Pneumococcal Conjugate Vaccine (PCV7) Effect on Antibiograms: Serotype and Susceptibility Rate Changes in the SENTRY Antimicrobial Surveillance Program (USA)

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SENTRY ANTIMICROBIAL SURVEILLANCE

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AMENDED ABSTRACT

Background: Introduction of PCV7 in the USA (2000) resulted in well documented decreases of invasive pneumococcal disease and antibiogram changes. Protection against common PCV7 vaccine serotypes (VS) achieved 73% in 2004, but non-vaccine serotypes (NVS) appear to have emerged. The impact on respiratory isolates from children pre- (1998-1999) and post- (2003-2004) vaccine were serotyped.

Methods: 704 *S. pneumoniae* (SPN) from children (85.1%) and adults were serotyped, equal numbers from pre- and post-vaccine periods. Antibiograms were generated by CLSI broth microdilution methods and analyzed by VS, NVS, individual serotypes and sampled intervals.

Results: Rank order of serotypes markedly changed (variation, pre- vs post-vaccine): 19, not F (+17%) > 19F* (-3%) > 6, not B (+1%) > 35 (+5%) > 11 (+3%) >15 (+4%) > 6B* (-6%) > 23, not F (+2%) > 3 (-3%) >33 (+2%), VS marked with *. Five of the PCV7 serotypes dropped from the top 10 in frequency, 4 with a prevalence of <1.7% (9V, 18C, 4, 23F) and all VS decreased in prevalence (-1 to -12%). Persisting 19(A) and 19F strains were generally multidrug-resistant (MDR; PEN, ERY, CLD, TET, T/S). VS and NVS strains post-vaccine were generally more R and harboured more isolates with elevated fluoroquinolone MIC values (CIP-R; see Table). VS 19F, 14, 6B, 23F and 9V were MDR-SPN (≥4 drugs R).

Organisms/year (no.)	% resistant:[a] PEN	ERY	CLD	CHL	(CIP)	CTX	TET	T/S
VS (344)								
1998-1999 (241)	35	42	11	16	(0.4)	5	28	57
2003-2004 (103)	59	72	34	10	(1.9)	9	52	74
NVS (360)								
1998-1999 (111)	7	19	2	4	(0.9)	2	8	31
2003-2004 (249)	17	31	8	0	(3.2)	1	10	37
19F (135)	56	67	31	15	(2.2)	10	60	66
19, not F (83)	23	47	18	1	(1.2)	3	24	66

a. Categories by CLSI criteria (2006). PEN = penicillin; ERY = erythromycin; CLD = clindamycin; CHL = chloramphenicol; (CIP) = MICs at ≥4 µg/ml for ciprofloxacin; CTX = ceftriaxone; TET = tetracycline and T/S = trimethoprim/sulfamethoxazole

Conclusions: Dramatic VS replacement (68.5 to 29.3%) was observed with increases in R among VS and NVS isolates from 1998-1999 to 2003-2004 (except CHL and CTX [NVS only]). The immediate post-PCV7 decrease in R observed in the SENTRY Program has quickly been replaced by escalating R among NVS pneumococcal isolates.

INTRODUCTION

The development of the heptavalent pneumococcal conjugate vaccine (PCV7) has produced a very favorable decrease of invasive infections caused by PCV7-related serotypes since its release in 2000. This positive impact was associated with a rapid emergence of non-PCV7 serotypes producing "replacement invasive disease", questioning the sustained effects of the vaccine. By 2002, it was recognized that not all PCV7 serotypes were equally diminished e.g. serotype 19F appears to be persisting and that pediatric-aged patients are becoming a reservoir for proliferation of non-PCV7 serotypes. This was substantiated by the observation that serotype 19A isolates have markedly increased among invasive cases in 2002 and beyond (CDC ABCs program).

Since antimicrobial resistance among the *Streptococcus pneumoniae* serotypes and clones can vary widely, alterations in the occurrences of these prevalent serotypes can profoundly change antibiograms. An example of multiple resistant serotypes are 23F (clonal complexes Tennessee^{23F}-4; Spain^{23F}-1; Taiwan^{23F}-15) and 19F (Taiwan^{19F}-14), the latter detected as having two resistance mechanisms for the macrolides. This investigation examined the antibiograms of the prevalent serotypes before (1998-1999) and after (2003-2004) the introduction of the PCV7. All testing was performed by the reference methods in GLP/CLIA compliant laboratories.

MATERIALS AND METHODS

Organisms: The SENTRY Antimicrobial Surveillance Program collection of *S. pneumoniae* isolates from the USA was screened for possible use in a mathematical model experiment (Mera et al., ICAAC Abstract G-0135, 2006). The strains (704 total) were selected for isolates dominantly from children <6 years of age (85.1%) and across the nine CDC census zones. The adult strains (ages 18->65 years) numbered 105. The collections were divided into pre-vaccine (1998-1999; 352 strains) and post-vaccine (2003-2004; 352 strains) groups. Strains by contributing laboratories in both groups were matched for numbers and patient age, where possible. Occurrence rates of these documented infection-causing isolates could not be assessed because of the resistance surveillance prevalence design (SENTRY Program). Demographic data such as age, sex, isolate source and geographic origin (state, zone) were available for additional study and results are presented elsewhere.

Susceptibility testing: All pneumococcal isolates were tested for susceptibility to >25 antimicrobial agents with nine (representing eight classes) reported here: penicillin (PEN), erythromycin (ERY), clindamycin (CLD), chloramphenicol (CHL), tetracycline (TET), trimethoprim/sulfamethoxazole (T/S), ceftriaxone (CTX), levofloxacin (LEV) and ciprofloxacin (CIP). Methods of the Clinical and Laboratory Standards Institute (CLSI) were utilized in cation-adjusted Mueller-Hinton broth supplemented with 2-5% lysed horse blood. Interpretations of susceptibility and resistance were taken from the current CLSI document M100-S16 (2006). Panels were produced under GMP conditions by TREK Diagnostics (Cleveland, OH) and all quality control results were within CLSI published MIC ranges. Multiple drug resistance was defined as resistance to ≥two of the following agents: PEN, ERY, TET, T/S or one of the fluoroquinolones.

Serotyping: The 704 *S. pneumoniae* were serotyped by the University Hygienic Laboratory (Iowa City, IA) using reagents obtained from Statens Serum Institut (Copenhagen, Denmark) via MiraVista Diagnostics (Indianapolis, IN). All tests were performed as specified in the product package insert for Quellung reactions.

Analyses: Transmission dynamics of these pneumococci were used to develop a mathematical model that was based on a linear mixed effects approach (reported separately). The antibiograms of pre- and post-vaccination were listed for the seven PCV serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) and the 10 most prevalent non-PCV7 serotypes (3, 6 not B, 11, 15, 19 not F, 22, 23 not F, 33, 35, 38).

RESULTS

- The SENTRY Program for the USA documented a marked change in susceptibility rates occurring in 2002 (Figure 1). The two year reduction in penicillin- and erythromycin-non-susceptibility rates coincided with the introduction of PCV7. However, resistances to the ß-lactams and macrolides recently (2004-2005) have returned to levels noted in 2000-2001.
- Serotyping of equal numbers of *S. pneumoniae* before and after the PCV7 introduction (1998-1999 versus 2003-2004 isolates) noted a remarkable shift in the proportion of vaccine serotypes (VS) from 68.5 to only 29.3%. This was associated with increasing resistance among both VS and non-vaccine serotype (NVS) isolates, except for chloramphenicol (VS and NVS) and ceftriaxone (NVS only).
- Table 2 shows the significant declines in VS isolates except for 19F (73 and 62 strains) and the predominant replacement by 19(A) not F, 6 not B, 35, 11, 15 and 23 not F serotype isolates. Serotype 19(A) not F became the leading serotype (20.5%), overall.
- Isolates of some clones of the key serotypes possess antibiograms with a great range of susceptibility, varying from pan-susceptible to multidrug-resistant (MDR; Tables 1 and 3). Serotypes 19F, 19(A) not F, 14, 6B, 6 not B, 23F and 9V would be defined as generally MDR. In contrast, serotypes 3, 18C, 22 and 4 were rarely resistant to the tested antimicrobials.

Figure 1. Trends in penicillin and erythromycin non-susceptible (intermediate and resistant) results in the SENTRY Antimicrobial Surveillance Program (USA, 1997-2005). Modified from Johnson et al. *Diagn Microbiol Infect Dis* 2006; 56: 69-74.

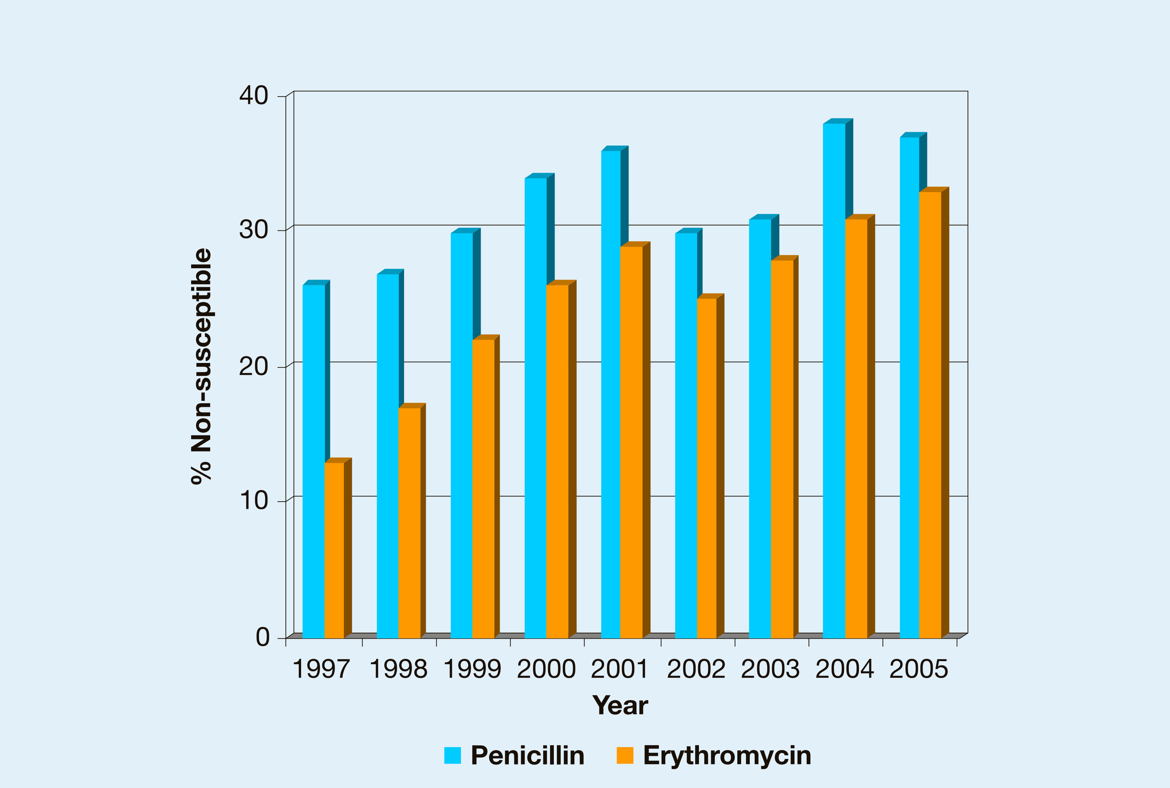

Table 1. Overall antibiograms of *S. pneumoniae* isolates categorized by vaccine and non-vaccine groups for the two monitored intervals (1998-1999 versus 2003-2004).

Time interval/vaccine group (no.)	% resistant:[a] PEN	ERY	CLD	CHL	TET	T/S	CTX	LEV	(CIP)
1998-1999									
Vaccine serotypes (241)	35	42	11	16	28	57	5	0	(0.4)
Non-vaccine serotypes (111)	7	19	2	4	8	31	2	0	(0.9)
2003-2004									
Vaccine serotypes (103)	59	72	34	10	52	74	9	0	(1.9)
Non-vaccine serotypes (249)	17	31	8	0	10	37	1	0	(3.2)
All strains									
Vaccine serotypes (344)	42	51	18	14	34	62	6	0	(0.9)
Non-vaccine serotypes (360)	14	27	6	1	9	35	1	0	(2.5)

a. CLSI (2006) breakpoint criteria. PEN = penicillin; ERY = erythromycin; CLD = clindamycin; CHL = chloramphenicol; TET = tetracycline; T/S = trimethoprim/sulfamethoxazole; CTX = ceftriaxone; LEV = levofloxacin; and (CIP) = ciprofloxacin at ≥4 µg/ml (Chen et al., 1999).

- The most noteworthy observations of resistance changes following PCV7 introduction were (Tables 1 and 3):
  - Although penicillin and macrolide resistance increased in VS and NVS strains, the greater NVS susceptibility rate resulted in a moderation of resistance rates for 2003-2004.
  - Also tetracycline, trimethoprim/sulfamethoxazole and chloramphenicol resistances declined or remained constant comparing pre- and post-vaccine intervals.
  - Fluoroquinolone resistance was rare, but first-step mutant subpopulations (% ciprofloxacin MICs at ≥4 µg/ml) increased post PCV7 introduction (Table 1) usually among serotypes 19F, 19(A) not F, 35, 11 and 15 (Table 3).

Table 2. Changes in *S. pneumoniae* serotypes among 704 strains before (1998-1999) and after (2003-2004) the introduction of PCV7 (SENTRY Program, USA).

Rank	Serotype (no): 1998-1999	2003-2004
1.	19F (73)[a]	19, not F (72)
2.	14 (53)	19F (62)
3.	23F (41)	6, not B (31)
4.	6B (39)	35 (25)
5.	6, not B (29)	11 (17)
6.	3 (22)	15 (17)
7.	9V (17)	6B (16)
8.	19, not F (11)	23, not F (13)
9.	18C (10)	3 (11)
10.	4 (8)	33 (10)
11.	35 (7)	14 (9)
12.	23, not F (7)	22 (9)
13.	11 (6)	38 (6)

Vaccine non-serotypes 15 (4), 38 (3), 33 (2) and 22 (2) = 3.1%

Vaccine serotypes 23F (6), 18C (5), 9V (4) and 4 (1) = 4.5%

a. Vaccine serotypes highlighted in red.

Table 3. Antibiograms for the 16 most encountered serotypes in this surveillance program.

Serotype (no.)	% resistant:[a] PEN	ERY	CLD	CHL	TET	T/S	CTX	LEV	(CIP)
19F (135)	56	67	31	15	60	66	10	0	(2.2)
19, not F (83)	23	47	18	1	24	66	3	0	(1.2)
14 (62)	36	47	8	5	13	57	13	0	(0.0)
6 not B (60)	20	55	5	3	9	57	0	0	(0.0)
6B (55)	22	46	18	7	19	66	0	0	(0.0)
23F (47)	51	45	9	38	40	75	17	0	(0.0)
3 (33)	0	9	0	0	3	3	0	0	(0.0)
35 (32)	41	13	0	0	0	9	0	0	(9.4)
11 (23)	0	17	0	0	0	22	4	0	(4.3)
9V (21)	57	43	0	0	5	81	0	0	(0.0)
15 (21)	0	29	14	0	18	5	0	0	(9.5)
23 not F (20)	15	10	0	0	5	35	5	0	(0.0)
18C (15)	0	0	0	0	0	13	0	0	(0.0)
33 (12)	0	17	0	0	0	92	0	0	(0.0)
22 (11)	0	0	0	0	10	0	0	0	(0.0)
4 (9)	0	0	0	0	0	0	0	0	(0.0)

a. CLSI (2006) breakpoint criteria. PEN = penicillin; ERY = erythromycin; CLD = clindamycin; CHL = chloramphenicol; TET = tetracycline; T/S = trimethoprim/sulfamethoxazole; CTX = ceftriaxone; LEV = levofloxacin; and (CIP) = ciprofloxacin at ≥4 µg/ml (Chen et al., 1999).

CONCLUSIONS

- The introduction of the PCV7 markedly altered the occurrence of invasive *S. pneumoniae* with decreases in six serotypes (14, 23F, 6B, 9V, 19C and 4) and subsequent replacement by 19(A) not F, 6 not B, 35, 11, 15 and 23 not F (Table 2).
- Inherent antibiogram differences in predominant clones within the prevalent serotypes greatly influenced the *S. pneumoniae* USA national antibiogram in 2003-2004.
- A moderation in resistance rates of these pneumococci was noted for ß-lactams, macrolides and other orally administered agents, but the risk of increased fluoroquinolone-resistant mutations may be increasing; however, more recent national trend statistics (Figure 1) indicates escalating penicillin and erythromycin non-susceptibility.
- Continued antimicrobial resistance surveillance with serotyping/epidemiologic studies will be required to guide therapeutic regimens, supplemented with the development of second-generation PCV products.

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