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Editorial

Pneumococcal disease and conjugate vaccines

Enfermedades neumocócicas y vacunas conjugadas

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The prevention of pneumococcal diseases is a global challenge that has been partially achieved through vaccination. Over the 20th century, pneumococcal polysaccharide vaccines (PPV) were introduced. Among them, the 23-valent pneumococcal polysaccharide vaccine (PPV23) has been linked to a decrease in the mortality of pneumococcal pneumonia. However this PPV23 did not exert a noticeable impact on the incidence of invasive pneumococcal disease (IPD).[1,2] On the contrary, the introduction of the pneumococcal conjugate vaccines (PCVs) at the beginning of this century has shown high efficacy preventing IPD caused by vaccine-types.[3,4] This protection is achieved in two ways: a direct effect in the vaccinated population and an indirect effect in the non-vaccinated population (herd protection) due to a reduction of the global pneumococcal load. This reduction is at the expense of the vaccine-serotype pneumococci that are colonizing the nasopharynx of children, which are the main pneumococcal reservoir. However, other non-vaccine serotype pneumococci could fill the gap led by the PCV-ones and replace their role in invasive disease.[5]

In Spain, three conjugate vaccines have been licensed, all of them under a voluntary basis: PCV7 in 2001 (which included serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F), PCV10 in 2009 (adding serotypes 1, 5 and 7F) and PCV13 (which replaced PCV7 in 2010 adding serotypes 3, 6A, and 19A). Even so, the government of the Madrid autonomous community decided to subsidize the PCVs in 2006 and this policy was maintained until May 2012. Then, the vaccine coverage in Madrid (around 95% 2009–2012)[4] has always been higher than in most of the remaining Spanish regions (around 50–60%).[6–8] Other regions progressively introduced the PCVs such as Galicia for PCV13 in 2011. After the national approval in 2015, all the autonomous communities included PCV13 (2+1 scheme) in the pediatric schedule throughout the 2015–2016 period. Also, different approaches for adult vaccination with PCV13 have been introduced over the last years.

In this issue two studies analyze the evolution of pneumococcal serotypes in the PCVs era in two regions with different vaccination strategies.[9,10] One of them performed in the island of Gran Canaria that had a low percentage of vaccinated children (48% in 2006 and 49% in 2014) until 2015. The second one from Madrid, where the percentage of vaccinated children was above 90% until 2012, when PCV13 was removed from the official vaccine schedule (though the uptake always remained above 65%).[11] It is not easy to analyze the impact of vaccines in the trends of pneumococcal disease. The influence of other factors such as natural fluctuations of serotypes and clones, geographic differences in the distribution of serotypes, or changes in flu activity could make the final analysis favorable or not. For instance, the marked fall of IPD after the PCV7 introduction in the US in the early 2000s was not observed in Europe.[3] In Spain, with a limited vaccine uptake, IPD increased after the PCV7 introduction due to an expansion of non-vaccine serotypes in both children and adults, especially those called epidemic serotypes (1, 7F, 5) which did not increase in the US .[12,13] The replacement of PCV7 by PCV13 in 2010 was followed by a sharp reduction in the overall incidence of IPD in Spain and other countries.[14–16]

In this way, the two studies showed a beneficial impact of the PCV13 introduction in the burden of IPD. The study from Gran Canaria[9] shows a significant decrease in the incidence of IPD after the PCV13 introduction (overall reduction of 66.4%) in the pediatric population (2001–2016 period). Although this decline was observed in young and older children, it was higher in children under 2 years old. Similarly, the results of the pneumococcal surveillance program of the Madrid autonomous community over 2008–2015[10] showed a significant decrease in the incidence of IPD after the PCV13 introduction (decrease of 32%). In fact, in the target population (children under 5) the remnant disease due to PCV13 serotypes was very low. Both studies linked the IPD reduction to a fall in the PCV7 and the additional PCV13 serotypes. However, a reduction of bacteraemia without focus was observed in Gran Canaria after the PCV13 introduction and this could reflect changes in the blood culture practice. This is a common limitation of the surveillance studies. Beside the overall reduction of the PCV13 serotypes 1, 5, 7F and 19A the impact on the incidence of serotype 3 has been controversial.[15] It is remarkable that both studies showed

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a marked fall in serotype 19A, a serotype usually associated to penicillin- and multidrug-resistance, which nearly disappeared in young children. Although less prominent, the same phenomenon was also observed in Madrid in the non-vaccinated population (older children and adults). On the other hand, the decrease of serotype 3 disease was only observed in the target population (children under 5) in Madrid and herd protection was not successfully achieved.[10] This is probably because of the low prevalence of this "adult" serotype colonizing children. Since Madrid recently started adult PCV13 vaccination, the analysis of the ongoing surveillance will be of high interest for the definition of future vaccine strategies.

The study from Gran Canaria did not detect any IPD related deaths in children throughout the PCV13 period. Before PCV13 introduction fatal outcomes were mostly linked to cases of meningitis or bacteremic pneumonia, whose number of episodes declined substantially. The reduction of pneumococcal meningitis in the pediatric population has been observed in other studies which is an important benefit for the severity of the disease, the mortality and sequelae.[11] Moreover, the decrease in mortality after the PCVs introduction agrees with recent reports that showed a decline in the mortality of children and also of adults as an indirect benefit of vaccination .[1,15] This fact was related to a reduction in the PCV7 serotypes that associated the higher fatality rates together with serotype 3.[1]

Another important finding of Santana et al. is an overall reduction in the rates of penicillin- and erythromycin-resistance after the PCV13 introduction linked to a reduction in serotypes 14 and 19A. This effect is related to a reduction of the multidrug resistance clones related to PCV7 serotypes [clonal complex (CC)$156^{9V,14}$, $CC15^{14}$ $CC88^{19F}$ and $CC81^{23F}$] and serotype 19A (CC320 and CC230), respectively.[12,16,17]

Finally, data from Madrid show a worrying increase of the non-PCV13 serotypes, suggesting serotype replacement.[5] This is in agreement with recently reported data from other countries such as England and Wales, where the PCVs have been included into the routine vaccination program since 2006.[18] In Madrid, these results are related to an increase in IPD mainly in two age groups: children under 5 years old, the target of the vaccination program, and adults over 59 years old, mostly a non-vaccinated population. Then, the connection between the reservoirs of pneumococci (children) and the people that are at a higher risk of having IPD (older adults) is emphasized. Among non-PCV13 serotypes, the rise in the incidence of serotype 8, which has become the first cause of IPD in the 2013–2015 period, is especially alarming. This serotype has demonstrated a high invasive disease potential among children after the PCV introduction.[19] Consequently, the emergence of non-vaccine serotypes showing invasiveness, such as serotypes 12F or 8, is worrying. Moreover, even when by Latasa et al. reported a decrease in the incidence of IPD after the PCV13 introduction, an increasing trend of disease has been observed since 2013, especially for children under 5 years old and adults over 59.

The introduction of the PCVs had a direct impact on the prevention of IPD and on the pneumococcal epidemiology. In England and Wales, it has been estimated that 40,000 episodes of IPD have been prevented since the introduction of PCV7.[18] Nevertheless, some doubts arise about the increase of the non-vaccine serotypes that could minimize the benefits of the vaccination programs. Thus, monitoring the incidence of IPD through surveillance programs continues being critical. In this issue, Santana and Latasa present their respective works regarding the pneumococcal epidemiology in two different Spanish regions after PCV13 introduction. Although differences in vaccine coverage between the two regions exist, a decrease in IPD after PCV13 introduction was clearly established by both works. However, the evidence for serotype replacement (especially serotype 8) detected in Madrid could compromise the effectiveness of the current vaccines in the prevention of the disease. These results highlight the need for developing new broader conjugate vaccines or preferably non-serotype based vaccines to preserve the efficacy of the immunization programs in the overall population.

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