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Editorial

Nasopharyngeal colonization and invasive disease in *Streptococcus pneumoniae*: Two critical aspects of the pneumococcal pathogenesis with many similarities

Colonización nasofaríngea y enfermedad invasiva por *Streptococcus pneumoniae*: dos aspectos críticos de la patogenia de neumococo con muchas similitudes

Asymptomatic colonization of the upper respiratory tract by *Streptococcus pneumoniae* (pneumococcus) is a prerequisite for the pathogenesis process and for the subsequent development of non-invasive and invasive diseases.[1] One of the major limitations for the development of preventive measures against pneumococcus is the wide diversity of serotypes that can potentially colonize and produce disease with up to 105 different serotypes described so far, three of them described in the past year 2023.[2–6] In the vaccine development field is crucial to understand not only the distribution of serotypes contributing to invasive pneumococcal disease (IPD) but also those associated with nasopharyngeal colonization. This knowledge is critical because vaccines diminishing the carrier state are essential for providing herd protection to non-vaccinated individuals. In Spanish children, PCV13 and PCV15 are currently authorized for pediatric use whereas PCV20 is still in the process of approval by the European Medicines Agency (EMA) although the Federal Drug Agency (FDA) in USA has already approved this vaccine for children. In adults, four vaccines are commercially available and used depending on the region's vaccine policy, the 23-valent polysaccharide vaccine (PPV23) and three conjugate vaccines PCV13, PCV15 and PCV20.[7]

In the first study related to this editorial, de Felipe et al.[8] evaluate the serotype distribution of nasopharyngeal colonization in Spanish children from a particular region (Sevilla) including the frequency of molecular genotypes that are circulating after the implementation of PCV13 in the vaccine calendar. This was a cross-sectional study containing nasopharyngeal strains from children of ages ranging 6 months to 5 years old comparing two periods (PCV7 vs. PCV13). Colonization rates were lower in the PCV13 period compared to the PCV7 although in both cases, colonization by vaccine serotypes clearly declined after the use of these vaccines. Reduction of serotype 19A was very strong whereas serotype 19F showed a high persistence rate when both periods were compared. Reduction of serotype 19A in carriage confirms the effectiveness of using PCV13 and demonstrates that the use of PCV13 has been a great prophylactic strategy to reduce the impact of this serotype causing IPD in children.[9] However, the high levels of serotype 19F found in the manuscript by de Felipe et al.[8] is not surprising as other authors have shown high prevalence rates of this serotype despite the introduction of PCV13.[10,11] Moreover, nasopharyngeal colonization by serotype 3 was scarce, which is very intriguing because this is a very prevalent serotype causing IPD in Spanish children despite conjugate vaccination and it is associated with high fatality rates.[9,12]

Among non-PCV13 serotypes, the authors observed a high proportion of cases by serotypes 15B/C and 11A that are consistent with similar studies analyzing nasopharyngeal carriage.[10,11] Hence, the rise of cases by these two serotypes might be counteracted by the pediatric use of PCV20 which includes 15B and 11A.[13]

From the molecular epidemiology perspective, it is interesting the increase in nasopharyngeal colonization in the PCV13 period of two particular genotypes such as ST6521 for serotype 11A and ST1766 for serotype 31. In the case of serotype 11A, this situation is worrisome because this genotype has been found to avoid very efficiently the host immune response and it has a great ability to form biofilms[14] as well as serotype 31 which is a good biofilm former.[15] In terms of invasive disease potential, these two aspects are very relevant because biofilm formation enhances the evasion of complement-mediated immunity and increases the potential to induce antibiotic resistance.[16] In this sense, serotype 11A has become the major cause of IPD associated with reduced susceptibility to penicillin, and serotypes 11A and 31 are associated with the highest fatality rates.[12] In addition, during the first pandemic year by SARS-CoV-2 the MIC_{90} to cefotaxime of Spanish clinical isolates of serotype 11A changed from 2 μg/ml to 4 μg/ml which is considered resistant and therefore, prevention of serotype 11A should be considered of high priority due to its marked invasive and resistant potential.[17]

In the second study related to this editorial, Losada-Castillo et al.[18] have characterized the serotype distribution of *S. pneumoniae* isolates from IPD cases in the Spanish region of Galicia and the susceptibility patterns of these strains during the period 2011–2021. The authors analyzed 2869 clinical isolates of all ages

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being highly representative those from blood culture (89.5%) followed by CSF (5.4%), pleural fluid (2.3%) and other samples (2.8%). Serotypes included in PCV13 showed a descending trend from 2011 to the last period evaluated (55.2% vs. 19.3%) whereas specific serotypes included in PCV20 that are not included in PCV13 or PCV15 showed an increasing trend from 12.5% to 41.3%. The rise of specific serotypes contained in PCV20 was observed in all age groups (children and adults). These results are consistent with national epidemiological data confirming the emergence of non-PCV13 serotypes especially those included in PCVs of broader coverage.[9]

Interestingly, serotype 3, which is one of the most prevalent serotypes of PCV13 in children and adults, showed a reduction trend from 17.2% (period 2011–2013) to 14.3% (period 2014–2017) and 11% (period 2018–2021). In contrast, serotype 8 (non-PCV13 serotype but included in PCV20 and PPV23), had a marked increase trend from 3.6% (period 2011–2013) to 16% (period 2014–2017) and 27.8% (period 2018–2021). Serotype replacement of serotype 8 in Spain occurred mainly in the adult population since 2015 being the major cause of IPD in adults in the last pre-pandemic year 2019 suggesting the importance of preventing this serotype.[9] The emergence of serotype 8 has been observed in other Spanish regions such as Madrid or even in other countries worldwide confirming that serotype replacement by this serotype is a generic event and is not specific of the Spanish region of Galicia.[12,19]

In terms of antibiotic resistance, the proportions of resistant strains decreased throughout the period of the study (2011–2021) showing a similar pattern observed in a previous national study by Sempere et al. when the period 2004–2020 was evaluated.[20] These results confirm that the use of PCVs in Spain, first PCV7 followed by PCV13 was an effective strategy to reduce the burden of disease caused by vaccine-covered serotypes associated with antibiotic resistance. In addition, when PCV13 was introduced in Galicia, the majority of isolates with multidrug resistance belonged to serotype 19A. This is consistent with national data confirming the emergence of this serotype after the use of PCV7 in Spain.[17] However, in the last period of the study (2018–2021) the authors observed an increase of serotypes 11A and 15A associated with penicillin and cefotaxime resistance. These results are in agreement with a national study recently published confirming the relevance of these serotypes, specially serotype 11A, as a major cause of resistance to β-lactam antibiotics even during the COVID-19 pandemic.[17] Hence, despite the high prevalence of serotype 8 as a major cause of IPD, its impact on antibiotic resistance was scarce because the majority of strains of serotype 8 were fully susceptible to the antibiotics tested as it has been reported previously for this serotype.[17]

Analysis of serotype distribution comparing the different vaccines available confirmed that for penicillin and cefotaxime, PCV13 and PCV15 would prevent the same proportion of resistant strains in Galicia whereas the use of broader spectrum vaccines such as PCV20 or the 23-valent polysaccharide (PPV23) would prevent a similar level of resistant strains. These findings correlate with previous results from the Spanish Pneumococcal Reference laboratory[17] and the reason is because serotypes 22F and 33F (included in PCV15, PCV20 and PPV23) and serotypes 2, 9N, 17F and 20 (included in PPV23 but not in PCV20) are fully susceptible to β-lactams. In the case of reduced susceptibility to cefotaxime, the use of PCV20 or PPV23 would prevent up to 92% of all the circulating isolates in Spain.[17] However, prevention of resistant strains to erythromycin would be improved with the use of broader spectrum vaccines such as PCV15, PCV20 and PPV23.

In summary, the use of PCVs in the pediatric population has clearly shown a significant impact in reducing the burden of disease caused by vaccine serotypes, although its influence on nasopharyngeal carriage is less known. The study conducted by de Felipe et al.[8] contributes valuable insights of the serotype and genotype distribution affecting the nasopharyngeal tract of vaccinated children, including the circulation of serotypes/genotypes associated to multidrug resistance. This holds particular epidemiological relevance, as the serotypes colonizing the upper respiratory tract have the potential to produce local and systemic infection or even disseminate to other children or the elderly population who are the major risk groups for developing IPD. In this point is where the second study by Losada-Castillo et al.[18] merits attention, as it unveils the serotype distribution of isolates causing IPD in a distinct Spanish region. Remarkably, the results, including the analysis of MDR prevalent serotypes, align closely with those of the first study. These findings underscore the importance of surveillance studies not only addressing the serotypes that produce IPD but also the serotypes involved in the carrier state. This dual approach is critical, as many of these carrier serotypes can subsequently emerge as major contributors to pneumococcal disease.

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Conflict of interest

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