



Editorial

Role of Vaccines in COPD Patients

Papel de las vacunas en pacientes con EPOC



The prognosis of patients with chronic obstructive pulmonary disease (COPD) depends, to a large extent, on the frequency of exacerbations.¹ The most frequent cause of them are respiratory infections.

Vaccines are effective preventive measures in patients with respiratory diseases, including those with COPD.² Classically, anti-pneumococcal and anti-influenza vaccination is usually recommended in subjects with this disease. Despite this, their use in these patients is far from optimal.^{3,4} On the other hand, with the recent development of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines and other new ones, it is necessary to update the indication of the different vaccines in COPD patients.

In relation to pneumococcal vaccination, there are two types of vaccines, polysaccharide and conjugate. Although the 23-valent polysaccharide is the one that has been used for the longest time, its efficacy against community-acquired pneumonia and COPD exacerbations is controversial, since the duration of the immune response is limited, as there is no humoral response dependent on T lymphocytes.⁵ In contrast, the 13-valent conjugate vaccine produces an immune response dependent on both B lymphocytes and T lymphocytes, thus generating an immunological memory and a more lasting effect.⁶ In this way, both international⁷ and national⁸ guidelines recommend pneumococcal conjugate vaccination in COPD patients.

Two new pneumococcal conjugate vaccines, the 15-valent and 20-valent vaccines, were recently approved in the United States for use in the elderly population and in the population with underlying diseases.⁹ Specific studies in the COPD population are still lacking, but it is possible that the indication of the pneumococcal vaccine in COPD patients will be updated in the future.

Unlike the pneumococcal vaccine, the influenza vaccine is an attenuated virus vaccine. This fact could justify the suboptimal rate of use of this type of vaccination in COPD patients. However, in a systematic review of the literature, no increase in COPD exacerbations was detected within 14 days of administration.¹⁰ In another meta-analysis of randomized clinical trials, influenza vaccination was shown to reduce exacerbations in COPD patients, although with a slight increase in local adverse reactions.¹¹ As in the case of the pneumococcal vaccine, the GOLD and GesEPOC guidelines recommend annual influenza vaccination in patients with COPD.^{7,8}

New influenza vaccines are currently being developed. The results of a phase 2b randomized clinical trial testing the efficacy of a non-typeable *Haemophilus influenzae* and *Moraxella catarrhalis*

vaccine for the prevention of COPD exacerbations were recently published.¹² Unfortunately, this study was not positive.

Although there are few data published to date on the rate of SARS-CoV-2 vaccination in COPD patients, this disease has been considered as a condition to prioritize its administration. Theoretically, COPD patients are at increased risk of SARS-CoV-2 infection due to their increased expression of the ACE2 molecule, the molecular target used by this virus to enter the epithelial cells of the respiratory tract. It is also described that the prognosis of coronavirus disease 2019 (COVID-19) is worse in COPD subjects, who have a higher risk of hospitalization, severe disease and mortality. Despite the urgency in the development of SARS-CoV-2 vaccines, there are no ongoing clinical trials whose main objective is to determine the efficacy of these vaccines in COPD patients, although this has been demonstrated in post-authorization studies.¹³ Regarding the risk of these vaccines, there are no specific studies conducted in COPD patients. However, it has been described that COPD is a frequent comorbidity in patients who have had a fatal event after vaccination, together with other comorbidities such as arterial hypertension, diabetes mellitus and dementia. In any case, if we consider the benefit/risk profile, SARS-CoV-2 vaccination is indicated in COPD patients,¹⁴ and this is reflected in the updated clinical practice guidelines.^{7,8,15}

Based on the recommendations of the Centers for Disease Control and Prevention (CDC), the indication of pertussis and herpes zoster vaccines is recommended for patients with COPD.¹⁶ The pertussis vaccine, integrated into the combined diphtheria, tetanus and pertussis vaccine, is usually administered in childhood, since it is included in the childhood immunization schedule. It is not usually necessary to indicate this vaccine in newly diagnosed COPD patients, since most of them have received it in childhood, but it is important to take it into account in the case of previously unvaccinated patients.

Herpes zoster is a disease that could cause severe respiratory disease in adult patients. The herpes zoster virus vaccine is also included in the childhood immunization schedule, so its indication in COPD patients is similar to what has been discussed in the case of pertussis vaccine. Thus, it is important to ask about the history of whooping cough and vaccination against it at the time of diagnosis of COPD, and indicate its administration in those patients who have not had the disease or received this vaccine before.

In addition to the vaccines mentioned above, there are unmet prevention needs in COPD patients. One of them is to prevent res-

piratory infections due to respiratory syncytial virus (RSV). RSV is one of the agents that most frequently causes respiratory infections and, specifically, exacerbation in COPD patients. The pharmaceutical industry has been developing a vaccine against RSV for decades, but to date there is still no licensed vaccine for this disease, due to its limited efficacy and the short duration of the immune response. However, in recent years clinical trials of new vaccines against RSV have been carried out, with more encouraging results.¹⁷

Another novelty is a sublingual autovaccine of a polyvalent preparation of inactivated bacteria, called Bactek[®]. This vaccine has previously been used as immunotherapy in patients with recurrent respiratory infections, with daily sublingual self-administration of a spray with the aim of stimulating the production of cytokines by macrophages and dendritic cells, such as the proliferation of CD4 lymphocytes.¹⁸ Clinical trials are underway to demonstrate its efficacy in COPD patients, and the results are expected to be published soon.

In conclusion, vaccines are effective preventive measures to reduce respiratory infections and exacerbations in COPD patients. It is important to indicate the pneumococcal, influenza and SARS-CoV-2 vaccines, without forgetting the indication of pertussis and varicella zoster vaccines in selected cases and to be aware of the development of new vaccines that may benefit COPD patients.

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Conflict of interest

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References

1. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:2355–65.
2. Halpin DM, Miravittles M, Metzendorf N, Celli B. Impact and prevention of severe exacerbations of COPD: a review of the evidence. *Int J Chron Obstruct Pulmon Dis*. 2017;12:2891–908.
3. Carreño-Ibáñez LV, Esteban-Vasallo MD, Domínguez-Berjón MF, Astray-Mochales J, González Del Yerro C, Iniesta-Fornies D, et al. Coverage of and factors associated with pneumococcal vaccination in chronic obstructive pulmonary disease. *Int J Tuberc Lung Dis*. 2015;19:735–41.
4. Giese C, Mereckiene J, Danis K, O'Donnell J, O'Flanagan D, Cotter S. Low vaccination coverage for seasonal influenza and pneumococcal disease among adults at-risk and health care workers in Ireland, 2013: the key role of GPs in recommending vaccination. *Vaccine*. 2016;34:3657–62.

5. Tin Tin Htar M, Stuurman AL, Ferreira G, Alicino C, Bollaerts K, Paganino C, et al. Effectiveness of pneumococcal vaccines in preventing pneumonia in adults, a systematic review and meta-analyses of observational studies. *PLOS ONE*. 2017;12:e0177985.
6. Froes F, Roche N, Blasi F. Pneumococcal vaccination and chronic respiratory diseases. *Int J Chron Obstruct Pulmon Dis*. 2017;12:3457–68.
7. Global Initiative for Chronic Obstructive Lung Disease. 2022 GOLD Reports [Internet]. Global Initiative for Chronic Obstructive Lung Disease – GOLD. Available from: <https://goldcopd.org/2022-gold-reports-2/> [accessed 1.5.22].
8. Miravittles M, Calle M, Molina J, Almagro P, Gómez JT, Trigueros JA, et al. Actualización 2021 de la Guía Española de la EPOC (GesEPOC). Tratamiento farmacológico de la EPOC estable. *Arch Bronconeumol*. 2022;58:69–81.
9. Kobayashi M, Farrar JL, Gierke R, Britton A, Childs L, Leidner AJ, et al. Use of 15-valent pneumococcal conjugate vaccine and 20-valent pneumococcal conjugate vaccine among U.S. adults: updated recommendations of the advisory committee on immunization practices – United States, 2022. *Morb Mortal Wkly Rep*. 2022;71:109–17.
10. Bekkat-Berkani R, Wilkinson T, Buchy P, Dos Santos G, Stefanidis D, Devaster JM, et al. Seasonal influenza vaccination in patients with COPD: a systematic literature review. *BMC Pulm Med*. 2017;17:79.
11. Kopsaftis Z, Wood-Baker R, Poole P. Influenza vaccine for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev*. 2018;6:CD002733.
12. Andreas S, Testa M, Boyer L, Brusselle G, Janssens W, Kerwin E, et al. Non-typeable *Haemophilus influenzae*-*Moraxella catarrhalis* vaccine for the prevention of exacerbations in chronic obstructive pulmonary disease: a multicentre, randomised, placebo-controlled, observer-blinded, proof-of-concept, phase 2b trial. *Lancet Respir Med*. 2022;10:435–46.
13. Butt AA, Omer SB, Yan P, Shaikh OS, Mayr FB. SARS-CoV-2 vaccine effectiveness in a high-risk national population in a real-world setting. *Ann Intern Med*. 2021;174:1404–8.
14. Mohseni Afshar Z, Babazadeh A, Janbakhsh A, Mansouri F, Sio TT, Sullman MJM, et al. Coronavirus disease 2019 (Covid-19) vaccination recommendations in special populations and patients with existing comorbidities. *Rev Med Virol*. 2021:e2309.
15. Villar-Álvarez F, Martínez-García MÁ, Jiménez D, Fariñas-Guerrero F, Ortiz de Lejarazu-Leonardo R, López-Campos JL, et al. Recomendaciones SEPAR sobre la vacuna COVID-19 en las enfermedades respiratorias. *Open Respir Arch*. 2021;3:100097.
16. Villar-Álvarez F, González-Barcala FJ, Bernal-González PJ. Pertussis vaccine in COPD and asthma: an old acquaintance is back. *Open Respir Arch*. 2022;4:100153.
17. Mejias A, Rodríguez-Fernández R, Oliva S, Peebles ME, Ramilo O. The journey to a respiratory syncytial virus vaccine. *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol*. 2020;125:36–46.
18. Alecsandru D, Valor L, Sánchez-Ramón S, Gil J, Carbone J, Navarro J, et al. Sublingual therapeutic immunization with a polyvalent bacterial preparation in patients with recurrent respiratory infections: immunomodulatory effect on antigen-specific memory CD4+ T cells and impact on clinical outcome. *Clin Exp Immunol*. 2011;164:100–7.

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