Enfermedades Infecciosas y Microbiología Clínica 39 (2021) 483–485

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Editorial

Impact of pneumococcal vaccination on clinical forms of invasive *Streptococcus pneumoniae* infection in pediatrics population

Repercusión de la vacunación antineumocócica en las formas clínicas de infección invasiva por *Streptococcus pneumoniae* en la población pediátrica

Dear Editor:

Pneumococcus is actually pneumococci. To date, 101 different serotypes of *Streptococcus pneumoniae* have been identified. From those serotypes, the ones taken into account are only the capsular antigens that define the serogroups and serotypes, because under the same serotype (number and letter) there are different genotypes.[1]

For years there has been a pneumococcal vaccine made from capsular polysaccharide antigens, specifically 23 serotypes. Theoretically, it is the vaccine with the broadest coverage to date. As the vaccine is made up exclusively of polysaccharide antigens, it has efficacy limitations due to the fact that they are thymus-independent antigens that do not induce immunological memory or secondary antibody responses and are very poorly immunogenic in young children, especially below the age of 2 years.[2]

The first conjugate pneumococcal vaccine was put to market at the beginning of the 21st century. Conjugate vaccines contain capsular polysaccharides bound to a protein carrier, which make the antigens become thymus-independent and, in this way, induce immunological memory and give rise to a rapid and robust secondary antibody response. Furthermore, they are immunogenic from the first months of life and lead to mucosal immunity, which reduces the state of nasopharyngeal carrier.[2]

This first pneumococcal conjugate vaccine was heptavalent: it contained capsular antigens from seven serotypes of *S. pneumoniae*. The choice of serotypes had been essentially made according to the prevalence in the United States of America.[3] Not all countries had the same distribution of prevalent serotypes, so the result of this vaccine was uneven. Where the vaccine covered most of the serotypes that cause serious infections – as it so happened in most states of the USA – there was a rapid and sustained decrease in the burden of invasive and serious pneumococcal infections in children.[4] In contrast, in countries where many pneumococcal infections were caused by serotypes other than the seven included in the vaccine, there was an early a shift in the pneumococcal serotypes responsible for infections. This shift outweighed the benefit, and often changed the characteristics of pediatric pneumococcal diseases.[5]

Regarding the situation in Spain, when the heptavalent conjugate pneumococcal vaccine was introduced, more than half of the invasive and serious pneumococcal infections were caused by serotypes not contained in the new vaccine,[6–8] which led to rapid replacement and doubtful effectiveness.[9]

Taking into account that the various serotypes of *S. pneumoniae* have different clinical behaviors,[10] the random modification of the circulating serotypes in a given population led to variable consequences: some foreseeable and others unpredictable. Some consequences were beneficial and others paradoxically harmful. Some were generalized, while others were more or less geographically localized according to the emerging serotypes and those that became predominant in replacement.

The main positive effect, practically universal, was the reduction in the rate of resistance to penicillin.[4,7] That was because were eliminated the serotypes that had been in the nasopharynx of children for many years in a carrier state, subjected to the repeated pressure of the antibiotics most commonly used in pediatrics such as amoxicillin (alone or combined with acid clavulanate) and some cephalosporins and macrolides. It should be noted that the use of macrolides has been related to an increase in pneumococcal resistance not only to macrolides but also to penicillin.[11]

Furthemore, the most important beneficial effect of the conjugate vaccine was the reduction of serious forms of pneumococcal disease, preventing mortality and sequelae. But that effect did not happen everywhere. In fact, it was not significantly appreciated in Spain, where there were even differences between Regions, specially significant in the case of meningitis.[6,8,12,13]

Another positive beneficial effect, in this case unexpected, was the decrease in the incidence of pneumococcal disease in the population over 65 years of age,[14] due to an indirect protective effect resulting from the lower transmission of pneumococci from children to their grandparents.

In some areas of Europe, including Catalonia, the net result of pneumococcal vaccination in children with the heptavalent conjugate vaccine has not been satisfactory. What was clear from the very beginning was the extraordinary effectiveness of the heptavalent conjugate vaccine in preventing infections due to the

DOI of original article: https://doi.org/10.1016/j.eimc.2020.08.022

https://doi.org/10.1016/j.eimce.2021.07.009

seven serotypes included. Thus, in general, the incidence of occult bacteremia, whose main etiological agents were *S. pneumoniae* serotypes 14 and 6A/B, followed by 19A/F, was reduced[8]; the number of meningitis changed little[12,13]; and the number of complicated pneumonia increased signifinantly.[15,16] Although the low frequency in absolute numbers of infections in patients with immunodeficiency, splenectomy, sickle cell disease or with anatomical risk factors such as cerebrospinal fluid fistulae prevents reliable conclusions from being drawn, it does not appear that they were significantly reduced either, which is not surprising since there are more than 90 pneumococcal serotypes left to cause them.

The most notable negative fact was the increase in the number and severity of lung infections. Although the possibility of relevant changes in the epidemiology of pneumococcal infections was predictable,[17] the increase in the number of cases of complicated pneumonia, with bacteremia,[15] empyema and/or lung necrosis[16] was not. This consequence occurred especially in places where serotypes 1, 3 and 19A were among the emerging replacers.[16,18] The three serotypes, very infrequent in the years prior to the generalized introduction of the heptavalent conjugate vaccine, have a significant tropism for the lung and a special aggressiveness; otherwise they are very different from each other. Serotype 1 is not usually part of the nasopharyngeal flora, it has an exceptional carrier status, and is consistently sensitive to penicillin. Serotype 3 and serotype 19A are often part of the nasopharyngeal flora, although they differ in other aspects: serotype 3 is more common in adults, has a thick capsule and so far vaccines have not been very effective against it; serotype 19A became a predominant colonizer in children after the introduction of the heptavalent conjugate vaccine and has a tendency to develop resistance to penicillin and other antibiotics.[7,12,18]

In the current issue of EIMC, González-Peris et al.[19] publish an interesting prospective observational study of pediatric cases of pulmonary infection with proven pneumococcal etiology. It includes bacteremic pneumonia without further complications, pneumonia with pleural effusion and necrotizing pneumonias. The study has been carried out in Catalonia, Spain, between 2012 and 2016, a period in which 13-valent pneumococcal vaccination was beginning after several years of vaccination with the heptavalent vaccine. It was not until mid-2016 that systematic vaccination with a 13-valent vaccine was introduced into the official immunization schedule in Catalonia, so in the years of the study and the previous ones, none of the conjugate vaccines had been part of the systematic vaccination schedule. However, around 50% of children under 2 years of age in Catalonia received the heptavalent vaccine in the years prior to the study, and a similar percentage had received the 13-valent vaccine at the beginning of the study, reaching 75% at the end of the study.

The patients were collected following an active surveillance protocol, with a rigorous methodology to know their vaccination status. The etiological search for *S. pneumoniae* was exhaustive, using both conventional culture and nucleic acid amplification technology in blood and pleural fluid when obtained.

During the 4.5 years of the study, 194 cases of pneumococcal pneumonia were identified. 18% were necrotizing pneumonias and most of these (77%) were associated with pleural effusion. No patient with necrotizing pneumonia had major predisposing risk factors or comorbidities; the majority (74.3%) were children under 5 years of age.

Serotypes 3, 1 and 19A, in this order, accounted for 71.4% of necrotizing pneumonias. When analyzing the complete series, serotype 3 was responsible for 48.6% of necrotizing pneumonias, 23.3% of pneumonia with pleural effusion, and 11.6% of bacteremic pneumonia without local complications. Serotype 1 had lower participation in necrotizing pneumonias, 14.3%, but higher in pneumonia with pleural effusion or empyema (31%) and in uncomplicated bacteremic pneumonia (14%).

Of the 194 pneumonias analyzed, 116 were complicated by pleural effusion or empyema and 35 were necrotizing, which means that 78% of the total were pneumonia with parenchymal or pleural complications, a staggering number. A fact that is worth highlighting is that more than 80% of necrotizing pneumonia or with pleural complications were caused by serotypes not included in the heptavalent vaccine but in the 13-valent vaccine. Of the children who had been correctly vaccinated with the 13-valent pneumococcal vaccine, there were only vaccine failures against serotype 3, which confirms the low efficacy of the vaccine against this serotype.

This study contributes to confirm the variable impact that immunization with the heptavalent pneumococcal conjugate vaccine has had in different populations. In the pediatric population of Catalonia, although the total number of invasive infections was reduced at the expense of the less serious entity (occult bacteremia), the most severe form (meningitis) was little changed and the number of severe pneumonias increased greatly. And, in general, this has ended up being the evolution in all places, reason why the initial heptavalent vaccine has been replaced by the 10-valent vaccine (where they do not have much presence of serotype 19A) or more usually the 13-valent (the one chosen in Spain). These, until now, have come to correct the situation by containing the main serotypes responsible for the serious forms that emerged during the heptavalent vaccine time.[20]

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