



## EDITORIAL

### No more excuses. . . This vaccine, yes!☆

### No más excusas. . . Esta vacuna, sí

J.J. Garcia-Garcia



Servei de Pediatria, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain

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*Streptococcus pneumoniae* (*S. pneumoniae*) is one of the leading pathogens that cause community-acquired infections. It has accumulated genetic mutations throughout its evolution, and at present more than 90 different serotypes of *S. pneumoniae* are known. Serotypes are identified based on the polysaccharide capsule that surrounds the cell wall. Despite the high number of serotypes, most cases of pneumococcal disease are caused by just a few of them. Serotype prevalence changes depending on time and age, and there is also geographic variation.<sup>1</sup>

In our setting, *S. pneumoniae* is the most prevalent causative agent of simple and complicated pneumonia, meningitis, occult bacteraemia, otitis, and acute sinusitis.<sup>2</sup> It is estimated that this pathogen causes 14.5 million cases a year of severe invasive pneumococcal disease (IPD) in children younger than 5 years, and is responsible for over half a million deaths that occur mostly in least developed and developing countries.<sup>3</sup>

Vaccines are one of our main means to fight *S. pneumoniae*. Unfortunately, the traditional polysaccharide vaccine

(23-valent) is only efficient in the adult population, as the immune system in children is immature and fails to produce an adequate response to vaccination. The considerable burden of pneumococcal disease in children younger than 2 years and the increasing drug resistance of pneumococcus led to the development of conjugated vaccines against pneumococcus (PCV).<sup>4</sup> Covalent attachment of pneumococcal polysaccharides to protein carriers makes these vaccines immunogenic in children younger than 2 years, inducing memory cells and reducing carriage of vaccine serotypes. The data of a study on the efficacy of the new heptavalent conjugate vaccine (PCV7) were published in 2000. The study showed a dramatic decrease in the rate of IPD.<sup>5</sup> Based on these data, several scientific associations recommended universal vaccination, and numerous countries included this vaccine in their routine immunisation schedules.

The PCV7 protects against serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, the types most frequently identified in cases of nasopharyngeal colonisation and historically associated with invasive disease in developed countries.<sup>6</sup> Later on, 2 other conjugate vaccines were introduced in Spain: the decavalent conjugate vaccine (PCV10), which protects against PCV7 types and also serotypes 1, 5, and 7F, and the 13-valent conjugate vaccine (PCV13), which protects against PCV10 types as well as serotypes 3, 6A, and 19A.

Widespread vaccination of the United States population with PCV7 proved to be effective in reducing the incidence of IPD.<sup>7</sup> However, a parallel and progressive increase in the

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E-mail address: [juanjo@hsjdbcn.org](mailto:juanjo@hsjdbcn.org)

incidence of IPD caused by non-PCV7 types was observed, mostly due to the increase of serotype 19A. Still, the previous overall incidence of IPD was not reached again.<sup>8</sup>

In Spain it is harder to evaluate the impact of PCV7 because it is not subject to epidemiological surveillance and because the vaccine is not included in the various routine immunisation schedules applied in the country, save for a few exceptions.

In a study conducted on children younger than 2 years at the Hospital Sant Joan de Déu, Muñoz-Almagro et al. observed that the incidence of IPD increased from 32.4 episodes per 100 000 inhabitants per year in the prevaccine period (1997–2001) to 51.3 episodes per 100 000 inhabitants per year in the postvaccine period (2002–2006), an increase of 58% (CI 95%, 2–145%).<sup>9</sup> Cases of IPD caused by non-PCV7 serotypes rose from 38% to 72% of the total.

A later study with data from 2 of the most important hospitals in the Barcelona metropolitan area showed an increase in the incidence rate of IPD from 76.2 to 109.9 episodes per 100 000 children younger than 5 years between 2007 and 2009, which consisted mostly in an increase in the incidence of pneumonia cases.<sup>10</sup> This study used polymerase chain reaction techniques for diagnosis in addition to bacterial cultures, providing a more accurate perspective of the actual impact of IPD in the population. The study also showed that most IPDs were caused by non-PCV7 serotypes (91%) and that most episodes occurred in children aged 2–5 years.

The study of González Martínez et al.<sup>11</sup> recently published in *ANALES DE PEDIATRÍA*, confirms that after the introduction of PCV7, there was replacement of the serotypes causing IPD, with an increase in the rates of IPD due to non-PCV7 types. This increase did not happen immediately, but over the 4 or 5 years that followed the introduction of PCV7, with the vaccine being included in the routine immunisation schedule, unlike what happened in the Barcelona area study.

The increase in IPD observed after the introduction of PCV7 in our setting could not be explained solely by this vaccine. Thus, the voluntary reporting registries that have been kept for a few decades at the Instituto Carlos III of Majadahonda already showed an increase of some serotypes, such as type 1, prior to the use of PCV7, which probably happens because serotype 1 has a pattern of epidemic waves.<sup>12</sup> The increase in other serotypes, such as 19A, could have been due to other factors, such as selective pressure by antibiotics, or to the more direct effect of serotype replacement after the disappearance of vaccine serotypes, as had been seen with serotype 1.<sup>13</sup> The increase of serotype 19 was observed both in countries where PCV7 was part of the immunisation schedule and in countries with partial or no coverage.<sup>14</sup> There is also the fact that pneumococci are naturally transformable, which may lead to capsular switching, a mechanism for the potential evasion of the host immune response.<sup>15</sup>

Four years after the introduction of the 13-valent vaccine, the first studies on its impact on IPD began to be published. Demczuk et al. described a decrease in the incidence of IPD in Canada from 18 cases per 100 000 children younger than 5 years in 2010 to 14 cases per 100 000 in year 2012, with a decline in PCV13 types from 66% to 41%.<sup>16</sup> A group of hospitals in the United States observed a 42% reduction in the rates of IPD in 2011 compared to the

2007–2009 period.<sup>17</sup> In England and Wales there is evidence of a sustained reduction in the number of reported IPD cases following the inclusion of PCV13 in the immunisation schedule, something that had not been observed in that country, even temporarily, after the introduction of PCV7.<sup>18</sup>

In Madrid, the Heracles study by Picazo et al. on vaccination with PCV13, which used to be part of the routine immunisation schedule of that Autonomous Community, showed a decline in the incidence of IPD from 17.09 (PCV7 period) to 7.70 (May 2011–April 2012).<sup>19</sup> The decline occurred in all forms of IPD and in all age groups, and was due to a lower incidence of IPD caused by serotypes 1, 5, and 19A, the additional serotypes included in PCV13. The rate of IPD caused by non-PCV13 types has not increased (3.6 vs. 3.31). What remains unclear is whether these excellent results will hold now that funding for this vaccine has been discontinued since April 2012 due to budgetary constraints.

In Barcelona, a comparative study of the 2007–2009 and 2012–2013 periods showed a 66% decrease in the number of cases.<sup>20</sup> This decrease occurred in the main serotypes that cause IPD, mostly in types 1 and 19A, and there has been no evidence of replacement by non-vaccine types. Currently, PCV13 types cause 77% of IPD in children younger than 5 years.

Lastly, an epidemiological surveillance study conducted in Navarre that compared the incidence of IPD in the 2004–2009 and 2010–2013 periods showed a 69% decrease in children younger than 5 years (from 60.7 cases per 100 000 to 18.7 cases per 100 000).<sup>21</sup> The incidence of episodes caused by PCV13 types has decreased by 79%, and there has been no evidence of changes in the distribution of the clinical presentation or the severity of infection. In Navarre, 78% of children younger than 2 years have received at least 1 dose of PCV, which suggests that herd immunity is contributing to the decrease.

In light of the growing evidence, the Comité de Vacunas de la Asociación Española de Pediatría (Advisory Committee on Vaccines of the Spanish Association of Paediatrics) recommends routine vaccination against pneumococcus in all children younger than 5 years, noting that PCV13 is the vaccine that offers the most protection against the circulating serotypes, and thus the one that can contribute most to controlling pneumococcal disease in Spain.<sup>22</sup>

In April 2006, Spain's Ministry of Health decided not to include vaccination against pneumococcus in the routine schedule, arguing that there was a lack of reliable epidemiological data, as well as the changes that might emerge in IPD as a result of the widespread use of this vaccine.<sup>23</sup> The reasons for the decision were questionable at best, and were properly refuted in time.<sup>24</sup> The protection offered by PCV13 is adjusted to the current dominant serotypes in our region; the available data do not suggest that serotype replacement will happen in the short-term, and experience in Spain and in other countries clearly indicates that introduction of the vaccine into the immunisation schedule does result in a reduction in the rates of IPD.

In this period of austerity imposed by the markets and a few highly influential economic agents who, it is worth recalling, were not elected by the public, we ought to take a long-term perspective and put people first. Including the pneumococcal vaccine in routine immunisation schedules nationwide would be enormously beneficial to society,

protecting all children alike regardless of family socioeconomic status, and may also have economic advantages in reducing the rate of severe IPD. In so doing, we would be joining 44% of the World Health Organization member countries that already have the vaccine in their schedules.<sup>25</sup> At present, we may find ourselves in the paradoxical situation of seeing children who come from developing countries where the vaccine is included in the immunisation schedule, while children in our country are only protected if their parents can afford to pay for it. This is not just an economic issue, but also a question of our social model. We have to protect the most vulnerable. It is time to stop making excuses.

## Conflicts of interest

JJGG has participated as a speaker in scientific events sponsored by Pfizer.

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