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American Review of Respiratory Medicine
Revista Americana de Medicina Respiratoria

ORIGINAL ARTICLE

ISSN 1852-236X

Update on Vaccination Recommendations in Adults with Respiratory Diseases. Document from the Argentinian Association of Respiratory Medicine for Pulmonologists, 2023

Actualización de las recomendaciones de vacunación en adultos con enfermedades respiratorias. Documento de la Asociación Argentina de Medicina Respiratoria para los neumonólogos, 2023

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Received: 07/10/2022
Accepted: 08/25/2023

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ABSTRACT

Adult smokers, subjects with comorbidities, and the elderly are at higher risk of getting pulmonary infections with worse outcomes. Community-acquired pneumonia caused by viruses, pneumococcus, other bacteria, and "atypical" microorganisms affects both healthy and sick adults. The influenza virus vaccine is designed the previous summer and is oriented towards the strains that are expected for the following season. Its effectiveness depends fundamentally on the viral variant which is ultimately responsible for the outbreak. The anti-pneumococcal polysaccharide vaccine has been since 1983 and it is expected to be replaced by more effective conjugate vaccines which prevent the infection due to the serotypes present in the vaccine. Immunization against SARS-CoV-2 diminished contagion and severity of COVID-19 remarkably. The acellular vaccine for *Bordetella pertussis* is not on the adult schedule, despite the fact that vaccinating adults strengthens contagion control in children. Double bacterial (diphtheria and tetanus), DTP (double + pertussis), measles, varicella, rubella, HPV, *Haemophilus influenzae*, meningococcal, herpes zoster, Argentine hemorrhagic fever, and yellow fever vaccines are, but their use is limited. New vaccines such as the one recently approved by the CDC (Centers for Disease Control and Prevention) against respiratory syncytial virus will soon be available.

Key words: Immunization; Influenza; Pneumococcus; Diphtheria; Tetanus; Herpes zoster, COVID-19; Respiratory syncytial virus; Vaccines

RESUMEN

Los adultos fumadores, con comorbilidades, y los ancianos tienen mayor riesgo de contraer infecciones pulmonares y de tener peor evolución. La neumonía adquirida en la comunidad debida a virus, neumococo, además de otras bacterias y microorganismos "atípicos" afecta tanto a adultos sanos como enfermos. La vacuna antigri-

Rev Am Med Resp 2023;23:4-21
https://doi.org/10.56538/ramr.BVIH9262

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pal se diseña el verano anterior orientada a las cepas esperadas para la temporada siguiente. Su eficacia depende fundamentalmente de la variante viral que finalmente sea la responsable del brote. La vacuna anti-neumocócica polisacárida existe desde 1983 y será inexorablemente reemplazada por vacunas conjugadas de mayor eficacia, que previenen la infección por los serotipos presentes en la vacuna. La inmunización contra SARS-CoV-2 aceleró la reducción del contagio y la gravedad de COVID-19 notablemente. La vacuna acelular para Bordetella pertussis no está en el calendario de adultos, aun cuando vacunarlos fortalece el control del contagio infantil. La vacunas doble bacteriana (difteria y tétanos), y triple (doble + pertusis), y contra sarampión, varicela, rubeola, HPV, Haemophylus influenzae, meningococo, herpes zóster, fiebre hemorrágica argentina y fiebre amarilla están disponibles, pero son de uso limitado. Nuevas vacunas, como la recientemente aprobada por los CDC contra el virus sincicial respiratorio, pronto estarán disponibles.

Palabras clave: Inmunización; Influenza; Neumococo; Difteria; Tétanos; Herpes zoster; COVID-19; Virus sincicial respiratorio; Vacunas

INTRODUCTION

The lung disease specialist devotes part of his/her consultation time to review the vaccination history of the patient. In 2015, the Argentine Association of Respiratory Medicine (AAMR) undertook the institutional initiative to develop vaccination recommendations for adults with respiratory diseases.[1] In recent decades, life expectancy and population age have increased, leading to a higher percentage of patients with comorbidities and individuals aged 65 and older (typical candidates for vaccination). This group was between 10% and 19% of the population in 2015, and it is expected to be between 25% and 29% by 2050.[2] In the eight years since the publication of our recommendation, the COVID-19 pandemic emerged, bringing significant advancements in vaccine development and notably impacting upon the awareness of the importance of this preventive practice, its perceived impact on disease prevention, and its morbidity and mortality consequences.[3]

The emergence of SARS-CoV-2 as the primary pathogen responsible for respiratory infections over the past three years has shown the strengths and weaknesses of the vaccination programs. Along with the approval of new vaccines worldwide in recent years, this compels us to carefully reevaluate our perspective and update recommendations on flu vaccination (FV), anti-pneumococcal vaccination (APV), anti-COVID-19 vaccination (ACV), *Bordetella pertussis* vaccine (BPV), herpes zoster vaccine (HZV), and respiratory syncytial virus (RSV) vaccine.[4]

The Ministry of Health of the Nation (MSAL) in Argentina, in a way similar to the practices of official public health agencies in other countries such as the Centers for Disease Control and Prevention (CDC) in the United States or the European Center for Disease Prevention and Control (ECDC) in Europe, provides vaccination recommendations for people from birth and throughout their entire life.[5]

Background

The MSAL has established a national vaccination schedule comprising 17 vaccines recommended for children starting from birth. This schedule includes explicit instructions regarding the number of doses, the time intervals between doses, booster shots, and descriptions of some special vaccination schedules.[5] It also specified different vaccine recommendations for certain at-risk population groups, including pregnant women, postpartum women, and healthcare personnel. Interestingly, in the schedule for individuals under 65 years without comorbidities, only the hepatitis B and double bacterial vaccines are mentioned. For pregnant women, postpartum women, and healthcare personnel, the same vaccines are recommended, adding necessary doses of DTP and MMR vaccines. For individuals aged 65 or older, or those under that age who have comorbidities, respiratory diseases, and smokers at an increased risk of experiencing viral and bacterial pulmonary

infections and their consequences, the flu and antipneumococcal vaccines are included, apart from those already mentioned.[5] There are SARS-CoV-2 vaccination schedules that are subject to changes depending on the evolution of the pandemic, and these changes can be difficult to predict.

Community-acquired pneumonia (CAP) occurs in more than 1% of individuals each year.[6] Possible pathogens of CAP include viruses, common bacteria, intracellular or atypical bacteria, fungi, and protozoa.[7] Infections caused by some of these pathogens can be prevented through immunization with vaccines. Therefore, the CDC in the United States recommend lifelong vaccination to provide immunity. However, vaccination rates in adults worldwide are low.[8]

At the beginning of the 20th century, the primary cause of death worldwide was acute pulmonary infection (characterized as influenza and pneumonia). Advances in medicine significantly improved life expectancy to around 80 years, and although pulmonary infections were no longer a leading cause of death compared to cardiovascular diseases, malignant tumors, unintentional injuries, and chronic respiratory diseases, during 2020 and 2021, COVID-19 became the leading cause of mortality in many countries, once again bringing infections to the forefront.[9]

Vaccination against influenza

The Influenza (flu) is characterized by annual epidemics that occur worldwide during the winter season (between April and October in the southern hemisphere and between October and April in the northern hemisphere). These epidemics can vary in severity. The flu typically presents with an acute onset, with or without fever, and includes general and respiratory symptoms that often improve within 7 to 10 days. In some cases, especially in individuals older than 65 years and in adults and children with chronic respiratory and cardiovascular diseases, metabolic diseases, renal failure, hemoglobinopathies, and immunosuppression (including HIV+), medical attention or hospitalization could be necessary, or even a fatal outcome could occur (10). Hence, the National Vaccination Schedule of the Ministry of Health in Argentina recommends the influenza vaccine starting from 6 months of age with no upper age limit for individuals at a higher risk of complications from the flu. Vaccination is also recommended for healthcare personnel, close contacts of immunosuppressed patients, and individuals who work in close contact with live birds.[10] The 2014 Vaccination Guideline of the MSAL already indicated that: “Patients older than 65 years will not require medical prescription to receive the flu vaccine”, in an attempt to reduce obstacles to achieving high vaccination rates. We must remember the importance of annual revaccination due to the decline in antibody titers and the loss of vaccine efficacy as a result of radical antigenic change in the hemagglutinin (H) or neuraminidase (N) components (antigenic shift) and minor changes in the structure of these proteins (antigenic drift) that the virus periodically undergoes.[11, 12]

The CDC in the United States simplified their influenza vaccination recommendation in 2010 (following the H1N1 pandemic) to “every individual of more than 6 months in the United States should get a flu vaccine each season, with rare exceptions”[13], clarifying that if vaccine supply is limited, priority should be given to individuals older than 65 years, individuals with comorbidities, and contacts of people at increased risk. This coverage limitation for cases of shortage is similar to the common recommendation in Argentina.

Of the 4 recognized types of influenza viruses, only types A and B currently cause epidemics in humans. Type A is further divided into different subtypes based on its surface proteins H and N. The two subtypes of Influenza A viruses circulating at the time of writing this document are A(H1N1) and A(H3N2). Influenza B viruses are classified into two currently circulating lineages: B/Victoria and B/Yamagata. The appearance of errors in the RNA-dependent polymerase during coinfections between humans and other species can modify the viruses, favoring the circulation of this variant in a new host.[14]

Since the late 1970s, the trivalent vaccine (containing two subtypes of influenza A virus and one lineage of influenza B virus) has been . In Argentina, the inactivated trivalent vaccine is and is directed towards the strain patterns recommended by the World Health Organization (WHO) for the relevant time period (10). Furthermore, for the past few years, the quadrivalent vaccine with two subtypes of A virus and with both lineages of B virus has also been. There is also an inactivated trivalent vaccine with an adjuvant that enhances the immunization effect. An adjuvant is

an ingredient that helps create a stronger immune response, improving its effectiveness, particularly in individuals aged 65 and older, individuals under 65 years with comorbidities and immunosuppressed subjects.[15] Finally, in Argentina, we will also have the high-dose influenza vaccine, recently approved by ANMAT (National Administration of Drugs, Food, and Medical Technology). While most vaccines contain 15 μg of each H antigen, the high-dose vaccine contains 60 μg of each antigen. [16] In August 2022, a feasibility study conducted in Denmark showed a 49% reduction in the risk of death associated with the high-dose vaccine and also demonstrated a 64% reduction in the incidence of hospitalization due to influenza or pneumonia compared to standard-dose vaccination in older adults.[17] Additionally, it's important to note that most inactivated influenza vaccines are manufactured through the method of influenza virus cultivation in embryonated eggs. However, there are also some vaccines produced from cell lines, which offer significant advantages such as the ability to produce larger quantities of vaccines more quickly. Cell-based vaccines have the additional benefit of avoiding the possibility of mutations that may arise during cultivation in embryonated eggs and not requiring the use of egg proteins, which can be beneficial for certain individuals with allergies or dietary restrictions.[18] There are also live-attenuated (of intranasal application) and recombinant vaccines, not currently in our country.[10]

In the year 2013, the first quadrivalent vaccine (two subtypes of A virus and two lineages of B virus) became[12], with a good safety profile. Adding a second B lineage to the influenza vaccine provides an increased immune response to the additional subtype without reducing the immune response to the other three subtypes or negatively affecting the safety and tolerance profile. By offering broader protection against different lineages of influenza B virus that co-circulate, the quadrivalent vaccine has the potential to further reduce morbidity and mortality related to influenza beyond what was achieved with trivalent vaccines.[19, 20] Currently, in the United States and several European countries, the quadrivalent vaccine has replaced the trivalent vaccine.[13, 15]

The group of patients seen by pulmonologists is generally characterized by having a high risk of suffering complications from severe influenza.[21] In adults, the influenza vaccination is recommended for individuals aged 65 and older and for those under 65 with chronic pulmonary disease or cardiovascular, renal, hepatic, or neurological disease, metabolic disorders, including diabetes, hemoglobinopathies, and immunosuppression (including HIV+). This includes a vast majority of the patients treated by a pulmonologist.

Furthermore, the seasonality of influenza poses a challenge to determine the optimal vaccination timing in Latin America. While in temperate climates like South America, there are peaks of activity during the winter months, in tropical and subtropical regions, influenza occurs throughout the year, especially during the rainy season.[22] Hive et al conducted an analysis based on influenza seasonality studies carried out by the CDC and the WHO, among others, collecting data from 138 countries located either wholly or partially between the 38th parallel north and south. They concluded that the main influenza season in most South American countries is between April and June.[23]

The efficacy and side effects of the influenza vaccine are measured like any other drug through randomized, double-blind clinical trials. Real-world effectiveness of authorized vaccines is assessed through effectiveness studies. Vaccine effectiveness is related to age, the presence of comorbidities, and real-world coverage of the circulating virus strains.

The effectiveness of the influenza vaccine is calculated every year by the CDC.[24] Figure 1 shows the effectiveness of the influenza vaccine measured during 16 of the last 17 influenza seasons in the northern hemisphere (it was not measured in the 2020-2021 season due to the low viral circulation caused by the strict isolation measures of the pandemic).

While the modest effectiveness of currently influenza vaccines may be surprising at first glance, as seen recently with the SARS-CoV-2 pandemic, the vaccine can prevent severe complications of the influenza. This includes a 26% reduction in ICU admissions and a 31% reduction in mortality among adults with influenza associated with hospitalization admission.[25, 26]

Anti-pneumococcal vaccination

Before 1945, pneumonia in adults was caused in over 90% of cases by *Streptococcus pneumoniae*. However, starting from 1950, the proportion of

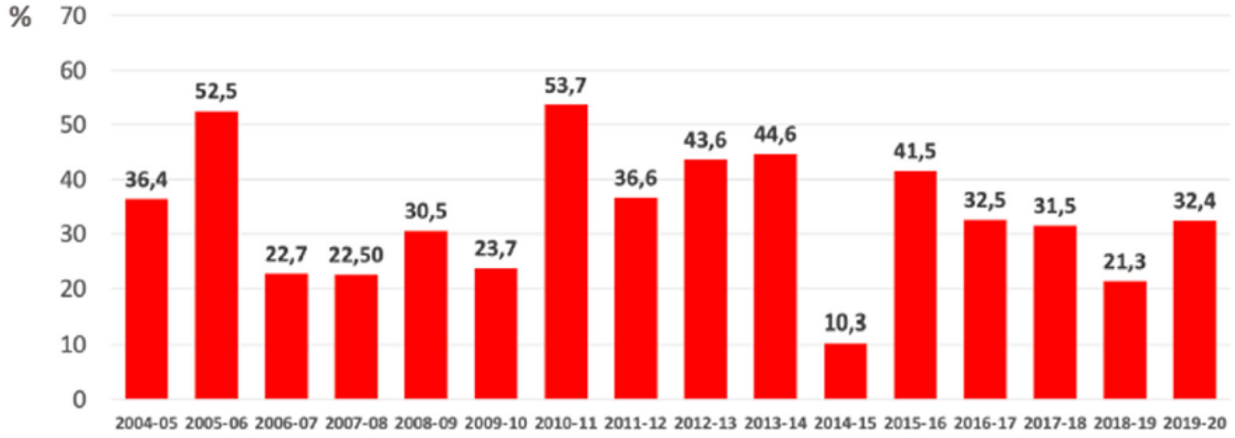

Figure 1. Estimated effectiveness of seasonal influenza vaccine from 2004-05 to 2019-20 (the 2020-21 period hasn't been considered due to the low circulation of influenza observed during the pandemic).[4]

pneumonia cases caused by this organism began to decrease. Currently, the pneumococci are present in less than 10%-15% of the cases, with this proportion being higher in Europe, likely due to differences in vaccination practices and smoking habits. Other pathogens such as gram-negative bacilli *Staphylococcus aureus*, *Chlamydia*, *Mycoplasma, and Legionella* are identified in a range of 2% to 5% of patients hospitalized for pneumonia. Viruses are found in 25% of patients, and approximately one-third of them have bacterial coinfections. It is important to note that in more than 50% of the cases, recent studies have failed to identify the causative organism, which remains the primary challenge in understanding lower respiratory infections.[27]

The 2023 Vaccination Schedule in Argentina does not specify indications for the anti-pneumococcal vaccine (APV); it only recommends a sequential schedule for adults. In the document "Technical Guidelines and Vaccinator Manual for Pneumococcal Vaccination, 2017-1028 Technical Strategy", the MSAL indicates that the APV should be administered to adults who are at high risk of invasive disease, including sickle cell anemia, congenital heart disease, chronic lung diseases, diabetes mellitus, chronic liver disease, cerebrospinal fluid fistula, functional or anatomical asplenia, cochlear implant, HIV infection, leukemia, Hodgkin's and non-Hodgkin's lymphomas, multiple myeloma, other neoplasms, chronic renal failure, nephrotic syndrome, chemotherapy or corticosteroid treatments, and organ transplants. Regarding revaccination, it states that individuals at high risk of invasive disease, such as functional or anatomical asplenia, chronic renal failure, nephrotic syndrome, HIV infection, transplantation, leukemia, lymphoma, multiple myeloma, other neoplasms, and immunosuppressive treatment, can receive one revaccination with the 23-valent pneumococcal polysaccharide vaccine (PPSV23). It also suggests that high-risk pregnant women who have not previously received the APV can receive it starting from the 16th week of gestation. It is advisable to take the APV, if applicable, when receiving the annual FV. Individuals aged 65 and older do not require a doctor's prescription to be vaccinated.[28]

Expert Consensus Document of the Latin American Thoracic Association (ALAT) and the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), concluded that tobacco consumption is a highly significant risk factor for the development of pneumococcal disease in its clinical forms of community-acquired pneumonia (CAP) and invasive pneumococcal disease (IPD).[29]

In our region, we have had the PPSV23 since 1983 (covering serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) and the 13-valent pneumococcal conjugate vaccine (PCV13) (covering serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F), conjugated with the CRM 197 carrier protein, since 2013. PCV13 was approved by ANMAT for individuals over 50 years of age in 2012 based on its higher immunogenicity for 10 of the 12 shared vaccine serotypes.[30] Pneumococcal vaccines are administered sequentially (PCV13 followed by

PPSV23) as recommended by the Advisory Committee on Immunization Practices (ACIP) in the United States for individuals older than 18 years with risk factors, including candidates and recipients of hematopoietic cell transplantation. In 2014, the ACIP started to recommend the PCV13 for adults aged ≥ 65 years.[31]

In 2015, Bonten et al published a double-blind, randomized, placebo-controlled parallel-group study that strikingly demonstrated that in vaccinated individuals, a single dose of the PCV13 vaccine results in a 45.6% decrease in the amount of first episodes of CAP caused by any of the serotypes present in the vaccine ($p < 0.001$); a 45.0% decrease in the amount of episodes of non-bacteremic/non-invasive CAP due to a serotype present in the vaccine ($p = 0.007$); and a 75.0% reduction in the number of first episodes of IPD ($p < 0.001$).($p < 0.001$).[31,32] A narrative report of Dunne et al compared the effectiveness of the PPSV23 and PCV13 vaccines in the same adult populations. They found that vaccine effectiveness varies between 10 and 11% for PPSV23, between 40 and 79% for PCV13, and 39 to 83% for the PCV13/PPSV23 vaccines. Vaccine effectiveness against pneumonia (of all causes) or lower respiratory tract infection varies between 8 and 3% for PPSV23 and between 9 and 12% for PCV13. These data confirm that the conjugate vaccine has higher efficacy in preventing lung infections in adults.[33] The latest addition is the 20-serotype conjugate vaccine (PCV20), which is indicated for active immunization to prevent pneumonia and invasive diseases caused by serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F of *Streptococcus pneumoniae* in adults older than 18. The PCV20 vaccine approved by the FDA (Food and Drug Administration) in 2021 and by the EMEA (European Medicines Agency) in 2022, was approved by ANMAT in mid-June 2023. PCV20 adds 7 new serotypes to the 13-valent vaccine, which could simplify vaccination schedules in the near future.[34,35]

The currently recommended pneumococcal vaccination regimen for immunocompetent adults in Argentina involves the sequential administration of the PCV13 vaccine, followed by the PPSV23 vaccine 12 months later. The PPSV23 requires a second dose after the age of 65 (provided that at least 5 years have passed since the first dose). In immunosuppressed patients, the sequential administration of PCV13 should be followed by PPSV23 at least 8 weeks later.[28] Under special circumstances (such as individuals who have had a splenectomy, those with sickle cell anemia, or those with cerebrospinal fluid fistula), it is recommended to administer a second dose of PPSV23 5 years after the first dose, and in these cases, eventually a third dose could be administered after the age of 65[36] (Figure 2). Vaccination using the 20-valent vaccine suggests a much simpler schedule, as shown in Figure 3.

COVID-19 vaccines

In November 2019, the appearance of a new animal-origin coronavirus capable of causing severe respiratory infections was reported in China, and the WHO declared it a pandemic in March 2020. Early that year, the virus was sequenced, enabling the rapid development of vaccines based on viral vectors and messenger RNA platforms. These vaccines have proven to be highly effective against severe forms of the disease in clinical trials and real-world settings, both in adults and in pregnant women, children, and adolescents.[3,37] It is estimated that the vaccines prevented the death of 19 million people in their first year of use.[38] Complete vaccination schedules provide protection ranging from 88% to 55% depending on the variant of interest, with the highest effectiveness against the Alpha variant and the lowest against Omicron.[39] In our country, the vaccination campaign using initially vaccines (Sputnik V, ChadOx1, and BBBIBP-CorV) was associated with significant reductions in infection and mortality.[40,41] When mRNA-based vaccines started to be used in children and adolescents, a measurable benefit was also obtained.[42] Evidence gathered from systematic reviews suggests that mRNA platform-based vaccines are associated with greater protection against the symptomatic disease.[43] Observational studies also show a decrease in the risk of developing the symptoms of the post-infection syndrome, also known as "long COVID" among vaccinated individuals.[44] It was also shown that heterologous vaccine schedules provided protection, and this strategy was used in some segments of the vaccination campaign.[45]

The ancestral virus was replaced by new variants with higher contagion rates. In November 2021, the Omicron variant was identified. Initially developed vaccines showed reduced neutralizing capacity towards this new variant, and immunity

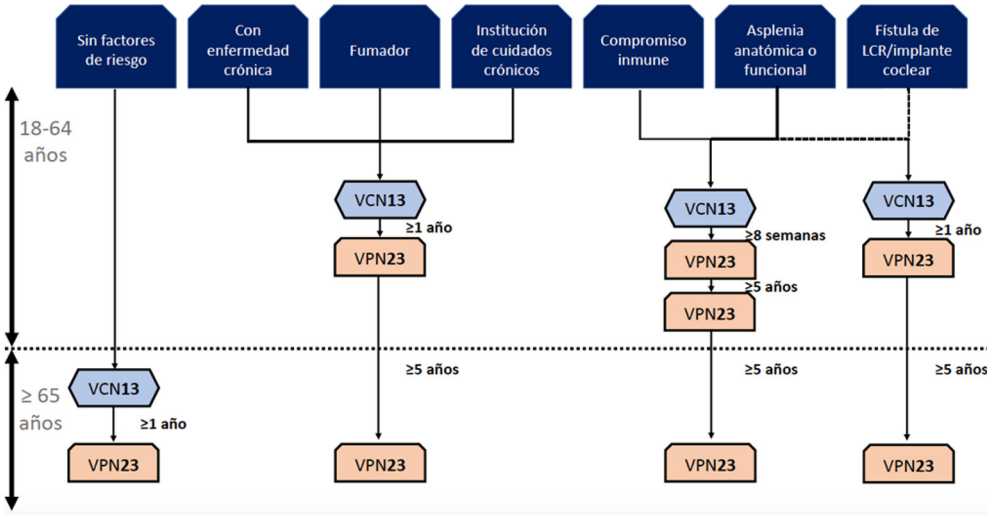

Figure 2. Sequential vaccination schedule of PCV13 and PPSV23 in adults according to age and risk factors, sequential vaccination schedule of 13-valent pneumococcal conjugate vaccine (PCV13) and 23-valent pneumococcal polysaccharide vaccine (PPSV23) in adults according to age (older or younger than 65 years), smoking habits, presence of comorbidities and patient immune status. It is preferable to administer PCV13 first and wait for at least 1 year before administering the other vaccine (except for immunosuppressed individuals, in which case the time interval between vaccines should be at least 8 weeks). In cases of cochlear implant or cerebrospinal fluid fistula with a high risk of infection, a sequential vaccine can also be given after 8 weeks. For immunosuppressed individuals, it is recommended that a second dose of PPSV23 be administered 5 years after the first dose, even before the age of 65.

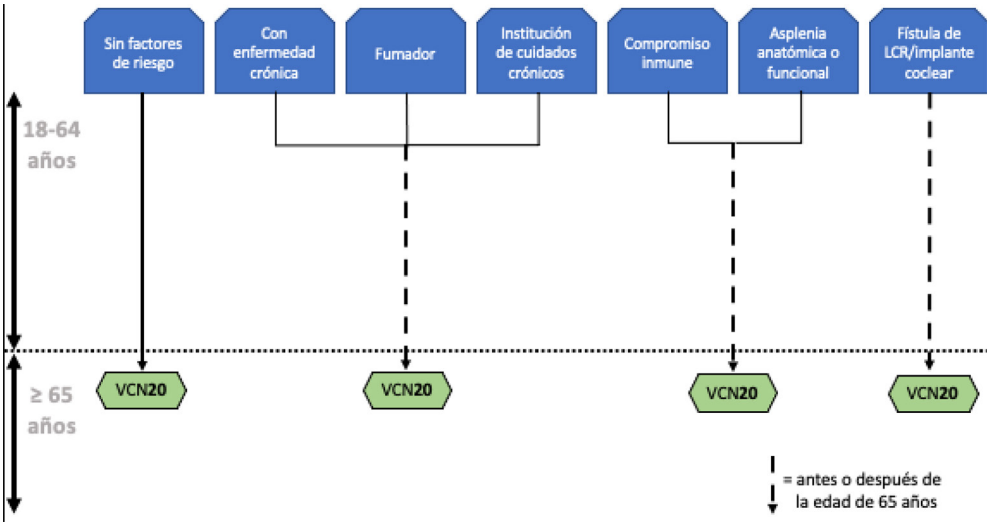

Figure 3. Possible vaccination schedule of PCV20 in adults according to age and risk factors, vaccination schedule of 20-valent pneumococcal conjugate vaccine (PCV20) in adults according to age (older or younger than 65 years), smoking habits, presence of comorbidities and patient immune status. Higher coverage and improved immunogenicity for the 7 strains added to PCV13 suggest achieving a better coverage compared to the sequential administration of PCV13 followed by PPSV23, in addition to the simplicity of the process.

declined more rapidly.[46] The administration of booster doses showed the additional effectiveness of a third dose compared to the primary series and of a fourth dose compared to the third, mainly in people over the age of 60.[47, 48] A 47% decrease in effectiveness against infections was observed at 280 days, with 75% effectiveness at 112 days to prevent hospitalization and death.[49] According to the Nominalized Federal Vaccination Registry, in Argentina, in May 2023, 9,314,083 people aged 50 or older had not yet received a booster dose in the last 6 months.[50]

In early 2022, bivalent vaccines targeting both the ancestral variant and the new sub-variant were introduced simultaneously.[51, 52] These vaccines have become the standard; however, evidence shows that the neutralizing antibody titers they induce are similar to those of monovalent vaccines.[53] Observational studies have confirmed that administering bivalent boosters provided 50% additional effectiveness to the doses of the primary series for individuals aged 50 to 64 who had previously received two doses. In contrast, the additional effectiveness was 22% for those over 65 who had received more than two doses.[54] The explanation for this lower comparative effectiveness of bivalent vaccines is "imprinting" a phenomenon in which the immune response is primarily configured against the antigens of the original variants presented by the first vaccines, and an equally efficient response is not achieved when other antigens are presented later. [55]

Evidence shows that stronger immunity is achieved when vaccine-induced immunity is combined with natural immunity from infection, a situation that is very common considering the high prevalence of infection in the communities.[56] The recommendations of the MSAL that were in force at the time of writing this document state that individuals of groups at high-risk of developing severe forms of the disease (individuals aged 50 and older, immunosuppressed individuals, and pregnant women) should receive a COVID-19 booster dose 6 months after their last dose, regardless of the number of previous booster doses received and with a minimum interval of at least 4 months since the last dose. People under 50 years old with comorbidities (chronic illnesses and obesity) and those at higher risk of exposure (healthcare personnel) and with strategic roles fall into the group at "medium-risk" of experiencing severe illness or death from COVID-19 infection. The recommendation for this group is to receive a new booster dose 6 months after the last dose received and, subsequently, they should receive a booster dose annually.

Individuals considered to be at low risk of suffering complications (people under 50 years without comorbidities) have access to COVID-19 booster vaccination, and it is recommended that they receive it annually.[50]

The most common adverse effects of the vaccination are mild local reactions.[57] The most concerning adverse effects reported have been the occurrence of thrombosis (primarily associated with the ChadOx1 vaccine) and myocarditis (linked to mRNA platform vaccines). While modest increases in the risk of hematological and vascular events after vaccination have been observed, this risk is much higher and prolonged for the virus infection itself.[58, 59] Myocarditis is a very rare event, occurring in 1.08 cases per 100,000 vaccinated individuals, and one every five events is severe. [60] In this case as well, myocarditis from SARS-CoV-2 infection is more common than myocarditis from vaccination, resulting in a risk-benefit ratio highly favorable for vaccination.[61]

Vaccines against pertussis

Pertussis, also known as whooping cough, is caused by the bacterium *Bordetella pertussis*. The classic respiratory disease is characterized by three stages: catarrhal, paroxysmal, and convalescent.[62] During the catarrhal stage, infected individuals experience rhinitis (inflammation of the nasal mucous membranes), occasional mild cough, and low-grade fever. The paroxysmal stage is characterized by spasmodic coughing, post-cough vomiting, and inspiratory wheezing. Symptoms gradually improve during the convalescent stage, which typically lasts from 7 to 10 days but can extend for months. Factors influencing the clinical presentation of whooping cough include age, immunity level, vaccination history, and the use of antibiotics at the onset of the disease.[63]

The MSAL recommends combined vaccination against pertussis, tetanus, diphtheria, *Haemophilus influenzae* type b, and Hepatitis B for infants and young children, through a series of 4 doses of the 5-in-1 or pentavalent vaccine, including diphtheria and tetanus toxoids and acellular pertussis (Argentina has the cellular component). This is followed by a dose of DTP (cellular triple bacterial) which is administered at school admission at 5 years of age.[5] Furthermore, the ACIP recommends a booster dose at age 11 of the Tdap vaccine (cellular triple bacterial vaccine with acellular pertussis, reduced diphtheria toxoid, and tetanus toxoid). Adults aged 19 to 64 who have never received the Tdap vaccine are also advised to receive a booster dose. During pregnancy, it is recommended that women receive a dose of Tdap after the 20th week, preferably between weeks 27 and 36, regardless of whether they have previously

received this vaccine or not. After receiving the Tdap vaccine, adolescents and adults are suggested to receive a booster dose of the Td vaccine (tetanus and diphtheria toxoids) every 10 years to ensure ongoing protection against tetanus and diphtheria and reduce the transmission of the latter.[5, 64]

Recently, the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guidelines have recommended Tdap vaccination for patients with chronic obstructive pulmonary disease who haven't been vaccinated during adolescence.[65]

Vaccine against herpes zoster

Herpes Zoster (HZ) is a neurocutaneous disease produced by the reactivation of the primary infection of the varicella-zoster virus (VZV). This reactivation results in chickenpox and the lifelong residence of the VZV genome in the dorsal root or cranial nerve ganglia.[66] The incidence and severity of HZ increase with age. More than 90% of patients over 50 years old worldwide have been infected with VZV and are therefore at risk of developing HZ, with an incidence of approximately 2-4.6 people per 1,000 individuals per year. [67-70] The incidence significantly increases in adults older than 80 years, reaching values between 10 and 12.8 cases per 1000 persons-year.[71] This implies that one every three individuals between the ages of 50 and 90 will experience some episode of HZ (72). Immunity to HZ, initially acquired innately (primoinfection) in children and young adults when they get chickenpox can be maintained either intrinsically or through extrinsic boosting. Intrinsic immunity is a subclinical response to reactivation of VZV, while extrinsic boosting happens asymptomatically through exposure to VZV in the community.[72,79] The risk of HZ increases in individuals aged 50 and older due to the effects of immunosenescence (cellular aging) or at any age due to immunosuppression caused by various conditions such as HIV, diabetes mellitus, COPD, chronic kidney disease, cardiovascular disease, among others, and/or by immunosuppressive treatments like chemotherapy in the oncological population, transplants, rheumatologic diseases, or interstitial lung diseases (70). HZ occurs when VZV-specific cell-mediated immunity fails to contain viral reactivation, presumably for being below a not-yet defined protective threshold, and the reactivated VZV continues to spread.[73, 74] HZ has multiple complications, with postherpetic neuralgia (10-15%) being the most common. It is characterized by chronic radicular pain that can persist for more than 3 months after the vesicular eruption of HZ, and it can become disabling and very difficult to treat. Chronic pain from postherpetic neuralgia can affect between 5% and 30% of individuals who develop HZ, with a higher frequency in older individuals, especially those over the age of 60.[70, 75] If it affects the eye region, especially after ophthalmic HZ, it can lead to complications such as keratitis, conjunctivitis, and even glaucoma, which can scar and leave severe lesions, including various degrees of blindness. In patients with severe immunosuppression, there can be serious and highly fatal complications such as disseminated HZ, myelitis, encephalitis, and/or cranial nerve paralysis.[76] A previous version of the document recommended the live attenuated vaccine against HZ containing the Oka VZV strain. This vaccine is authorized for use in adults aged 50 and older. Medical literature has shown that this vaccine has 51.3% effectiveness in preventing HZ and 66.5% effectiveness in reducing postherpetic neuralgia in people aged 60 or older. However, its efficacy decreases with age, dropping from 69.8% in adults aged 50-59 to 37.6% in those aged 70 or older. Furthermore, it is contraindicated in individuals with immunosuppression, as live attenuated vaccines could cause illnesses in this population.[77] In 2015, a new recommendation was introduced, and in 2017, the FDA voted unanimously on the recommendation of a new recombinant vaccine that contains an antigen a glycoprotein called gE (a fragment of VZV) along with an adjuvant called AS01B to boost the immune response. Two doses separated by 2-6 months have an efficacy of 97.2% in reducing the risk of HZ in adults aged 50 and older.[75, 77] The duration of its efficacy has been studied over the years, showing it maintained an efficacy of 87.9% for HZ prevention 4 years after having received two doses.[71] Many individuals with asthma and almost all patients with COPD, idiopathic pulmonary fibrosis, and other chronic lung conditions are older than 50 years, the age at which this vaccine should begin to be used.[1] Given the fact that adults aren't normally used to vaccine compliance monitoring, pulmonologists can be considered one of the healthcare providers best suited to recommend this vaccine as part of preventive healthcare measures for their patients, positively influencing their attitudes and beliefs.[78]

Vaccine against respiratory syncytial virus

The respiratory syncytial virus (RSV) is a common cause of respiratory tract infections that can lead to severe illness, often affecting infants and older adults. During the winter months, an estimated 700,000 to two million cases of RSV are reported. In the United States, RSV infections in older adults account for approximately 177,000 hospitalizations and 14,000 deaths annually.[79] In Argentina, there are approximately 7,000,000 adults aged 65 and older; about 0.2% of them are expected to experience severe RSV infections, which amounts to around 14,000 patients on average.[80] Pneumonia, COPD exacerbations or asthma require hospitalization in patients who acquire severe RSV infection. 10% of these patients will die as a consequence of the infection.[81] In many cases, children are the source of infection for older adults, while in other cases, the children can be infected by older adults. Recently, the FDA has approved a vaccine against RSV for adults. The effectiveness of this vaccine was 94.1% (95% confidence interval, 62.4 to 99.9) against severe disease (pneumonia) and 71.7% (95% CI, 56.2 to 82.3) against RSV causing exacerbation of associated respiratory disease.[82] In Argentina, this vaccine has not yet been submitted to ANMAT for approval; thus, it is not yet.

Vaccination recommendations for adults from the pulmonologist's point of view

Vaccines are important for preventing diseases and disease complications throughout life. However, vaccine coverage in adults is generally low and there is still a long way to go before meeting established goals. Among the vaccines recommended for adults, the ones that stand out are those against influenza and pneumococcus, as they aim to prevent respiratory complications. These vaccines are especially important for patients with chronic lung diseases such as COPD, asthma, and chronic bronchitis. This committee proposes that, in addition to the specific vaccination schedule recommendations, healthcare providers should follow the guidelines of the Ministry of Health and other relevant organizations so as to simplify adult vaccination recommendations according to different age groups, always trying to complement such recommendations and not reduce them.

Vaccination recommendations for specific diseases

Bronchial asthma

Asthma is a chronic respiratory disease characterized by persistent inflammation where various types of cells play a significant role. This inflammation causes symptoms in susceptible individuals, associated with variable but widespread airflow obstruction, which can be reversed spontaneously or with treatment. The inflammation also increases bronchial hyperreactivity to various stimuli.[83] All asthmatic patients fall under the category of chronic lung diseases, recognized among the annual FV recommendations and COVID-19 guidelines established by the MSAL and the 2022 Global Initiative for Asthma (GINA) (9, 79). The CDC, through its 2030 immunization agenda (Healthy People 2030), aims to reduce the morbidity and mortality of diseases that can be prevented through vaccination and ensure access to new and existing vaccines for the entire population. Immunization is a global health success story. Since 2010, more than 116 countries have introduced vaccines that they hadn't used previously, some of which are against deadly conditions like CAP (84). A systematic review conducted by Boikos et al found a positive association between asthma and IPD. This finding supports the idea of considering asthma a high-risk disease that requires the administration of pneumococcal immunization. [85] Therefore, basing on the cited information, expert consensus documents, the Spanish Asthma Management Guidelines (GEMA 5.3), and the CDC, APV administration is recommended for patients with asthma.[86, 87]

Chronic obstructive pulmonary disease

COPD is a heterogeneous disease characterized by chronic respiratory symptoms (cough, dyspnea, sputum production, and/or exacerbations) due to abnormalities in the airways and/or alveoli that result in airway obstruction (65). Exacerbations are primarily caused by viral infections that can suffer bacterial superinfection, leading to increased inflammation and originating symptoms and an impact on quality of life and survival. People with COPD suffer from CAP more frequently, and COPD is associated with reduced survival following a CAP episode (88). COPD is a well-recognized

chronic lung disease listed among the annual FV and APV recommendations of the National Guidelines for the Control of Vaccine-Preventable Diseases and the Ministry of Health and Gender of the Autonomous City of Buenos Aires (89). The GOLD guidelines, the Spanish COPD guidelines (GesEpoc), and the national guidelines for COPD diagnosis and treatment from the MSAL recommend the FV and APV with varying levels of evidence[90, 91] The FV with inactivated viruses appears to reduce the frequency of exacerbations and severe illness requiring hospitalization. [92,93] It is also effective in reducing the number of influenza infections by 40% and could be associated with a lower risk of ischemic cardiac events. [94,95] In terms of efficacy, evidence suggests that the likelihood of not acquiring acute respiratory infections related to influenza in individuals vaccinated with FV (trivalent, fragmented, and inactivated virus) is 76%. In patients with mild, moderate, or severe COPD, vaccine effectiveness was 84%, 45%, and 85%, respectively.[96] Systematic reviews haven't shown an effect of the FV on mortality, the number of hospitalizations for influenza-like illness, or the need for mechanical ventilation.[92, 96] The aforementioned guidelines agree on the APV recommendation for being one of the comorbidities included in the CDC's recommendations. A systematic review by the Cochrane Collaboration found that the APV reduces the incidence of CAP and exacerbations in COPD patients.[97] They also found that vaccination reduces the risk of CAP and COPD exacerbations without an impact on the risk of confirmed pneumococcal pneumonia.[97, 98] Regarding safety, reported local and systemic adverse effects are mild.[92, 97, 98]

Smoking

Evidence from population-based studies indicates a higher risk of influenza-like illness (ILI) among smokers. A survey conducted in 5943 individuals in Great Britain found that tobacco use was one of the six factors associated with ILI in the multivariable analysis.[99] FV and APV are formally recommended for smokers, regardless of age, the presence of comorbidities, or immune status, even in the absence of other risk factors.[29, 100, 101]

Other chronic lung diseases

Acute exacerbations of chronic lung diseases are often associated with viral and bacterial pathogens. These exacerbations contribute to lung function deterioration and poor quality of life, and place an additional burden on individuals, families, communities, and the healthcare sector. Therefore, preventing exacerbations is crucial in clinical management. Several vaccines offer protection against respiratory pathogens (*Streptococcus pneumoniae, Bordetella pertussis*, influenza, RSV, and SARS-CoV-2) that can trigger exacerbations, but the evidence supporting their effectiveness in the prevention of exacerbations of chronic lung diseases is limited.[102] Much research focuses on other chronic lung diseases like COPD, asthma, and cystic fibrosis. Bronchiectases receive less attention than other chronic respiratory diseases in children and adults. The role of existing vaccines against pathogens associated with the disease has not been sufficiently studied, and the evidence of benefit is limited.[103] Nevertheless, due to the risk of complications such as severe pneumonia, IPD, and hospitalization as a consequence of influenza, it is recommended that children and adults with bronchiectasis (BQT) receive vaccines in accordance with the national immunization program for high-risk groups.[5] Additionally, it's important to consider the role of maternal immunization during pregnancy, as severe respiratory infections in early childhood are associated with the development of bronchiectasis.

Vaccination recommendations from the pulmonologist's point of view

Taking into consideration the patient's history and age, supported by the availability of different vaccines, the recommendations of the MSAL and recent publications, the Lung Infection Department of the Argentine Association of Respiratory Medicine formulates the following recommendations for pulmonologists with regard to the vaccination of adults with lung diseases.

Adults aged 18 to 65 years, without a history of lung disease and without close contact with individuals at high risk of complications if they contract influenza:

They can receive an annual FV, preferably the quadrivalent vaccine (containing two strains of influenza A and two strains of influenza B), even if they do not have a specific indication. They should be inquired about the last dose they received of the Td vaccine, which should be repeated every 10

years. It is recommended that one of the doses of the Td vaccine that are going to be administered over their lifetime be given with the Tdap vaccine if the patient has never been vaccinated with an acellular pertussis vaccine. They can receive a primary series of the ACV and then an annual booster dose.

Pregnant women

The FV is recommended during any trimester of the pregnancy; and the Tdap vaccine is recommended after the 20th week of gestation in each pregnancy.

Adults aged 18 to 65 years, with a history of lung disease, smoking, other comorbidities, or contact with high-risk patients who may experience complications if they contract influenza:

Annual FV, preferably the quadrivalent vaccine, and the APV according to the schedule outlined in **Figure 2**. They should be inquired about the last dose they received of the Td vaccine, which should be repeated every 10 years. It is recommended that one of the doses of the Td vaccine that are to be administered over their lifetime be given with the Tdap vaccine if the patient has never been vaccinated with an acellular vaccine against pertussis. They can receive the primary series of the ACV and booster doses every 6 months.

Individuals older than 18 years and younger than 65 who have undergone a splenectomy, or those with sickle cell anemia, or cerebrospinal fluid fistula:

Annual FV, preferably the quadrivalent vaccine, and the APV according to the schedule outlined in Figure 2. Td vaccine every 10 years. It is recommended that one of the doses of the Td vaccine that should be given over their lifetime be administered with the Tdap vaccine if the patient has never been vaccinated with an acellular pertussis vaccine (Figure 1). They can receive the primary series of the ACV and booster doses every 6 months.

Adults between 50 and 65 years old, in good health:

Their schedule only recommends the administration of the 2-in-1 Td vaccine every 10 years throughout their life. It is recommended that one of the doses of this vaccine be administered with the Tdap vaccine. Healthy individuals older than 50 years should be vaccinated against HZ. The recombinant vaccine is administered in 2 doses separated by 2 to 6 months.

Individuals older than 65 years, with or without comorbidities

The annual FV, preferably the quadrivalent type, or the trivalent type with adjuvant, and the APV according to the schedule outlined in Figure 2. Td vaccine every 10 years. It is recommended that one of the doses of the Td vaccine that should be given over their lifetime be administered with the Tdap vaccine if the patient has never been vaccinated with an acellular pertussis vaccine. If they haven't been vaccinated against HZ yet, it is recommended that they do so. They can receive the primary series of the ACV and booster doses every 6 months.

Patients of any age admitted to the intensive care unit with respiratory failure or heart failure

Vaccine against herpes zoster. Annual FV, preferably the quadrivalent type, and the APV according to the schedule outlined in Figure 2. Td vaccine every 10 years. It is recommended that one of the doses of the Td vaccine that should be given over their lifetime be administered with the Tdap vaccine if the patient has never been vaccinated with an acellular pertussis vaccine. If they haven't been vaccinated against HZ yet, it is recommended that they do so. They can receive the primary series of the ACV and then an annual booster dose.

Summary of recommendations in Table 1

CONCLUSIONS

Chronic respiratory diseases are a growing health problem, especially regarding tobacco consumption and the aging of the population associated with the constant updates in immunization and prophylaxis in all individuals with and without risk factors. This becomes a paradox arising from advances in medical care over the last decades.

Under this scenario, the pulmonologist plays a fundamental role as a guide, especially after the emergence of COVID-19, where many specialties referred patients for consultation on new vaccines, co-administration with FV and APV and other vaccines, and time interval between doses, among other things.

Additionally, the pulmonologist also faces the consequences of the lack of prevention of respira-

TABLE 1. Summary of vaccination recommendations from the pulmonologist's point of view

Population	FV	APV	Td	Tdap	ACV	HZV
Adults aged 18-64 years without lung disease or any other comorbidities*; no close contact with individuals at risk if they contract influenza	X[1]	X[1]	X[2]	X[3]	X[4]	
Adults aged 18-64 years who have comorbidities* or smokers or with close contact with individuals at risk if they contract influenza	X	X	X[2]	X[3]	X[5]	
Pregnant women	X			X[6]		
50-64 years old, healthy						X[7]
≥ 65 years old, with or without comorbidities*		X	X[2]	X[4]	X[5]	X[7]
Hospitalized at the Intensive Care Unit due to respiratory or heart disease	X	X	X[2]	X[4]	X[5]	

References: FV: annual flu vaccine; APV: anti-pneumococcal vaccine; Td: tetanus-diphtheria booster; Tdap: tetanus-diphtheria, acellular pertussis booster; ACV: anti-COVID-19 vaccination; HZV: anti-herpes zoster vaccine.
* Comorbidities: lung disease, heart, renal, or chronic hepatic disease, congenital or acquired immunosuppression, neuromuscular disease affecting secretion management, morbid obesity (>40 BMI), individuals living in chronic care facilities or nursing homes; groups of people that can transmit the disease to high-risk individuals.
[1]Can be received without precise indication; [2]every 10 years; [3]if the patient never received it, replace one dose of Td with Tdap; [4]primary series and annual booster dose; [5]primary series and booster dose every 6 months; [6]in pregnant women after week 20, [7]two doses separated by 2-6 months

tory infections, such as exacerbations of COPD, of asthma, CAP, and other infectious disorders. As a result, the pulmonologist is the specialist who prescribes and informs the most about vaccines as the best method for the prevention of infectious conditions in chronic diseases.

The objective of this writing committee is to promote the constant updating of adult pulmonologists so that they are prepared to play a direct role in the recommendation of vaccines to their patients.

Conflict of interest

CML is a medical consultant for Pfizer since 2012; he has participated in clinical trial protocols as an investigator, adjudicator, or member of the Safety Monitoring Board for Novartis, Boehringer, Bayer, and Pfizer in the past; he has been a speaker for Pfizer since 2010. LP has participated as a speaker for Glaxo on obstructive diseases in adults and as a consultant for Merck Sharp & Dohme. AJV has served as a consultant for Sanofi, GSK, Novartis, and Pfizer. The rest of the authors have no conflicts of interest related to the topic of this publication.

Document funding

This document is sponsored by SANOFI, Pasteur, and SEQUIRUS laboratories.

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