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## The relationship between pneumococcal serotypes and antibiotic resistance



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### ABSTRACT

*Streptococcus pneumoniae* (SP) causes significant burden of disease, including invasive pneumococcal disease and noninvasive diseases such as pneumonia and acute otitis media. SP has at least 93 different capsular serotypes, with the various serotypes having different propensities for producing disease or developing antibiotic resistance. An increase in the prevalence of antibiotic-resistant SP serotypes has been observed globally. The objective of this paper was to examine the relationship between antibiotic resistance and SP serotypes, with a primary focus on studies published in the past 10 years. Changing trends in antibiotic resistance and serotype distribution during this time, including those before and after the introduction of 7-valent pneumococcal conjugate vaccine (PCV7), were analyzed. Factors that influence the prevalence of antibiotic-resistant serotypes include antibiotic selection pressure, the use of PCV7, and the emergence and spread of antibiotic-resistant clones. The emergence of multidrug resistant serotype 19A is of particular concern. Antibiotic-resistant SP is a global problem that must be addressed through multiple strategies, including national vaccination programs, antibiotic control programs, and ongoing surveillance.

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## Contents

1. Introduction	T26
2. Current epidemiology of pneumococcal antibiotic resistance	T26
2.1. Penicillin resistance	T26
2.2. Macrolide resistance	T27
2.3. Fluoroquinolone resistance	T27
2.4. Multidrug resistance	T27
3. Effects of antibiotic consumption on SP resistance	T28
4. Relationship between serotypes and antibiotic resistance	T29
4.1. Serotypes and resistance in countries without PCV7 in their NIPs (or prior to PCV7 introduction or with low uptake of PCV7)	T29
4.1.1. Changing trend of serotype 19A	T29
4.2. Serotypes and antibiotic resistance in countries after the addition of PCV7 in the NIP	T29
4.2.1. Changing trend of serotype 19A	T30
5. Strategies to decrease SP antibiotic resistance and problems	T31
6. Conclusions	T32
7. Disclosures	T32
References	T32

## 1. Introduction

The prevalence of antibiotic-resistant *Streptococcus pneumoniae* (SP) has increased globally. The pattern of changes in antimicrobial susceptibility varies among serotypes and geographic regions [1–5]. Prevalence of resistant serotypes may be influenced by several factors, including overuse of antibiotics [4, 6–10], attendance in overcrowded institutions (e.g. daycare centers) [11–16], and low rates of vaccination [16].

Three pneumococcal conjugate vaccines (PCVs) are currently licensed for use in children. The 7-valent PCV (PCV7) was approved in the US in 2000 and in Europe in 2001 for use in children, and is now widely used throughout the world. PCV7 contains pneumococcal capsular polysaccharide serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to CRM<sub>197</sub>, a non-toxic diphtheria toxoid. Recently, the 10-valent (PCV10; additional serotypes 1, 5, 7F) and 13-valent (PCV13; additional serotypes 1, 3, 5, 6A, 7F, 19A) PCVs were licensed for use in children in the US, Europe, and other countries.

PCV7, which is given primarily to children aged <2 years, has reduced carriage rates and incidence of pneumococcal disease caused by vaccine serotypes (VT) and the related serotype 6A, and has indirect (herd) effects that have led to decreased incidence of VT disease in unvaccinated children and adults [11, 17–29]. Increased incidence of disease and nasopharyngeal carriage of non-PCV7 serotypes (NVT) has been observed following the introduction of PCV7 in national immunization programs (NIPs) [24, 30–32]. In particular, the NVT 19A has emerged as an increasingly important cause of invasive pneumococcal disease (IPD) in the US and other countries [33].

The objective of this paper is to examine the relationship between antibiotic resistance and SP serotypes, with a primary focus on studies published in the past 10 years

after the introduction of PCV7. Changing trends in antibiotic resistance and serotype distribution before and after PCV7 introduction are analyzed, as well as the effects of programs designed to reduce antibiotic usage levels.

## 2. Current epidemiology of pneumococcal antibiotic resistance

### 2.1. Penicillin resistance

Penicillin resistance is currently defined based on minimum inhibitory concentration (MIC) breakpoints as determined by the Clinical and Laboratory Standards Institute in 2008 [34–36], taking into account the mode of administration (oral or parenteral) and disease type (meningitis or non-meningitis) [34, 35].

Most studies cited in this paper have used the pre-2008 MIC breakpoints (intermediate: 0.12–1.0 mg/L; and resistant:  $\geq 2.0$  mg/L). Resistance rates varied depending on whether the pre-2008 or 2008 MIC breakpoints were used, limiting the comparability of studies using the different breakpoints. Overall trends in penicillin resistance are reported here; specific serotypes are discussed later in this paper.

Prevalence rates of penicillin non-susceptible pneumococci (PNSP) (i.e. those with intermediate susceptibility or resistance) varied widely among countries that did not include PCV7 in their NIPs. In Asia, PNSP rates in 2000–2001 ranged from 7.8% to 92% [2]. However, on application of the 2008 breakpoints in non-meningeal isolates from Asian countries, prevalence of penicillin resistance (MIC  $\geq 8.0$  mg/L) markedly decreased to <5% during 2008–2009 (Song, unpublished data). Other regions also showed moderately high rates of PNSP based on the pre-2008 breakpoints. In the southern and eastern Mediterranean region, the overall PNSP rate was 25% in 2003–2005 [37]. In 10 Latin American countries, PNSP rates were 30.5%

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