Decreasing rates of resistance to penicillin, but not erythromycin, in *Streptococcus pneumoniae* after introduction of a policy to restrict antibiotic usage in Taiwan

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ABSTRACT

A 16% decline in rates of penicillin resistance in *Streptococcus pneumoniae* isolates in Taiwan between 1998–1999 (25%) and 2001 (9%) was associated with a 46% decrease in total penicillin and other cephalosporin usage in 2001 compared with 1999. However, erythromycin resistance in *S. pneumoniae* remained high (94%), despite a 45% decrease in macrolide consumption between 1999 and 2001.

Keywords Antibiotic use, erythromycin, penicillin, resistance, *Streptococcus pneumoniae*

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Taiwan has one of the highest levels of antibiotic resistance in the world [1] and, since 1996, has also become one of the epicentres for pneumococcal resistance to penicillin and macrolides [2–4]. A nationwide surveillance system (Surveillance of Multicentre Antimicrobial Resistance; SMART) has monitored antimicrobial resistance since 1998 [1,2]. Many measures to address high resistance rates, including enforcement of prescription-filling practices in the pharmacy (starting in 1997) and educational programmes dealing with appropriate antibiotic use (starting in 1998), have been instituted. Surveillance of antimicrobial resistance and strict control of antibiotic usage are important objectives for the Department of Health [1,2,5].

In February 2001, a new regulation was introduced, under which the costs of antimicrobial agents used in treatment of ambulatory patients with acute upper respiratory tract infections without evidence of bacterial involvement are not reimbursed [5].

Use (defined daily doses (DDDs)/1000 population/day) of antimicrobial agents in treatment of ambulatory patients decreased by 11% in 2000 compared with 1999 (26.5 vs. 29.7 DDDs), and, following implementation of the regulation, by a further 25% in 2001 compared with 2000 (26.5 vs. 19.8 DDDs) [5]. There was an 11% reduction in the use of antimicrobial agents for treating respiratory tract infections (including upper respiratory tract infections and non-upper respiratory tract infections) in 2000 compared with 1999 (16.1 vs. 18.0 DDDs), and a further 38% reduction in 2001 compared with 2000 (18.0 vs. 10.0 DDDs) [5]. Use of penicillins and cephalosporins in treatment of ambulatory patients declined from 15.7 DDDs/1000 population/day in 1999, to 14.0 in 2000, and 8.5 in 2001, while use of macrolides declined from 2.9 DDDs/1000 population/day in 1999, to 2.5 in 2000, and 1.6 in 2001. In addition, overall reductions of 46% and 45% occurred in the use of penicillins/cephalosporins and macrolides, respectively, in 2001 compared with 1999. Use of quinolones was 0.59, 0.61 and 0.51 DDDs/1000 population/day in 1999, 2000 and 2001, respectively [5].

Fig. 1 shows the annual incidences of penicillin-non-susceptible (zone diameter around a 1 μg-oxacillin disk of ≤19 mm, with corresponding MICs of ≥0.12 mg/L) *Streptococcus pneumoniae* and erythromycin-resistant *S. pneumoniae* among the 2362 clinical isolates of *S. pneumoniae* tested between 1984 and 2003 at the National Taiwan University Hospital with the standard disk-diffusion method. The isolation frequency of penicillin-non-susceptible *S. pneumoniae* increased markedly from 1993, with a peak of 86% in 1999, and subsequently declined to 70% in 2003. In contrast, stepwise increases in the frequency of erythromycin-resistant *S. pneumoniae* occurred after 1984, exceeding 90% by 1997, and reaching a plateau of 94% between 2001 and 2003.

Fig. 2 shows the frequency of isolation of penicillin-sensitive, -intermediate and -resistant,

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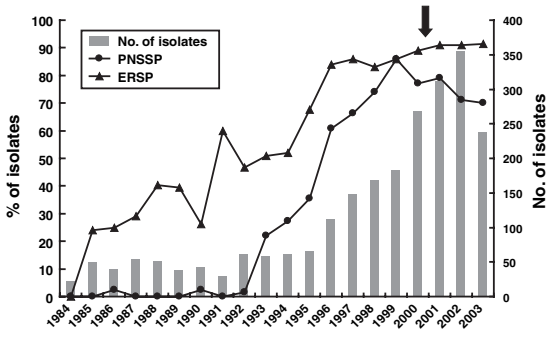

Fig. 1. Trend of decreased susceptibility to penicillin (PNSSP) and erythromycin (ERSP) among *Streptococcus pneumoniae* isolates recovered at the National Taiwan University Hospital between 1984 and 2003. The black arrow indicates the year when the National Health Insurance non-reimbursement policy for restriction of antibiotic use was implemented.

as well as erythromycin-resistant, clinical isolates of *S. pneumoniae*, as determined by agar dilution, in the periods November 1998 to May 1999, January 2000 to December 2000, January 2001 to December 2001, and August 2003 to December 2003. These isolates were from various clinical samples received at multiple medical centres participating in the SMART programme in different regions of Taiwan. The decrease in the frequency of penicillin resistance among *S. pneumoniae* isolates between 1999 and 2001 was associated significantly with the decreased use of penicillin and cephalosporins (r = 0.8008 (Pearson's correlation coefficient); p 0.4088) and macrolides (r = 0.8446; p 0.3596).

A left shift of the penicillin MIC distribution with time was also noted, with MIC_{50}s of 1 mg/L, 1 mg/L, 0.5 mg/L and 0.5 mg/L, and MIC_{90}s of 4 mg/L, 2 mg/L, 2 mg/L and 1 mg/L, respectively, in isolates from 1998 to 1999, 2000, 2001 and 2003. Among the erythromycin-resistant isolates collected in these periods, 60–67% exhibited high-level resistance to erythromycin (MICs >64 mg/L) [3,4]. Increasing rates of resistance to levofloxacin (MICs ≥8 mg/L) in these four periods were also observed, from 0.4% (one isolate), to 1.0% (two isolates), 0.4% (three isolates), and 2.6% (five isolates) [3,4].

Differential selective pressure for resistance and dissemination of resistant clones is thought to be responsible for geographical and chronological differences in resistance rates [6]. In Canada, a 20% decline in penicillin-non-susceptible *S. pneumoniae* isolates was noted between 1997–1998 and 2000–2001, corresponding to a 14% decline in total antibiotic consumption [7]. Other studies from the USA and several European countries have indicated that rates of penicillin and macrolide non-susceptibility among pneumococcal isolates collected after 2000 have stabilised, or even decreased, compared with trends in the early 1990s [7]. However, using active surveillance data for *S. pneumoniae* isolates in the USA, McCormick *et al.* [6] observed a decline in the proportion of isolates resistant to penicillin alone between 1996 and 2004, but a rise in erythromycin resistance during the same period [6]. Moreover, some of the success in reducing rates of non-susceptibility to penicillin or macrolides may have come at the expense of increasing resistance to fluoroquinolones, probably associated directly with increased use of these agents for the treatment of respiratory tract infections, because of the fear of growing penicillin and macrolide resistance [7]. In Taiwan, although data regarding antibiotic consumption during 2003 are not yet available, the use of fluoroquinolones is expected to have increased following the recent

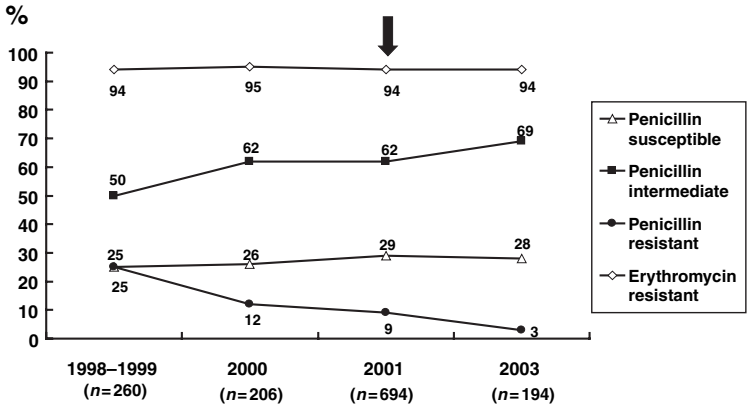

Fig. 2. Frequency of three categories of susceptibility to penicillin and resistance to erythromycin among *Streptococcus pneumoniae* isolates collected from multiple medical centres in Taiwan. The black arrow indicates the year when the National Health Insurance non-reimbursement policy for restriction of antibiotic use was implemented.

introduction of newer agents (levofloxacin in 2001 and moxifloxacin in 2002).

Rates of resistance decline appear to be slower than rates of resistance emergence, and appear to vary with different classes of agent. Appropriate use of antimicrobial agents appears to be the most important factor in limiting the spread of drug resistance among pneumococci. In Taiwan, the decreasing selective pressure for resistance, associated with a government policy of restricting antibiotic use for acute respiratory tract infections without evidence of bacterial involvement, has resulted in a decline in erythromycin resistance in *Streptococcus pyogenes* [8] and in penicillin resistance in pneumococci; however, the impact of this policy on macrolide resistance in *S. pneumoniae* is not yet clear. The present results indicate that continuous enforcement of the policy to limit use of antimicrobial agents is warranted. Such programmes may protect the effectiveness of newer antimicrobial agents and limit the emergence of resistance. Active surveillance of antimicrobial resistance through a nationwide system, and use of better anti-pneumococcal vaccines, are also required.

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RESEARCH NOTE

Distribution of *mef*(A)-containing genetic elements in erythromycin-resistant isolates of *Streptococcus pyogenes* from Italy

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ABSTRACT

In total, 124 *Streptococcus pyogenes* isolates were obtained from throat cultures of different symptomatic patients. All isolates showed M-phenotype macrolide resistance and contained the macrolide efflux gene *mef*(A). The isolates were screened for the presence and insertion site of *mef*(A)-containing genetic elements. In 25.8% of the isolates, *mef*(A) was found to be carried by elements belonging to the Tn*1207.3*/Φ10394.4 family inserted in the *comEC* gene, while 74.2% contained chimeric elements with a different genetic structure and chromosomal location, probably associated with the recently described 60-kb *tet*(O)–*mef*(A) element.

Keywords Efflux, erythromycin resistance, genetic structure, macrolide resistance, *mef*(A), *Streptococcus pyogenes*

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The acquisition of erythromycin resistance by group A streptococci (*Streptococcus pyogenes*) is associated frequently with an efflux system that

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