

Editorial

Impact of the Different Pneumococcal Serotypes on Chronic Respiratory Patients in Current Vaccination Strategies



Impacto de los diferentes serotipos de neumococo en pacientes con enfermedades respiratorias crónicas en las actuales estrategias de vacunación

Community-acquired pneumonia (CAP) represents a devastating event for older adults, particularly those with chronic respiratory diseases (CRD). *Streptococcus pneumoniae* is the leading pathogen responsible for CAP. Patients with CRD are significantly more vulnerable, with a 1.3–13.5-fold increased risk of pneumococcal pneumonia and a 1.3–16.8-fold higher likelihood of developing invasive pneumococcal disease (IPD).¹ This elevated risk is compounded by additional factors such as smoking and comorbidities that exacerbate disease severity and outcomes.

A Spanish cohort study identified CRDs as independent predictors of pneumococcal CAP (HR 2.66; 95% CI 2.47–2.86).² Specifically, patients with chronic obstructive pulmonary disease (COPD) exhibit a 2–5 times higher risk of pneumococcal CAP, with infections often triggering acute exacerbations, increased hospitalizations, and higher mortality rates. Asthma also poses a significant risk for IPD (OR 2.44; 95% CI: 2.02–2.96).³ The underlying vulnerability in CRD patients is attributed to compromised local immunity. This includes impaired innate and adaptive immune responses, epithelial damage that weakens the respiratory barrier, mucociliary dysfunction that impairs pathogen clearance, and frequent corticosteroid use, persistent airway colonization by pathogens such as *S. pneumoniae* and *Haemophilus influenzae*, which further predispose to infection.⁴

The main virulence determinant of *S. pneumoniae* is its polysaccharide capsule, which defines its classification into more than 100 different serotypes. The capsule enables pneumococcus to adhere to and colonize the nasopharynx and protects deeper antigenic structures.⁵ Another function of the capsule is to inhibit phagocytosis by neutrophils and macrophages, preventing opsonization and interfering with complement activation, thereby hindering the immune system's ability to eliminate the pneumococcus.⁶

Not all pneumococcal serotypes have the same pathogenic effect, and the polysaccharide capsule may differ in their ability to colonize, invade, and cause disease in CRD patients. In Spain, the serotypes most frequently causing CAP requiring hospitalization are 3 (7.8%) and 8 (7.9%). Serotype 3 is highly invasive and has been linked to severe CAP and increased mortality, especially in people with COPD. A study conducted in COPD patients in a Spanish hospital between 2013 and 2016 found that the most frequent serotypes in acute exacerbations were 11A (11%), followed by non-typeable

(11%) and 6C (10%). In the case of IPD, serotypes 3 and 8 stand out (14% each).⁷ Published information on pneumococcal serotypes in other CRDs is very limited.

A systematic review and meta-analysis, mainly including European studies, identified serotypes 3, 6A, 11A, 15A, 19F, and 31 as associated with higher mortality.⁸ Specifically, serotype 31 showed a mortality rate of 31.4%, followed closely by 11A with 30.1%. Serotypes 3, 19A, and 19F have been identified as significant risk factors for the development of respiratory failure in pneumococcal pneumonia. Moreover, serotypes 3 and 19A are frequently associated with severe systemic complications, including septic shock, while serotypes 1, 5, 7F, and 19A are more commonly implicated in invasive manifestations such as pleural effusion, empyema, and necrotizing pneumonia, reflecting their heightened pathogenic potential and tissue-destructive capacity.^{9–11}

The increased virulence of specific serotypes is not the result of a single factor but rather a synergistic combination of mechanisms. Among the principal determinants of enhanced virulence is the expression of a polysaccharide capsule, which significantly impairs opsonophagocytic clearance by host immune cells. This structural feature enables the pathogen to circumvent early innate immune defenses, thereby facilitating persistent colonization and systemic dissemination. Additionally, a diverse array of surface adhesins facilitates effective colonization of the nasopharyngeal mucosa and subsequent invasion of host tissues. This combination contributes to a sustained and elevated bacterial load, which perpetuates a cycle of inflammation and drives profound dysregulation of the host immune response, including excessive cytokine release and impaired pathogen recognition. It is further speculated that the high mortality associated with certain serotypes may be attributable to additional virulence factors, such as the ability to form biofilms that protect against both immune attack and antibiotic penetration, mechanisms of immune evasion including antigenic variation, and the presence of antibiotic resistance genes that complicate treatment and promote persistence of infection.¹²

Knowledge of local epidemiology as well as the relationship between pneumococcal serotypes and specific severe complications of pneumonia should be a determining factor in the design of pneumococcal vaccines.

Fortunately, most of these serotypes are included in the pneumococcal vaccines available on the market. The expansion of conjugated pneumococcal vaccines has been key in reducing morbidity and mortality from pneumococcal diseases in children and adults. Conjugate vaccines were designed to stimulate a T-cell-dependent immune response by linking a carrier protein to polysaccharide antigens, increasing immunogenicity and generating long-lasting immune memory, unlike polysaccharide vaccines.¹³ There are currently three conjugate vaccines marketed for adults in Spain (PCV13, PCV15, and PCV20), and a fourth one covering 21 serotypes received EMA marketing authorization on March 24, 2025, introducing eight additional serotypes and representing a strategic shift in vaccine design to better match circulating strain.¹⁴ The strategy for evolving conjugated vaccines (PCV15 and PCV20) has been to add serotypes to those contained in PCV13. However, PCV21 has changed that strategy by modifying the serotype composition, adding 8 unique serotypes and not covering some others. Thus, the objective is to cover a wider distribution of serotypes and adapt according to those circulating. Therefore, extended PCVs including more serotypes are being investigated. In the pipeline, the next potential vaccines are 24-valent and 31-valent PCVs.

Despite expanded serotype coverage and recent advances, persistent gaps remain due to non-vaccine serotypes, serotype replacement, waning immunity, especially in patients with chronic respiratory diseases, and epidemiological diversity. These limitations highlight the urgent need for serotype-independent vaccine strategies.¹⁵ These stimulate the immune system against conserved proteins, particularly surface adhesins present in all *S. pneumoniae* strains, offering broader and potentially universal immunity. Recombinant vaccines using pneumococcal protein candidates include pneumococcal surface protein A (PspA), pneumolysin, and others; recombinant protein-boosted PCVs or inactivated whole-cell vaccines.¹⁶ Various types of pneumococcal protein-based experimental vaccines have been formulated [multiple antigens presenting system (MAPS) and mRNA vaccines].

Vaccine selection must therefore target virulent serotypes prevalent especially in chronic respiratory patients to reduce severe outcomes, while future universal vaccines offer promise for broader protection.

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