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Review

Nasopharyngeal microbial interactions in the era of pneumococcal conjugate vaccination

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ABSTRACT

The nasopharynx of children is often colonised by microorganisms such as *Streptococcus pneumoniae* (the pneumococcus) that can cause infections including pneumonia and otitis media. In this complex environment, bacteria and viruses may impact each other through antagonistic as well as synergistic interactions. Vaccination may alter colonisation dynamics, evidenced by the rise in non-vaccine serotypes following pneumococcal conjugate vaccination. Discovery of an inverse relationship between *S. pneumoniae* and *Staphylococcus aureus* carriage generated concern that pneumococcal vaccination could increase *S. aureus* carriage and disease. Here we review data on co-colonisation of pathogens in the nasopharynx, focusing on *S. pneumoniae* and the impact of pneumococcal vaccination. Thus far, pneumococcal vaccination has not had a sustained impact on *S. aureus* carriage but it is associated with an increase in non-typeable *Haemophilus influenzae* in acute otitis media aetiology. Advances in bacterial and viral detection methodologies have facilitated research in nasopharyngeal microbiology and will aid investigation of potential vaccine-induced changes, particularly when baseline studies can be conducted prior to pneumococcal vaccine introduction.

Contents

1. Introduction

Colonisation of the nasopharynx is considered a prerequisite for two major childhood diseases, bacterial pneumonia and otitis media. Pneumonia is the leading cause of death of children under the age of five years worldwide [1]. The Gram-positive bacterium *Streptococcus pneumoniae* (the pneumococcus) is the most

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common cause of pneumonia in this age group and can cause invasive diseases such as septicaemia and meningitis. It is responsible for at least 800,000 infant deaths per year, the vast majority of which occur in low-income countries [2]. Otitis media is the most frequently reported paediatric bacterial infection, with approximately 80% of children experiencing an episode by the age of three years [3]. Otitis media is predominantly caused by *S. pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* [4,5] and can cause long-term hearing damage that may impair language development [3,6]. Nasopharyngeal carriage serves as the major reservoir for maintaining these bacterial species within a population [7].

Many environmental, genetic, and socio-economic factors influence the likelihood of nasopharyngeal carriage of a particular species [7–10]. The biological relationships within the nasopharynx are complex: often children carry more than one serotype of *S. pneumoniae*, together with other bacterial pathogens such as *H. influenzae* and *M. catarrhalis* and commensal flora. Since nasopharyngeal carriage is important in the development of disease within an individual as well as in the maintenance and spread of pathogens within a population, understanding the dynamics of bacterial colonisation is important for improving respiratory disease prevention and treatment. Although conjugate vaccines against *S. pneumoniae* reduce carriage of the serotypes contained in the vaccine, there is little or no impact in most populations on the overall prevalence of pneumococcal carriage as other serotypes become more common [11,12]. This process, known as serotype replacement (see Weinberger et al. [12]) is exemplified by increased carriage and disease prevalence caused by serotype 19A, observed in several populations following the introduction of seven valent pneumococcal conjugate vaccine (Prevnar®; PCV7) [13,14].

In 2004, two studies identified an inverse relationship between the nasopharyngeal carriage of *S. aureus* and vaccine-type strains of *S. pneumoniae* in healthy children, indicating a competitive interaction between the two species [15,16]. These findings raised concerns that widespread pneumococcal vaccination could increase *S. aureus* carriage and subsequent disease [17]. Additionally, pneumococcal vaccination has been associated with shifts in otitis media aetiology, with non-typeable *H. influenzae* (NTHi) surpassing *S. pneumoniae* as the dominant causative organism in several studies [4,18–20]. Combined, these observations prompted further investigations into microbial interactions in the respiratory tract.

Here we review clinical studies on the nasopharyngeal co-colonisation by pathogens in children and the effects of pneumococcal conjugate vaccination. Although other pathogens such as *Streptococcus pyogenes* can colonise the respiratory tract, this review focuses on *S. pneumoniae*, *S. aureus*, *H. influenzae*, and *M. catarrhalis* as these species are most commonly examined in nasopharyngeal carriage studies. Like *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* are common colonisers of the nasopharynx and major causes of paediatric infections. Although *S. aureus* primarily resides in the anterior nares [21] and displays different age-related colonisation patterns from *S. pneumoniae* (highest in neonates and older children) [15,16], it can cause of childhood pneumonia [22] and often is examined in the context of pneumococcal vaccination due to its inverse relationship with pneumococci, which is generally but not always limited to vaccine-type pneumococci. Community acquired methicillin-resistant *S. aureus* infections in children have risen dramatically since 2000 [23], the same year PCV7 was introduced in the United States, although no direct links have been established.

We also discuss experimental studies relating to mechanisms of microbial interactions and highlight emerging areas of research in this area, including investigations on nasopharyngeal microbiota and interactions between bacteria and respiratory viruses (Fig. 1). Greater understanding of microbial interactions in the respiratory tract is needed, as these interactions may influence disease development and vaccine outcomes. Note that we present an overview of published clinical and experimental studies rather than a systematic review. Relevant studies were identified by searching PubMed for articles (published in English and Spanish) on the four bacteria of interest combined with the following terms: “vaccination”, “PCV”, “colonisation” and “co-colonisation” (British and American spelling), “carriage”, “nasopharynx”, “influenza”, “otitis”, “microbiota”, “bacterial interference”, and also by searching publications citing the two original studies that identified the negative relationship between *S. pneumoniae* and *S. aureus* [15,16].

2. Colonisation dynamics in healthy children

Examining bacterial carriage in healthy children is key to understanding potential interactions between colonising species and the impact of pneumococcal vaccination on the nasopharyngeal environment. During illness, an active respiratory tract infection is likely to alter nasopharyngeal biology. Xu et al. [24] recently demonstrated that nasopharyngeal colonisation patterns differ between healthy children and at the onset of acute otitis media (AOM). High densities of causative organism(s) may reduce the relative proportion of other colonising species [25], and infection may stimulate an innate immune response that could affect resident bacteria [26]. Additionally, children with current or recent infections typically are treated with antibiotics that may have differential effects on colonising species [27]. Results from selected studies on bacterial associations in healthy children are summarised in Table 1, with examples highlighted below.

3. *S. pneumoniae* and *S. aureus*

Numerous studies have confirmed the negative association between *S. aureus* and *S. pneumoniae* (specifically vaccine-type pneumococci in most but not all studies) in a variety of paediatric populations [28–32]; Table 1. Three studies did not report a negative association. One was performed in a population with high PCV7 vaccine coverage, where carriage of vaccine-type *S. pneumoniae* was rare [33], and two other studies did not analyse vaccine-type and non vaccine-type *S. pneumoniae* separately [9,34].

The biological mechanisms driving the negative association between *S. pneumoniae* and *S. aureus* remain unclear. *S. pneumoniae* can kill *S. aureus in vitro* via the production of soluble hydrogen peroxide [35], which has been shown to induce lysogenic prophages in *S. aureus* [36]. However, this ability does not appear to play a significant role in colonisation. In a neonatal rat model, hydrogen peroxide production by *S. pneumoniae* did not affect *S. aureus* colonisation densities [37]. In humans, bactericidal abilities of *S. pneumoniae* and susceptibility of *S. aureus* did not differ between strains isolated from co-colonised children and non co-colonised children [38], nor was co-colonisation found to be associated with particular bacterial genotypes [39]. The presence of the pneumococcal pilus, which aids in adhesion and influences host immune responses [40,41], was shown to lower the odds of co-colonisation with *S. aureus* significantly, suggesting that it may be a determinant of bacterial interference *in vivo* [42]. Vaccine-type strains of *S. pneumoniae* are significantly more likely to carry the pilus gene *rrgC* [43], which may be one explanation why negative associations between *S. aureus* and pneumococci are typically limited to vaccine serotypes.

Host immunity likely plays a role in the inverse relationship between *S. aureus* and *S. pneumoniae*, as it was not observed in HIV-positive children [44,45]. Examination of anti-pneumococcal or anti-staphylococcal antibodies in infants found that serum IgG