(A)/*erm*(TR) positive; all telithromycin-nonsusceptible *erm*(B) strains (n = 4) were *emm* type 28. All strains were from different geographic regions of Germany.

TABLE 2. Characteristics of three telithromycin-resistant *S. pyogenes* strains[a]

Strain	Town	Federal state	Source	MIC (μg/ml)			Resistance genotype	MLST[b]	*emm* type	L22 (*rplV*)	L4	*rrl* D2 (23S rRNA)	*rrl* D5a (23S rRNA)	*rrl* D5b (23S rRNA)	*erm*(B) (ORF Tn*917*)
				TEL	ERY	CLI									
PY31	Bad Hersfeld	HE	Throat	4	32	1	*erm*(B)	52	28	WT	WT	WT	T2166C	WT	WT
PY152	Neukirchen	SN	Throat	16	32	0.25	*erm*(B)	52	28	WT	WT	WT	T2166C	WT	WT
PY178	Trier	RP	Throat	8	32	32	*erm*(B)	52	28	WT	WT	WT	T2166C	WT	WT

[a] Abbreviations: HE, Hessen; SN, Saxony; RP, Rhineland Pfalz, TEL, telithromycin, ERY, erythromycin; CLI, clindamycin; MLST, multilocus sequence type, WT, wild type; ORF, open reading frame.

[b] All strains showed MLST 52 with the following alleles: *gki-11*, *gtr-6*, *murl-14*, *mutS-5*, *recP-9*, *xpt-17*, and *yqiL-19*.

DISCUSSION

The worldwide increase in antibiotic resistance in these species has become a serious infectious disease problem within the last 20 years. Prior to the early 1990s, penicillin resistance remained uncommon among clinical isolates of *S. pneumoniae* in Germany despite the emergence of this problem in many parts of Europe, e.g., Hungary, Spain, and France (2). In contrast, decreased susceptibility to macrolides in *S. pyogenes* and to β-lactams and macrolides in *S. pneumoniae* has only recently been reported in Germany (4, 21, 23) and is comparable to resistance rates reported from The Netherlands (10) and Northern European countries (18). Highly penicillin-resistant strains are extremely rare in Germany, as documented by this and other studies. As in many other countries, macrolide resistance in pneumococci has overcome the level of β-lactam resistance in Germany, and rates are still increasing in both *S. pneumoniae* and *S. pyogenes* (21, 23, 28).

The rate of erythromycin A resistance in pneumococci documented by the present study (17.4%) is significantly higher than those reported earlier by our working group. A study on pneumococcal respiratory tract infections of strains collected in Germany between 1998 and 1999 covered 358 infections of children <5 years of age; the rate of clarithromycin resistance was 9.2%. The latter and the present studies both used the same laboratory network, and the data should therefore be comparable. Thus, it is alarming to note that the rate of macrolide resistance in pneumococcal respiratory tract isolates in children has nearly doubled within the last 2 years (23).

In addition, a similar increase to even higher levels of macrolide resistance has been reported for pneumococcal invasive disease in both children and adults in Germany (21, 28).

It is noteworthy that there is a parallel macrolide resistance profile in *S. pyogenes* and *S. pneumoniae* in children in Germany. In the present study a rate of 13.7% of macrolide resistance was documented in *S. pyogenes* strains.

In a study by Adam et al. performed between December 1995 and May 1998 in children, macrolide resistance was documented for 6.0% of all *S. pyogenes* strains tested ($n = 4.698$) (1). Brandt et al. recently reported macrolide resistance to be present in 17 of 216 (7.9%) *S. pyogenes* strains isolated from throat infections in the Aachen region of Germany between January 1997 and July 1997 (4). Again, these data suggest that, as for pneumococci, the frequency of macrolide resistance is increasing in Germany.

Methylation of a ribosomal target and active efflux of erythromycin A are the two most important factors involved in the resistance of streptococci to macrolides. Among macrolide-resistant pneumococci in Germany, efflux and MLS_B strains are equally distributed, as documented here. Similar data have recently been reported from Canada and the United States, where ~50% of macrolide-resistant *S. pneumoniae* harbor *mef*(A) (11, 13). In contrast, in many European countries, such as France and Spain, the spread of macrolide resistance among pneumococci is mainly due to *erm*(B)-positive strains (9, 19).

Other newer macrolides such as clarithromycin, azithromycin, and roxithromycin are incapable of overcoming MLS_B resistance (22). In the present study, the new ketolide telithromycin demonstrated excellent activity against pneumococcal strains, including macrolide-resistant isolates, thus confirming recently published data (16, 22).

In addition, our study showed that there is a clear correlation between genotype profile and phenotype susceptibility patterns in *S. pyogenes*: *erm*(A) strains showed high-level resistance to erythromycin and susceptibility to telithromycin; all those highly resistant to macrolides and intermediate or resistant to telithromycin had the *erm*(B), as recently described by Bemer-Melchior et al. (3) and by Javala et al. (12).

New macrolide resistance genotypes (L4, L22, and 23S rRNA) and mutations others than *mef*(A) and *erm*(B) were not observed in the present collection of pneumococcal strains. The three telithromycin-resistant *S. pyogenes* strains showed wild type for L4, L22, and the *erm* gene, but a new mutation in the 23S rRNA was detected. The role of this mutation needs to be determined by further transformation experiments. In addition, it is a striking finding of the present study that all telithromycin resistant *erm*(B) *S. pyogenes* strains belonged to a single *emm* type (*emm* 28) and MLS type (ST 52), indicating the likelihood of clonal relatedness of strains.

The *mef*(A) gene was not found in *erm*-positive strains, contrary to observations in a recent study from Finland (14).

In summary, the present study demonstrated the dramatic increase of macrolide resistance in *S. pneumoniae* and *S. pyogenes* strains in Germany. Telithromycin showed excellent activity against macrolide-resistant *S. pneumoniae* possessing the *mef*(A) or *erm*(B) genotype and against *S. pyogenes* possessing the *mef*(A) and *erm*(A) genotype. In view of their excellent activity against macrolide-resistant strains, ketolides may be an attractive alternative for the treatment of respiratory tract infections caused by these important pathogens.

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