

Newsletter New Vaccine Breakthroughs

💉 Why Is Serotype 3 Still a Problem in Pneumococcal Disease?

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✉️ Editor's Note / Introduction

Welcome to this edition of Newsletter New Vaccine Breakthrough—your trusted source for insights into vaccine science, policy, and innovation.

👉 This issue covers:

1. The Persistent Challenge of Serotype 3
2. Clinical Impact of Serotype 3
3. Mechanisms Behind Vaccine Evasion
4. Vaccine Effectiveness and Serotype 3
5. Public Health Implications

Let's dive in. 💬

📝 1. The Persistent Challenge of Serotype 3

🧠 Despite inclusion in vaccines like PCV13 and 23 valent vaccine, serotype 3 remains a leading cause of invasive pneumococcal disease (IPD) ([Harboe et al., 2009](#); [van Hoek et al., 2012](#); [Grabenstein and Musey, 2014](#); [World Health Organization, 2020](#)). Rates of disease attributable to serotype 3 have not declined since inclusion of serotype 3 in PCV13 ([Centers for Disease Control and Prevention, 2015](#); [Ladhani et al., 2018](#); [Wijayasri et al., 2019](#); [Goettler et al., 2020](#)). Understanding the reasons behind its persistence is crucial for effective prevention strategies.



S. pneumoniae isolates expressing most capsule types make **(A)** small round colonies similar to doughnuts on blood agar plate, but **(B)** serotype 3 and 37 pneumococci develop characteristically large mucoid colonies. From [Song et al. \(2013\)](#).

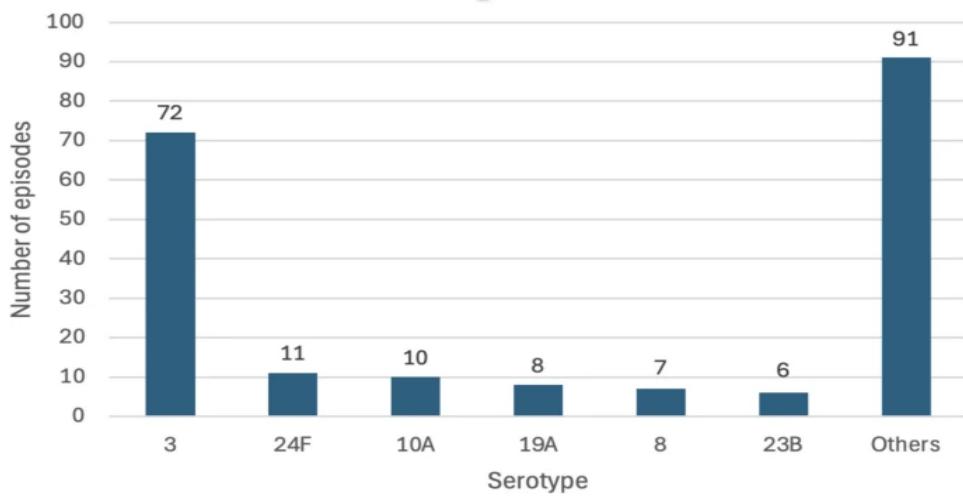
- ◆ **Sugar-Coated Killer: Serotype 3 Pneumococcal Disease**

Capsular polysaccharide (CPS), which surrounds the bacteria, is one of the most significant and multifaceted contributors to *Streptococcus pneumoniae* virulence. Capsule prevents entrapment in mucus during colonization, traps water to protect against desiccation, can serve as an energy reserve, and protects the bacterium against complement-mediated opsonization and immune cell phagocytosis. Among these, serotype 3 is perhaps the most problematic as serotype 3 infections are characterized as having severe clinical manifestations including empyema, bacteremia, cardiotoxicity, and meningitis; consequently, with a fatality rate of 30%–47%. Moreover, serotype 3 resists antibody-mediated clearance despite its inclusion in the current 13-valent conjugate vaccine formulation. The role of capsule in pneumococcal pathogenesis and the importance of serotype 3 on human

disease. We discuss how serotype 3 capsule synthesis and presentation on the bacterial surface is distinct from other serotypes, the biochemical and physiological properties of this capsule type that facilitate its ability to cause disease, and why existing vaccines are unable to confer protection. We conclude with discussion of the clonal properties of serotype 3 and how these have changed since introduction of the 13-valent vaccine in 2000.

2. Clinical Impact of Serotype 3:

- ◆ [in a prospective study in Catalunya](#) comprising all children < 18 years with IPD during a 5-year period (January 2018–December 2022) showed that serotype 3 is currently the most common serotype, responsible for many vaccine failures in fully vaccinated children. Serotype 3 often leads to complicated pneumonia in patients without underlying health conditions. These findings underscore the need for ongoing surveillance of IPD patterns to decide on the optimal vaccine strategy for future use.



3. Mechanisms Behind Vaccine Evasion

◊ Capsular Polysaccharide Shedding:

[Pneumococcal capsule shedding](#), or the release of capsular polysaccharides (CPS), is a key virulence factor that enhances pneumococcal invasion of host cells and its ability to cause invasive disease. [While the capsule primarily](#) protects against phagocytosis, shedding also plays a role in how pneumococci interact with epithelial cells. [Shedding significantly increases](#) the ability of

pneumococci to invade epithelial cells, a crucial step in the development of invasive pneumococcal disease.

- ◆ **High Antibody Requirement**

Studies indicate that [serotype 3](#) requires significantly higher antibody concentrations for protection compared to other serotypes. To overcome this competition, [higher antibody concentrations](#) are needed to ensure that sufficient antibodies are available to bind to the bacteria and trigger immune responses like phagocytosis.

- ◆ **Unique Capsule Synthesis Pathway**

The unique capsule synthesis pathway that some bacteria use, differing from the more common "[wzy-dependent](#)" pathway, is the synthase-dependent pathway; this distinctive mechanism allows certain serotypes of bacteria, like *Streptococcus pneumoniae* [serotypes 3 and 37](#), to produce a capsule that is resistant to antibodies generated by vaccines targeting the common wzy-dependent pathway, thereby contributing to their ability to evade the immune system.

⌚ 4. Vaccine Effectiveness and Serotype 3:

PCV13 shows reduced effectiveness against serotype 3, with some studies reporting [vaccine failures](#) even in fully vaccinated individuals. While the PCV13 vaccine offers protection against various pneumococcal serotypes, including serotype 3, studies have shown that the [vaccine's effectiveness against serotype 3](#) may be lower compared to other serotypes. Specifically, some studies suggest a lower antibody response to [serotype 3 compared to other serotypes](#) included in the vaccine. This reduced effectiveness has been observed in both children and adults, though the specific impact can vary depending on the clinical presentation of the disease.

[PCV15 immunogenicity studies](#) showed that PCV15 has numerically improved antibody response against serotype 3 compared with PCV13, whereas PCV20 missed one of the noninferiority endpoints against serotype 3 in the pivotal phase 3 study.

Thanks for reading!

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