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Increased Prevalence of Erythromycin Resistance in Streptococci: Substantial Upsurge in Erythromycin-Resistant M Phenotype in *Streptococcus pyogenes* (1979–1998) but Not in *Streptococcus pneumoniae* (1985–1999) in Taiwan

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ABSTRACT

A total of 394 nonduplicate isolates of *Streptococcus pyogenes* collected from 1979 to 1998 and 267 nonduplicate isolates of *Streptococcus pneumoniae* collected from October, 1998, to May, 1999, in Taiwan were evaluated. Among the 220 erythromycin-resistant (MIC, ≥1 μg/ml) *S. pyogenes* isolates, 35% had an M phenotype and 65% had an ML phenotype (inducible resistance [iML], 0.5%, and constitutive resistance [cML], 64.5%). Among the 243 erythromycin-resistant *S. pneumoniae* isolates, the majority (65.4%) had an ML phenotype (iML, 0.4%, and cML, 65%) and 34.6% had an M phenotype. A substantial upsurge in the incidence of M-phenotype erythromycin-resistant isolates was found with time for *S. pyogenes* (0% in 1979–1984 and 100% in 1997–1998), and an increasing incidence of M-phenotype among erythromycin-resistant *S. pneumoniae* was also noted (<20% before 1994 and 45.4% in 1999). All *S. pyogenes* and all but four *S. pneumoniae* isolates exhibiting a cML or iML phenotype had harbored the *ermAM* gene. The presence of the *mefA* gene was demonstrated in all isolates of *S. pyogenes* and the *mefE* gene in all but four *S. pneumoniae* isolates exhibiting the M phenotype. Due to the increasing susceptibility of *S. pyogenes* and *S. pneumoniae* isolates to clindamycin, susceptibility tests of these two organisms to macrolides and clindamycin should be performed simultaneously in the clinical microbiology laboratory, particularly in areas with high rates of macrolide resistance.

INTRODUCTION

A RECENT RESURGENCE IN THE INCIDENCE of infections caused by *Streptococcus pyogenes* and *Streptococcus pneumoniae* and in their associated mortality and morbidity has been documented in many parts of the world.[5,30] Meanwhile, the increased clinical use of erythromycin and its macrolide derivatives, mostly for upper respiratory tract infections, has been related to increased resistance of *S. pyogenes* and *S. pneumoniae* to these antibiotics worldwide.[7,26,30] In Taiwan, a remarkable upsurge of erythromycin resistance in *S. pneumoniae* and a high incidence of erythromycin-resistant *S. pyogenes* and other streptococci have been well demonstrated.[6,12–16,36] An increasing proportion of macrolides among all antimicrobials used in Taiwan was noted from 3.9% in 1995 to 5.9% in 1998 (personal communication). The widespread use of macrolides in Taiwan might contribute to this phenomenon.[6,12,14,15]

For streptococci, three distinct erythromycin-resistant phenotypes exist, *i.e.*, M (resistant to 14- and 15-membered macrolides but not to 16-membered macrolides, lincosamides, and streptogramin B compounds), MLS_B (resistant to macrolides, lincosamides, and streptogramin B compounds) constitutive, and MLS_B inducible.[20,27] Recent studies showed that the distribution of erythromycin-resistant phenotypes of *S. pyogenes* and *S. pneumoniae* strains isolated varied geographically.[3,4,9,10,17,19,20,23,24,28,29,31,35,37] The aim of the present study was to investigate the secular trends and mechanisms of macrolide resistance among *S. pyogenes* and *S. pneumoniae* isolates collected during the past 15–20 years in Taiwan.

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MATERIALS AND METHODS

Bacterial isolates

From January, 1979, to December, 1998, a total of 394 isolates of *S. pyogenes* were preserved for study. These isolates were recovered from various clinical specimens of patients treated at National Taiwan University Hospital (NTUH), a tertiary-care referral center with 2,000 beds in northern Taiwan. Of these isolates, 309 were recovered from throat swab samples, 69 from blood samples, and the others from other sources. A total of 276 isolates of *S. pneumoniae* were collected from October, 1998, to May, 1999, from five major teaching hospitals in Taiwan.[16]

Antimicrobial susceptibility testing

The following antimicrobial agents were provided by their manufacturers for use in this study: penicillin, erythromycin, clindamycin, tetracycline, chloramphenicol, and rifampin (Sigma Chemical Co., St. Louis, MO), vancomycin (Eli Lilly & Co., Indianapolis, IN), cefotaxime and teicoplanin (Marion Merrell Dow, Cincinnati, OH), cefepime (Bristol-Myers Squibb, Princeton, NJ), azithromycin (Pfizer Inc., New York, NY), clarithromycin (Abbott Laboratories, Abbott Park, IL), quinupristin-dalfopristin (Rhone-Poulenc Rorer, Collegeville, PA), and linezolid (Pharmacia & Upjohn, Kalamazoo, MI). For *S. pneumoniae* isolates, only penicillin, erythromycin, clarithromycin, azithromycin, clindamycin, chloramphenicol, and tetracycline were tested in this study.

MICs of these agents for all *S. pyogenes* isolates and the 267 *S. pneumoniae* isolates collected from the five major teaching hospitals were determined by the agar dilution method according to the guidelines established by the National Committee for Clinical Laboratory Standards (NCCLS).[22] Using a Steers replicator, an organism density of 10^4 colony-forming units (CFU)/spot was inoculated onto the appropriate plate with various concentrations of antimicrobial agents and incubated at 37°C in ambient air. The following organisms were included as control strains: *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619.

To determine the secular trend of erythromycin resistance patterns, data on the disk diffusion susceptibilities to erythromycin and clindamycin of 1,155 isolates of *S. pneumoniae* isolates recovered from 1985 to 1999 in NTUH were also analyzed.

Determination of resistance phenotypes and genotypes

The resistance phenotypes of erythromycin-resistant (erythromycin MICs, ≥0.5 μg/ml) *S. pyogenes* and *S. pneumoniae* were determined by the double-disk test with erythromycin disk (15 μg) and clindamycin disk (2 μg) (BBL Microbiology Systems, Cockeysville, MD), as described previously.[27]

TABLE 1. *In Vitro* SUSCEPTIBILITIES OF ISOLATES OF 394 ISOLATES OF *S. pyogenes* RECOVERED FROM 1979–1998 AND 267 ISOLATES OF *S. pneumoniae* RECOVERED FROM OCTOBER 1998 TO MAY 1999

Bacteria (number of isolates)/ antimicrobial agent	*MIC (μg/ml)*[a]			*% of isolates*		
	Range	*50%*	*90%*	*S*	*I*	*R*
S. pyogenes (*n* = 394)						
Penicillin G	0.00375–0.06	0.015	0.015	100.0	0.0	0.0
Cefotaxime	0.0075–0.03	0.015	0.03	100.0	0.0	0.0
Cefepime	0.00375–0.06	0.015	0.06	100.0	0.0	0.0
Erythromycin	0.06–>512	16	>512	42.9	1.3	55.8
Clarithromycin	<0.03–>512	16	>512	38.5	2.6	58.8
Azithromycin	<0.03–>512	16	>512	28.1	19.1	52.8
Clindamycin	0.03–>512	0.25	>512	63.1	0	36.9
Tetracycline	0.06–128	32	64	27.8	0	72.2
Chloramphenicol	1–64	4	32	50.7	5.8	43.5
Rifampin	0.03–0.25	0.25	0.25	—	—	—
Vancomycin	0.25–0.5	0.25	0.5	100.0	0.0	0.0
Teicoplanin	0.25–0.5	0.5	0.5	100.0	0.0	0.0
Q/D	0.25–1	0.5	1	100.0	0.0	0.0
Linezolid	0.5–2	1	1	100.0	0.0	0.0
S. pneumoniae (*n* = 267)						
Penicillin G	0.012–8	1	4	24	51	25
Erythromycin	0.03–>512	512	>512	9	0	91
Clarithromycin	0.12–>512	>512	>512	5	0	95
Azithromycin	0.5–>512	>512	>512	3	0	97
Clindamycin	0.03–>256	>256	>256	40	0	60
Chloramphenicol	2–32	8	16	30	0	70
Tetracycline	4–64	32	64	0	1	99

S, Susceptible; I, intermediate; R, resistant; Q/D, quinupristin/dalfopristin.
[a]50% and 90%, MIC_{50} and MIC_{90}, respectively.

TABLE 2. PERCENTAGES OF 220 ISOLATES OF *S. pyogenes* AND 243 ISOLATES OF *S. pneumoniae* EXHIBITING AN ERYTHROMYCIN-RESISTANT PHENOTYPE AND GENOTYPE

Bacteria[a] *(number of resistant isolates)/resistance gene*	*Number (%) of isolates exhibiting indicated erythromycin-resistant*[b] *phenotype*		
	cML	*iML*	*M*
S. pyogenes (220)	142 (64.5)	1 (0.5)	77 (35.0)
mefA	0	0	77
ermAM	142	0	0
ermTR	0	0	0
S. pneumoniae (243)	158 (65.0)	1 (0.4)	84 (34.6)
mefE	0	0	80
ermAM	154	0	0

[a]*S. pyogenes* isolates were collected from 1979 to 1998 and *S. pneumoniae* isolates were collected from October, 1998, to May, 1999.

[b]Denotes isolates with erythromycin MIC of ≥1 μg/ml.

The presence of *ermAM* (*ermB*), *ermTR*, and *mefA* gene sequences in chromosomal DNA of erythromycin-resistant *S. pyogenes* and *ermAM* (*ermB*) and *mefE* gene sequences in erythromycin-resistant *S. pneumoniae* isolates was investigated by PCR with primers as described previously.[10,17,31,32]

RESULTS

Antimicrobial susceptibilities

Table 1 shows the MIC ranges, the MIC values at which 50% of isolates were inhibited (MIC_{50}), and the MIC_{90} values of the 14 antimicrobial agents for isolates of *S. pyogenes* and *S. pneumoniae*. More than half of the isolates were nonsusceptible (including intermediate and resistant) to erythromycin (57.1%), clarithromycin (61.4%) and azithromycin (71.9%). More than 90% of *S. pneumoniae* isolates were resistant to macrolides and tetracycline; otherwise 40% of the isolates tested were susceptible to clindamycin. All isolates were susceptible to quinuprisitin-dalfopristin and linezolid.

Resistance phenotypes and trend of resistance

Among the 220 erythromycin-resistant (MICs, ≥1 μg/ml) *S. pyogenes* isolates, 65.0% had an ML phenotype and 35.0% had an M phenotype (Table 2). Of the 243 erythromycin-resistant *S. pneumoniae* isolates, 34.6% had an M phenotype. Only one each of *S. pyogenes* and *S. pneumoniae* isolate exhibited in iML phenotype. *S. pyogenes* isolates with a cML phenotype had MIC_{90} values of >4-fold (azithromycin), 8-fold (chloramphenicol), to >16-fold (erythromycin and clarithromycin) higher than those of M-phenotype isolates (Table 3). Isolates of *S. pneumoniae* with an M phenotype had MIC_{90} values of macrolides >16-fold lower than those of cML isolates (Table 3).

A remarkably stepwise increase in erythromycin resistance

TABLE 3. *In Vitro* SUSCEPTIBILITIES OF 394 ISOLATES OF *S. pyogenes* AND 267 ISOLATES OF *S. pneumoniae* ACCORDING TO ERYTHROMYCIN SUSCEPTIBILITIES

Bacteria and antimicrobial agent	*MIC (μg/ml)*[a] *of erythromycin-susceptible isolates/M-phenotype/cML phenotype*		
	Range	*50%*	*90%*
S. pyogenes (*n* = 394)			
Erythromycin	0.06–0.25/16–32/>512	0.12/32/>512	0.25/32/>512
Clarithromycin	0.06–0.25/16–32/>512	0.12/32/>512	0.25/32/>512
Azithromycin	0.25–0.5/32–128/>512	0.5/64/>512	0.5/128/>512
Clindamycin	0.06–0.25/0.12–0.25/>512	0.12/0.25/>512	0.25/0.25/>512
Tetracycline	0.06–64/0.25–128/8–128	4/32/64	16/64/64
Chloramphenicol	2–8/2–4/1–64	4/4/32	4/4/32
S. pneumoniae (*n* = 267)			
Erythromycin	0.03–0.25/4–16/16–>512	0.12/4/>512	0.25/8/>512
Clarithromycin	0.12–0.25/4–16/4–>512	0.25/8/>512	0.25/8/>512
Azithromycin	0.5–1/2–64/32–>512	0.5/16/>512	0.5/32/>512
Clindamycin	0.03–0.12/0.06–0.25/256–>512	0.06/0.12/>512	0.12/0.25/>512
Tetracycline	4–64/16–64/32–64	4/32/64	16/64/64
Chloramphenicol	2–8/2–4/1–64	4/8/16	16/16/16

[a]50% and 90%, MIC_{50} and MIC_{90}, respectively.

(from 24% in 1985, 52% in 1994, to 86% in 1999) among the 1,155 isolates of *S. pneumoniae* obtained from 1985 to 1999 was found. However, the rates of clindamycin resistance (all clindamycin-resistant isolates were resistant to erythromycin) peaked in 1997 (63%) and declined in 1999 (47%). Rates of erythromycin resistance among 394 isolates of *S. pyogenes* ranged from 33.3% in 1979–1980, 63.3% in 1985–1986, 59.2% in 1993–1994, to 53.3% in 1997–1998. The incidence of erythromycin resistance and clindamycin susceptibility in *S. pyogens* (M phenotype) and *S. pneumoniae* (presumptive M phenotype) isolates during the study period are shown in Fig. 1. A dramatic increase of M phenotype erythromycin-resistant isolates was found with time for *S. pyogenes* (0% in 1979–1986, 17.2% in 1987–1988, 77.3% in 1995–1996, and 100% in 1997–1998), and increasing incidences with time were also found for *S. pneumoniae* (<20% before 1994, 28.4% in 1996, and 45.4% in 1999). The only one *S. pyogenes* isolate that exhibited an iML phenotype was found in 1996.

Resistance genotypes

The *ermAM* gene was detected in all isolates of *S. pyogenes* and all but four *S. pneumoniae* exhibiting cML or iML phenotype. The presence of the *mefA* gene was demonstrated in all isolates of *S. pyogenes* and the *mefE* gene in all but four *S. pneumoniae* isolates exhibiting an M phenotype. None of the *S. pyogenes* and *S. pneumoniae* isolates with an M phenotype contained an *ermAM* gene. None of the *S. pyogenes* and *S. pneumoniae* isolates had an *ermTR* gene.

DISCUSSION

The rapid increase in the incidence of M phenotype in erythromycin-resistant *S. pyogenes* isolates with time and varied rates of M phenotype in recently isolated erythromycin-resistant *S. pneumoniae* strains have been documented in studies from many countries.[4,9,10,17,19,20,23,24,28,31] However, compared with our study, the reported incidences of erythromycin resistance in these two species were relatively low (<20%) in most of these studies and the majority of the isolates subjected to phenotype determination were collected during a more limited time period. The data in this study are unique, because no previous studies have investigated the secular trends (for more than a 15-years period) of erythromycin-resistant phenotype distri-

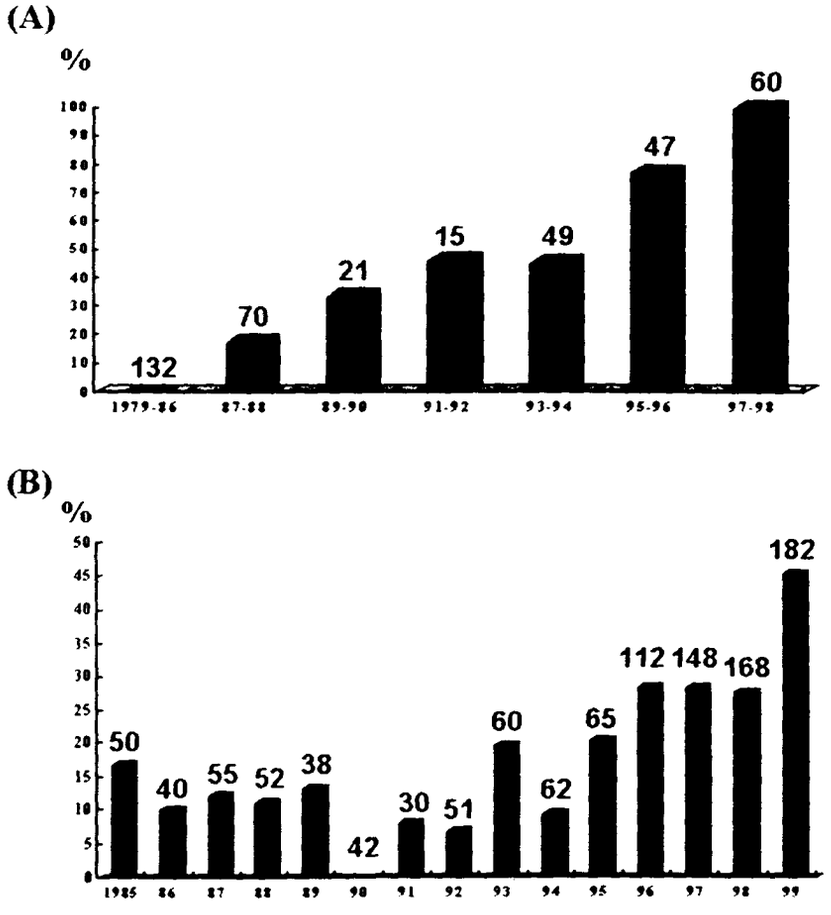

FIG. 1. Incidence of erythromycin-resistant and clindamycin-susceptible isolates of *S. pyogenes* and *S. pneumoniae* collected from National Taiwan University Hospital. **(A)** Erythromycin-resistant M phenotype isolates of *S. pyogenes* recovered from 1979 to 1998. The erythromycin-resistant M phenotype was determined for the isolates with erythromycin MICs, ≥ 1 μg/ml using the double-disk method. **(B)** Isolates of *S. pneumoniae* (resistant to erythromycin and susceptible to clindamycin by the disk diffusion method) recovered from 1985 to 1999.

bution among *S. pyogenes* and *S. pneumoniae* isolates, both with high incidences of resistance to macrolides.

Two facets regarding the secular trends in macrolide resistance of clinical isolates of *S. pyogenes* and *S. pneumoniae* in this study from Taiwan are of substantial interest. First, compared with our previous studies,[13-15] a remarkable upsurge in macrolide resistance among *S. pneumoniae* with time was found. However, a similar scenario was not found for erythromycin resistance in *S. pyogenes* isolates, which remained relatively stable (45–65%). Second, we found a simultaneous rapid emergence of erythromycin-resistant M phenotype in these two organisms, particularly in *S. pyogenes* isolates.

The distribution of erythromycin-resistant phenotypes has varied with time in studies from various geographic areas (Table 4).[9,10,17,19,23,24,28,29,31] Recent isolates of erythromycin-resistant *S. pyogenes* from different countries had a tendency to possess the M phenotype (42.2–97.4%).[9,10,19,23,31] However, variations in the proportion of *S. pneumoniae* isolates possessing the M phenotype varied remarkably from 5.8% in a study from European countries to 84.8% in studies from United States.[17,24,28,29,31] In previous studies from Taiwan, the difference of M phenotype distribution between recent *S. pyogenes* (77.3% in 1996–1997 and 100% in 1998–1999 from NTUH) and *S. pneumoniae* (only 34.6% in isolates from different parts of Taiwan in 1998–1999) isolates was significant. Further studies are needed to elucidate the discrepancies of M phenotype distribution between these two organisms, which have been exposed to the same environment of high selective pressure from macrolides.[18,23,35] In the interim, there are no convincing data pertaining to antibiotic usage patterns in Taiwan that might explain this observation.

Previous studies showed that nearly all macrolide resistance in streptococci is due to the *ermAM* and *mef* genes, but some uncommon genes might exist in *ermAM*- and *mef*-negative M phenotype strains.[10,17] M phenotype *S. pneumoniae* strains that carried both *mefA* and *mefE* genes identified by a hybridization study have been reported.[22] Furthermore, some *S. pneumoniae* had both *ermAM* and *mef* genes in isolates, which phenotypically appeared to be ML.[17] In the present study, not all erythromycin-resistant isolates of *S. pyogenes* and *S. pneumoniae* contained either the *ermAM* or the *mef* gene. This finding is similar to most previous investigations.[10,17,19,32-34] Although the *ermTR* gene was found in *S. pyogenes* strains with iMLS phenotype,[19,37] none of our erythromycin-resistant isolates, including the strains with iML phenotype, harbored this gene. Further molecular studies should be performed to find out the possibility of coexistence of *mefA* and *mefE* genes in our M-phenotype *S. pneumoniae* isolates and mutations in genes for either 23rRNA or ribosomal proteins in ML phenotype isolates of *S. pneumoniae* that did not harbor *erm* or *mef*.[33]

In Taiwan, we are continuously concerned with the persistently high incidence of macrolide resistance among respiratory bacterial pathogens, especially in *S. pneumoniae*. Although erythromycin or a newer macrolide is still suggested as the drug of choice or as an alternative to empirical treatment of upper or lower respiratory tract infection in many countries with a low incidence of macrolide resistance, this suggestion is not recommended in areas with high incidence of macrolide resistance in this organism.[2,11] Nevertheless, some studies have reported that the newer macrolides, such as azithromycin and clarithromycin, are still considered suitable drugs of choice for the empirical treatment of respiratory infection if there is a pre-

TABLE 4. SUMMARY OF DATA FROM SELECTED REPORTS FROM VARIOUS COUNTRIES ON THE DISTRIBUTION OF ERYTHROMYCIN-RESISTANT PHENOTYPES IN RECENT ISOLATES (AFTER 1990) OF *S. PYOGENES* AND *S. pneumoniae*

Bacteria	*Number of ER isolates (total number of isolates, % of ER isolates)*	*Country (year)*	*Number (%) of isolates exhibiting indicated ER[a] phenotype*			*Reference*
			cMLS$_B$	*iMLS$_B$*	*M*	
S. pyogenes						
	45 (396, 11.4)	Finland (1994–1995)	2 (4.4)	24 (53.3)	19 (42.2)	(19)
	39 (222, 17.6)	Spain (1996)	1 (2.6)	1 (2.6)	37 (94.8)	(9)
	309 (2,561, 12.1)	Spain (1997–1998)	8 (2.6)	0 (0.0)	301 (97.4)	(23)
	387	Italy (1995–1998)	64 (16.5)	120 (31.0)	203 (52.5)	(10)
	28	Ireland, Sweden (1993–1995)	2 (7.1)	5 (17.9)	21 (75.0)	(31)
	54 (107, 50.5)	Taiwan (1995–1998)	4 (7.4)	1 (1.9)	49 (90.7)	(PR)[c]
S. pneumoniae						
	66	United States, France, and South African (1993–1995)	10 (15.2)	0 (0.0)	56 (84.8)	(31)
	114	United States (1994–1995)	39 (34.2)	0 (0.0)	75 (65.8)	(29)
	147 (5029, 2.9)[b]	Canada (1993–1996)	64 (43.5)	—	82 (55.8)	(17)
	59 (594, 9.9)	Belgium (1995, 1997)	54 (91.5)	0 (0.0)	5 (8.5)	(20)
	69 (302, 22.8)	Italy (1993–1997)	65 (94.2)	0 (0.0)	4 (5.8)	(24)
	375 (1113, 33.)	Spain (1996–1997)	369 (98.4)	1 (0.3)	5 (1.3)	(3)
	302 (1601, 18.8)	United States (1997–1998)	83 (27.5)	5 (1.7)	214 (70.8)	(28)
	243	Taiwan (1998–1999)	158 (65.0)	1 (0.4)	84 (34.6)	(PR)[c]

[a]Denotes erythromycin-resistant (ER) isolates with erythromycin MIC ≥ 1 μg/ml.

[b]Included one isolate resistant to erythromycin and quinupristin.

[c]PR, Present report. (Because streptogramin B was not tested, strains stated as the MLS$_B$ phenotypes in this table were ML phenotypes.)

dominance of low-level resistance mediated by *mefE* in the *S. pneumoniae* populations.[2,8,17,20] This is because these newer macrolides have favorable bronchopulmonary pharmacokinetics, and reports of treatment failure are relatively uncommon.[1,25] Studies of the clinical efficacy of macrolide treatment for respiratory infections with relevant microbiological data are needed to understand fully the clinical importance of low-level macrolide resistance in *mef*-containing *S. pneumoniae* isolates. In Taiwan, however, under the present situation of a high incidence of macrolide resistance in *S. pneumoniae* isolates with a predominance of cML phenotype, the clinical use of a macrolide as a choice of empirical treatment for suspected bacterial respiratory infections is discouraged.

Although clindamycin MIC breakpoints and the inhibitory zone diameter for *S. pyogenes* and *S. pneumoniae* have been included in the NCCLS guidelines,[22] routine testing of clindamycin against these two organisms is not recommended, apparently due to the belief that macrolide resistance is common in the ML phenotype. Obviously, with the increasing proportion of M phenotype in these two organisms in Taiwan, clinical laboratories should add clindamycin to the list of routinely tested drugs, and susceptibilities to clindamycin in erythromycin-resistant isolates can be further indicative of a low magnitude of macrolide resistance on most occasions. In addition, clindamycin instead of a macrolide might have an emerging role in the empirical treatment of patients with penicillin-resistant *S. pneumoniae* infection, clinical failure after penicillin treatment for *S. pyogenes* infections, and for penicillin-allergic patients, particularly in children with pneumococcal infections because fluoroquinolones are not approved for general use in this population.[11,24,28]

In summary, we report an increase in the prevalence of streptococcal erythromycin resistance in recent two decades in Taiwan, with a concurrent increase in the prevalence of *mef* relative to the *ermB* gene. The increased prevalence appears to have occurred selectively in *S. pyogenes* over *S. pneumoniae*. The only solution to the problem of macrolide resistance in Taiwan is to decrease the inappropriate or frequent empirical use of macrolides. Furthermore, knowledge of the macrolide resistance mechanism and its prevalence with time in a given geographic area may impact the choice of empirical treatment especially if the most common resistance type (*mef*) is likely to respond to macrolide treatment.

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