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Editorial article

Pneumococcal vaccination in times of COVID-19☆

Vacunación antineumocócica en tiempos de COVID-19

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Infections caused by *Streptococcus pneumoniae*, mainly invasive pneumococcal disease (IPD) and pneumococcal pneumonia (PP), are a major health problem in the world.[1] The existence of more than 90 different serotypes of *S. pneumoniae* has so far greatly complicated the development and evaluation of successive pneumococcal vaccine formulations.[2]

The c̈lassic2̈3-valent pneumococcal polysaccharide vaccine (PPV23) was marketed in 1983 and has been recommended ever since for people over 60-65 years of age and adults with high-risk conditions or susceptibility to pneumococcal infection, initially reporting an efficacy of 40-60% in IPD prevention due to vaccine serotypes (representing 80-90% of circulating serotypes when the vaccine was marketed) among healthy immunocompetent individuals, although a protective effect against PP is more uncertain.[3]

After it was found that PPV23 was not immunogenic in young children, a heptavalent pneumococcal conjugate vaccine (PCV7) was developed years later which was found to be immunogenic in children and contained the 7 most common serotypes in American children when the vaccine was marketed in 2000. Initially, this vaccine showed a high level of clinical efficacy in preventing IPD caused by vaccine serotypes among vaccinated children, although differences in effectiveness were also found in different geographical areas depending on the previous prevalence of serotypes in each region. Unlike the polysaccharide vaccine (which has no effect on nasopharyngeal colonization), it soon became apparent that, in those countries where PCV7 was introduced as a routine childhood vaccine, vaccination also had an indirect protective effect in the unvaccinated child and adult population by reducing nasopharyngeal colonization and circulation of the 7 serotypes contained in the vaccine, resulting in a significant reduction in the global incidence of IPD during the first years after the introduction of PCV7.[4]

Despite the undeniable initial success of PCV7, as a consequence of the well-known phenomenon of serotype replacement and the emergence of new serotypes not contained in the vaccine, PCV7 was replaced years later by a new generation of conjugate vaccines progressively incorporating more serotypes (PCV10 and PCV13). In view of the good results observed in children, the n̈ewP̈CV13 was also approved for possible use in adults (in addition to the classic PPV23).[4]

There is now considerable uniformity in recommending PCV13 in children. However, there is controversy over ẅhom and whichp̈neumococcal vaccine (PPV23 and/or PCV13) to use in adults. In fact, the recommendations on pneumococcal vaccination in adults are heterogeneous according to different organizations, scientific societies, countries and regions.[5–8]

PPV23 has been recommended (and publicly funded in Spain for 20 years) for all people over 65 years of age and adults 18–64 years of age in some risk situations (immunosuppressed, chronic heart/respiratory disease, severe kidney/liver disease, diabetes and/or alcoholism).[5]

PVC13, initially a paediatric vaccine, was authorized for possible use in adults in 2011, and different organisms (*Centers for Disease Control and Prevention* [CDC], Ministry of Health) approved in 2012 the recommendation of PCV13 (sequentially with PPV23) in patients considered to be at very high risk (anatomical or functional asplenia, immunocompromised, cerebrospinal fluid fistulae or cochlear implant).[9] Since then, these indications have been publicly funded in Spain.[5]

In 2014, after evaluating the data provided by the CAPITA study,[10] the CDC recommended the routine use of PCV13 (sequentially PCV13 + PPV23) for all people over 65 years of age (with or without other risk factors),[11] although they recognized that the degree of evidence of this recommendation was only moderate and, in fact, some experts were against this recommendation. In fact, the Ministry of Health in Spain did not adopt it in its recommendations.[5,11]

Since then, the use of PCV13 in adults has been progressively extended in clinical practice to other groups considered to be at ïntermediateïrisk (e.g., chronic respiratory disease, heart disease, or diabetes), although without public funding in most autonomous communities in our country.[5,8]

The main advantage of PCV13 is its theoretical better immunogenicity, with the main disadvantages being its high cost and lower serotype coverage compared to PPV23. However, the currently available evidence does not allow us to determine which of them has greater clinical practice ëffectiveness.̈ Contrary to what some

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professional societies suggest in our country,[8] the question about ẅhich pneumococcal vaccine is better in adultsr̈emains open. The rationale for dual vaccination (sequentially PCV13 + PPV23) aims to add the advantages of each of the two vaccines but ignores the issue of the more than questionable efficiency (cost-effectiveness) of this measure at present.[12]

The results reported by the CAPITA study, a clinical trial that evaluated the efficacy of PCV13 versus placebo in 85,000 people over 65 years of age in the Netherlands during 2009-2012,[10] could not demonstrate a significant efficacy of PCV13 to prevent IPD and/or PP in the subgroup of immunosuppressed patients (which are precisely those for whom this vaccine is most indicated). Likewise, although the aforementioned CAPITA study showed significant vaccine efficacy in preventing IPD and PP caused by any of the 13 vaccine serotypes, this should be interpreted with caution since the efficacy estimates reported do not differ essentially from those estimated for PPV23 in the latest Cochrane review,[3] and also the total number of cases prevented among the vaccinated subjects of the CAPITA study was relatively low (namely, 21 cases of IPD and 27 of PP prevented out of a total population of more than 300,000 person-years vaccinated).[10]

After the CAPITA trial, in 2018, 3 observational studies were published that evaluated the effectiveness of PCV13 in American and European adults, showing divergent results,[13–15] and even one of them (which included a cohort of more than 2 million people over the age of 50 with follow-up during 2015–2016 in Catalonia) reported an unexpected increase in incidence and adjusted risk of hospitalization for pneumonia (pneumococcal and all-cause) among vaccinated subjects.[15]

In its latest update (November 2019), the CDC withdrew its previous recommendation for routine PCV13 administration to all people over 65 years of age after considering that the widespread use of PCV13 in children has reduced (and continues to reduce) the incidence of IPD/PP caused by PCV13 serotypes in adults (due to an indirect protective effect of childhood vaccination by reducing nasopharyngeal colonization and circulation of PCV13 serotypes in the population).[6] In this report, the CDC recommends PPV23 alone for all persons over 65 years of age and only recommends routine vaccination with PCV13 for immunosuppressed individuals and possibly for some individuals who are considered by clinical judgement to be at very high risk of pneumococcal infection.[6]

In Spain, while the Ministry of Health maintains recommendations very similar to the current CDC recommendations,[5,6] in addition to immunosuppressed patients, a consensus document of 18 professional societies recommends p̈neumococcal PCV13 vaccination to both healthy immunocompetent subjects >65 years of age as well as those with other underlying diseases or risk factors such as chronic respiratory disease (including COPD, severe asthma, and diffuse interstitial lung disease), chronic liver disease, chronic cardiovascular disease (including chronic heart failure, ischemic heart disease, valvular heart disease, congenital, hypertension with cardiac involvement and patients with cerebrovascular pathology), diabetes mellitus treated with oral antidiabetics or insulin, alcohol abuse, smokers and ex-smokers:[8]

The main grounds for a general recommendation of pneumococcal vaccination in adults with at-risk conditions and/or advanced age are supported by the higher incidence of IPD and PP in these individuals,[1,8] but there is actually no clear evidence of the effectiveness of vaccination (which is different from vaccine efficacy) in these people.[3,5,6,15] In fact, having an increased risk of pneumococcal infection does not necessarily imply that vaccinating these individuals will be an effective and efficient measure in practice. The above indications are, in our opinion, greatly overestimated as they include patients with any magnitude of increased risk (from 10 to 12 times in immunocompromised patients to only 1.2–1.5 times in diabetics or smokers).[8]

In our opinion, currently, the systematic administration of PCV13 in the elderly is not justified, according to the current recommendation of the CDC and the Public Health Commission of the Ministry of Health,[5,6] and contrary to what was proposed in the manifesto of the 18 professional societies published in the *Spanish Journal of Chemotherapy*.[8] In this regard, it should be noted that the first version of the aforementioned manifesto was published in 2013 (i.e. surprisingly 2 years before the final results of the CAPITA trial were published in 2015), its conclusions are biased as they are limited to proposing that PVC13 be administered preferentially (without specifying whether or not it is also advisable to administer PPV23 after a few months to increase serotype coverage), and most of the signatory authors have conflicts of interest in the subject (which should be a reason for reflection for everyone).

It should be noted that the total number of IPD cases notified to the Microbiological Information System in Spain has grown steadily in recent years (from 1,237 cases in 2014 to 3,796 cases in 2018) despite the increase in pneumococcal vaccination coverage.[16] Although this upward trend may be influenced by some changes introduced in the reporting system (IPD is a notifiable disease since 2016), an exhaustion of the current potential impact of vaccination programmes with PCV13 (and also PPV23 which shares 12 serotypes with it) cannot be ruled out.

There are no published data on the population incidence of IPD and/or PP during 2020 in our country, although some microbiologists and clinicians have confirmed a reduction in cases diagnosed during the COVID period compared to previous years. In Catalonia, in a population cohort that includes 2,234,000 people over 50 years of age assigned to 274 Basic Health Areas managed by the *Catalan Institute of Health*, during 2019 there were 762 hospitalized cases of IPD (ICD-10 diagnostic codes: G00.1, A40.3 and/or B95.3), while this figure was 7.6% lower during 2020 (704 cases). An even greater reduction in PP (ICD-10: J13) has been observed with a 21.9% decrease in the number of cases during 2020 (1,794 cases) compared to 2019 (2,296 cases) (author's data, from of the SIDIAP-EPIVAC3 study pending publication).

A considerable decrease in IPD cases has also been reported during the COVID period in other countries such as England, where the incidence of IPD during 2019-2020 was 7.6/100,000; n = 3,964 cases) which represents a decrease of 30% compared to the 2018-2019 period (10.9/100,000; n = 5,666 cases), with significant reductions reported in all age groups and observing a serotype distribution similar to previous years.[17]

It has been argued as a rationale for expanding public funding for PCV13 in adults that IPD/COVID coinfections are associated with a high case fatality rate (9–32% in different series).[18,19] It is true that these coinfections have a high mortality rate (mainly in the elderly and patients admitted to the ICU) but in reality the case fatality rate is not substantially higher than that described so far in IPD in elderly patients and/or with comorbidities.[1]

Although unlikely (little evidence to date), a possible interrelationship between *S. pneumoniae* and SARS-CoV-2[18] may exist. However, the rarity to date of IPD/COVID coinfections (0.1-3% in different studies),[18] age distribution and serotype distribution (similar to previous years) does not, in our opinion, justify a modification of the current pneumococcal vaccination recommendations during these difficult times.

In the next few years, with the arrival of a conjugate vaccine with a serotype coverage close to or similar to the current PPV23 (e.g., PCV20),[20] the main problem to address in relation to pneumococcal vaccination will be "who to vaccinate/revaccinate" and not "which vaccine to use".

A new technology pneumococcal vaccine (one that can provide complete protection regardless of serotype) is an exciting goal that remains unresolved for many years, perhaps closer to being approved based on the experience with the COVID vaccines.

Conflict of interests

The author declares that he has no conflict of interest on the subject.

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References

1. Torres A, Cillóniz C, Blasi F, Chalmers JD, Gaillat J, Dartois N, et al. Burden of pneumococcal community-acquired pneumonia in adults across Europe: a literature review. Respir Med. 2018;137:6–13.
2. Hausdorff WP, Feikin DR, Klugman KP. Epidemiological differences among pneumococcal serotypes. Lancet Infect Dis. 2005;5:83–93.
3. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infections in adults (review). Cochrane Database Syst Rev. 2013;1:CD000422.
4. Campins Martí M. Vacunas antineumocócicas. Nuevas vacunas conjugadas para el adulto. Enferm Infecc Microbiol Clin. 2015;33:617–24.
5. Ministerio de Sanidad, Consumo y Bienestar Social. Vacunas y Programa de Vacunación. Enfermedad Neumocócica Invasiva. Recomendaciones de vacunación actuales acordadas en el Consejo Interterritorial de Sistema Nacional de Salud (CISNS). Available from: https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/vacunas/profesionales/enfNeumococicaInvasiva.htm [accessed 30/11/2021].
6. Matanock A, Lee G, Gierke R, Kobayashi M, Leidner A, Pilishvili T. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: updated recommendations of the ACIP. MMWR Morb Mortal Wkly Rep. 2019;68:1069–75.
7. Bonnave C, Mertens D, Peetermans W, Cobbaert K, Ghesquiere B, Deschodt M, et al. Adult vaccination for pneumococcal disease: a comparison of the national guidelines in Europe. Eur J Clin Microbiol Infect Dis. 2019;38:785–91.
8. Gonzalez-Romo F, Picazo JJ, García Rojas A, Labrador Horrillo M, Barrios V, Magro MC, et al. Consenso sobre la vacunación anti-neumocócica en el adulto por riesgo de edad y patología de base. Actualización 2017. Rev Esp Quimioter. 2017;30:142–68.
9. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2012;61:816–9.
10. Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015;372:1114–25.
11. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2014;63:822–5.
12. Treskova M, Scholz SM, Kuhlmann A. Cost effectiveness of elderly pneumococcal vaccination in presence of higher-valent pneumococcal conjugate childhood vaccination: systematic literature review with focus on methods and assumptions. Pharmacoeconomics. 2019;37:1093–127.
13. McLaughlin JM, Jiang Q, Isturiz RE, Swerdlow DL, Gessner BD, Carrico RM, et al. Effectiveness of 13-valent pneumococcal conjugate vaccine against hospitalization for community-acquired pneumonia in older US adults: a test-negative design. Clin Infect Dis. 2018;67:1498–506.
14. Prato R, Fortunato F, Cappelli MG, Chironna M, Martinelli D. Effectiveness of the 13-valent pneumococcal conjugate vaccine against adult pneumonia in Italy: a case-control study in a 2-year prospective cohort. BMJ Open. 2018;8:e019034.
15. Vila-Corcoles A, Hospital I, Ochoa-Gondar O, Satue E, Diego C, Vila-Rovira A, et al. Clinical effectiveness of 13-valent and 23-valent pneumococcal vaccination in middle-aged and older adults: the EPIVAC cohort study, 2015-2016. Vaccine. 2020;38:1170–80.
16. Centro Nacional de Epidemiología. Instituto de Salud Carlos III. Resultados de la vigilancia Epidemiológica de las enfermedades transmisibles. Informe anual. Años 2017-2018. Madrid; 2020. Available from: https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documents/INFORMES/INFORMES%20RENAVE/RENAVE_Informe_anual__2017-2018.pdf [accessed: 10/12/2011].
17. Amin-Chowdhury Z, Aiano F, Mensah A, Sheppard CL, Litt D, Fry NK, et al. Impact of the COVID-19 pandemic on invasive pneumococcal disease and risk of pneumococcal coinfection with SARS-CoV-2: prospective national cohort study, England. Clin Infect Dis. 2021;72(5):e65–75.
18. McIntosh SDG, Feemster K, Rello J. Protecting adults at risk of pneumococcal infection and influenza from exposure to SARS-CoV-2. Hum Vaccin Immunother. 2021 http://dx.doi.org/10.1080/21645515.2021.1957647
19. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020;81:266–75.
20. Hurley D, Griffin C, Young M, Schwartz HI, Narejos Perez S, Dowell A, et al. Safety, tolerability, and immunogenicity of a 20-Valent Pneumococcal Conjugate Vaccine (PCV20) in adults 60 to 64 years of Age. Clin Infect Dis. 2021;73:e1489–97.