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Impact of vaccination on the epidemiology and prognosis of pneumonia

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ABSTRACT

Adults with lung diseases, comorbidities, smokers, and elderly are at risk of lung infections and their consequences. Community-acquired pneumonia happen in more than 1% of people each year. Possible pathogens of community-acquired pneumonia include viruses, pneumococcus and atypicals. The CDC recommend vaccination throughout life to provide immunity, but vaccination rates in adults are poor.

Tetravalent and trivalent influenza vaccine is designed annually during the previous summer for the next season. The available vaccines include inactivated, adjuvant, double dose, and attenuated vaccines. Their efficacy depends on the variant of viruses effectively responsible for the outbreak each year, and other reasons.

Regarding the pneumococcal vaccine, there coexist the old polysaccharide 23-valent vaccine with the new conjugate 10-valent and 13-valent conjugate vaccines. Conjugate vaccines demonstrate their usefulness to reduce the incidence of pneumococcal pneumonia due to the serotypes present in the vaccine.

Whooping cough is still present, with high morbidity and mortality rates in young infants. Adult's pertussis vaccine is available, it could contribute to the control of whooping cough in the most susceptible, but it is not present yet in the calendar of adults around the world.

About 10 vaccines against SARS-CoV-2 have been developed in a short time, requiring emergency use authorization. A high rate of vaccination was observed in most of the countries. Booster doses became frequent after the loss of effectiveness against new variants. The future of this vaccine is yet to be written.

Keywords: immunization, influenza, community acquired pneumonia, prevention, respiratory pathogens.

INTRODUCTION

Lower respiratory tract infections are the 4th leading cause of death in the world according to the WHO [1]. Adults with lung diseases such as COPD, asthma, bronchiectasis, diffuse parenchymal lung diseases and diseases that target other organs (heart, kidneys, liver, immune system), smoking and neuromuscular diseases, are at risk of contracting lung infections and suffering its consequences, many of these infections can be prevented through vaccination.

In 2016, it was estimated that 336.5 million lower respiratory tract infections occurred in the world (32.2 per 100,000) [2]. In the US, community-acquired pneumonia (CAP) accounted for more than 4.2 million ambulatory care visits in 2016 and 1.3 million emergency department visits in 2017.

The US Centers for Disease Control (CDC) recommend vaccination throughout life to provide immunity. However, for various reasons, vaccination rates in adults are poor [3]. In this brief review we will review the vaccines of importance to the pulmonologist.

ETIOLOGY OF COMMUNITY ACQUIRED PNEUMONIA

Knowledge of the etiology of this disease has changed over the last century in the same way that medicine in general has, going from limited knowledge to the discovery of the role of bacteria and respiratory viruses and their impact in the human being. In general, the most frequent aetiologies have evolved during the last 8 decades, on the one hand, from the appearance of new diagnostic methods that did not exist at the beginning of the 20th century, and on the other hand, from the impact of the use of the different antimicrobials, particularly for the treatment of bacterial infections. It all started with direct examinations and cultures of secretions normally free of pathogenic microorganisms such as blood, pleural fluid, and

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Table 1 Etiology of community-acquired pneumonia in 2,329 adult patients		
Microorganism	Cases per 10000 adults per year	Incidence/10000 per year (IC 95%)
Human rinovirus	2.0	(2.7-2,3)
Influenza A y B	1.5	(1.3-1.8)
<i>Streptococcus pneumoniae</i>	1.2	(1.0-1.4)
<i>Metapneumovirus</i>	0.9	(0.7-1.2)
Parainfluenza	0.8	(1.0-1.4)
Respiratory sincitial virus	0.9	(0.7-1.2)
Coronavirus	0.6	(0.4-0.7)
<i>Mycoplasma pneumoniae</i>	0.5	(0.4-0.7)
<i>Staphylococcus aureus</i>	0.4	(0.3-0.6)
<i>Legionella pneumophila</i>	0.4	(0.2-0.5)
Adenovirus	0.4	(0.2-0.5)

Nasal and oropharyngeal swabs were taken in 2,272 patients (98%), blood cultures in 2,103 (91%), and urinary antigen detection in 1,973 (85%). Some pathogen was found in 38% of the patients, including viruses in 27% and bacteria in 14%. Rhinovirus, influenza, and *S. pneumoniae* were the most frequent and the highest burden was observed in the oldest. Modified from Jain S, et al. [3].

various fluids and secretions. Then, the existence of bacteria that were not identified with current methods was recognized and agents such as respiratory viruses and "atypical" bacteria such as *Mycoplasma pneumoniae*, *Chlamydomypha pneumoniae*, *Legionella pneumophyla*, etc., began to be identified by serological methods or special cultures, not recognizable by current methods. Later, high-specificity urinary antigen tests appeared to detect recent infection by *Legionella* and pneumococcus. More recently, molecular studies such as polymerase chain reaction (PCR) have begun to be used for clinical diagnosis, which allows different viruses, bacteria, fungi, and parasites to be detected with very high sensitivity in different tissues and body fluids.

For this reason, the map of possible pathogens has now expanded significantly for both normal and immunosuppressed hosts. Jain et al. searching for the etiology of community-acquired pneumonia requiring hospitalization systematically using the available microbiological studies including the use of PCR in 2,320 individuals over 18 years of age, with radiologically confirmed CAP, they found that among the 12 main causes of acute pneumonia, 7 are viruses and that rhinovirus and influenza are more frequent than pneumococcus in this infection [4] (Table 1). In today's world, vaccines have been taking an increasingly important role in the prevention of respiratory infections. The health system of most countries in the world does not have a family doctor who is aware of most of the personalized care needs of a healthy or chronically ill individual, as is the case with pediatricians who perform their role in the care of healthy children, leading preventive measures and controlling the progress of the immunization schedule. In this sense, the pulmonologists sometimes function as "the

adult's pediatricians", since in their routine visit, they must, among other things, review the immunization history of their patients.

A transcendental aspect that ranks the importance that vaccines aimed at preventing respiratory infections are occupying is the fact of the increase in life expectancy in the world. Thus, the percentage of people over 65 years of age was less than 20% in Latin America in 2015 and between 20 and 24% in Spain, but it is expected that by 2050 it will increase between 10 and 30% in Latin America, and more than 30% in Spain.

We will briefly review the salient aspects of the vaccines that the pulmonologist must handle.

INFLUENZA

This virus has in its structure a series of proteins and nucleic acids that are potential targets for the development of vaccines. It occurs annually in outbreaks of variable virulence that can occur between fall and spring. The virus poses ongoing challenges to vaccine development and vaccination strategies. The greatest interest is focused on the 17 subtypes of the hemagglutinin protein and the 10 subtypes of the neuraminidase that generate the theoretical possibility of having 170 different variants of the virus, each of which represents a significant change in the entity of the virus, and this change it manifests itself with the disappearance of the immunity that was sustained by another of these variants (antigenic shift). In addition, there may be minor changes that do not include the replacement of any of these proteins (antigenic drift). However,

Table 2	Indications for influenza vaccination (CDC, ACIP).
GROUPS WITH INCREASED RISK OF COMPLICATIONS	
Severe maturational delay	
Genetic syndromes and severe congenital malformations	
Chronic respiratory conditions such as asthma, fibrocystic disease, COPD, bronchiectasis, etc...	
Chronic heart diseases such as heart failure, etc...	
Chronic renal, hepatic, hematological or metabolic pathology	
Congenital or acquired immunosuppression (HIV, chemotherapy, or chronic corticosteroid (> 2mg Kg/day of prednisone or equivalent > 14 days), hematopoietic cell transplant, solid organ).	
Neuromuscular diseases that affect secretion management.	
Morbid obesity (>40 BMI)	
Residents in nursing homes or long-term care institutions.	
Advanced age	
GROUPS THAT MAY TRANSMIT INFLUEZA TO HIGH-RISK PEOPLE	
Health personnel	
Employees in nursing homes or long-term care facilities.	
Cohabitants of high-risk people,	

Modified from CDC [5]

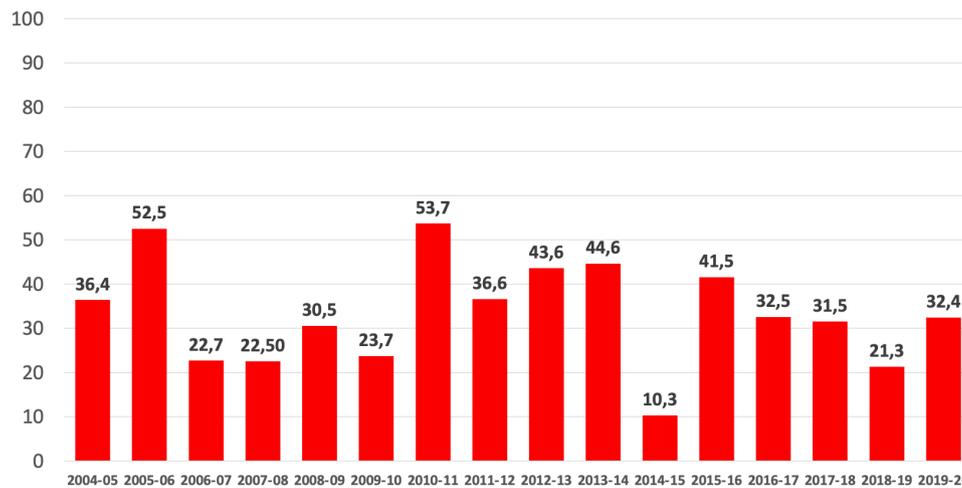


Figure 1 | Percentage of CAP due to pneumococcus according to the review of studies on the etiology of CAP published during the last century [7, 8].

er, only 3 types of antigenic structures have been recognized so far in the virus (H1N1, H2N2 and H3N2), the drift is much more frequent and justifies the annual changes in the composition of the vaccine.

The vaccine available annually is developed considering the probable type of virus for the next influenza season during the summer of each hemisphere (north or south). At present, the conventional vaccine is trivalent (2 A viruses, lately H3N2 and H1N1) and the rest for influenza B. Currently, the quadrivalent vaccine that incorporated a second type of B virus is in

use. Annual vaccination begins in the fall. There are inactivated vaccines with and without adjuvant for intramuscular or intradermal route, with double dose, and attenuated vaccine.

The indications of using this vaccine can change from country to country but in general they are similar throughout the world. Table 2 shows the indications according to the CDC [5].

The result of the vaccine is measured in 2 ways, the ideal is randomized clinical trials where the efficacy is measured in which one group receives the vaccine and the other the placebo; the other way is observational studies of effectiveness,

Table 3	Indications of anti-pneumococcal vaccination (CDC, ACIP).
GROUP WITH INCREASED RISK OF COMPLICATIONS	
Older than 65 years without comorbidities Under 65 with any of the following comorbidities: <ul style="list-style-type: none"> • CSF leak, cochlear implant Sickle cell anemia or other hemoglobinopathy Anatomic or functional asplenia Congenital immunosuppression or immunosuppression produced by an underlying disease such as HIV infection, chemotherapy or chronic corticosteroid treatment (> 2mg Kg/day of methylprednisone or its equivalent for > 14 days), hematopoietic cell transplant, solid organ transplant Chronic renal failure/nephrotic syndrome Leukemia or lymphoma Hodgkin's disease Widespread metastatic cancer Iatrogenic immunosuppression including radiotherapy Multiple myeloma Smoker	

Modified from [5] <https://www.cdc.gov/flu/prevent/whoshouldvax.htm>

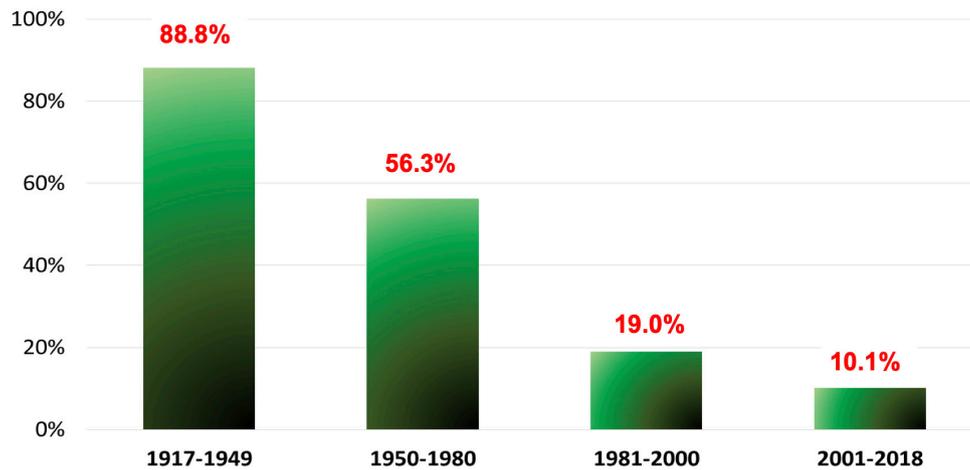


Figure 2 CDC estimate of influenza vaccine effectiveness for the 2004–05 through 2019–20 seasons. The 2020–21 season was not considered due to the low circulation of influenza observed during the pandemic. (Modified from: CDC seasonal Flu Vaccine Effectiveness Studies, 26 Aug, 2021 [6].

in which comparing the frequency with which vaccinated and unvaccinated get influenza or influenza-like illness. The results indicate that the vaccine has an impact on morbidity and mortality in immunized vs. non-immunized groups at risk. Such results are estimated annually by the CDC and if there is a low effectiveness in the observed result, this may be due to poor choice of target strain or to other reasons (Figure 1).

PNEUMOCOCCI

Streptococcus pneumoniae is the classic pathogen of CAP,

its importance as a pathogen has been significantly reduced during the last century due to the convergence of the appearance of antibiotics in the middle of the last century and the high rates of vaccination for about 10 years from the development of conjugate vaccines in infants throughout the world, and secondarily from the vaccination of the rest of the population, particularly those over 60 years of age and people with comorbidities (Figure 2).

S. pneumoniae is a common respiratory pathogen that frequently causes "non-invasive" respiratory disease (otitis, sinusitis, pharyngitis, bronchitis, and CAP) and less frequently

invasive disease (bacteremia, severe CAP, empyema, meningitis, endocarditis, etc). The latter produces severe clinical pictures that may require intensive care and develop serious complications, including higher mortality.

In 1977 a pneumococcal vaccine was licensed that protected against 14 serotypes, in 1983 it was expanded to protect against 23 serotypes. This is a polysaccharide vaccine called PPSV23. It remained in force for more than 20 years since with penicillin and later the appearance of other antibiotics, the morbidity and mortality of this disease fell significantly (Alexander Fleming, discoverer of penicillin at the time, was encouraged to predict that the pneumonia would be the first infectious disease eradicated from the planet). Unfortunately, the PPSV23 vaccine was shown to be effective in preventing invasive pneumococcal disease, but the same did not occur with respect to non-invasive disease, and it did not work in children under 2 years of age. In 2000, a 7-serotype conjugate vaccine (PCV7) was licensed for infants. It drastically reduced mortality from invasive disease, especially meningitis. In the past decade, the 10-valent and 13-valent conjugate vaccines were approved, which improved its coverage in children and, a few years later, demonstrated their efficacy in reducing the incidence of invasive and non-invasive disease in those over 65 years of age, and from there began to be used especially in the elderly and people with comorbidities.

Currently, the 13-valent conjugate vaccine has been incorporated into the adult vaccination schedule. Given that the latest conjugate vaccine available (13-valent) has a coverage that is sufficient to cover approximately 50% of circulating serotypes, the use of sequential schemes of both types of vaccine, PPSV23-valent and PCV13, is recommended in adults, in

a consistent manner to cover this situation. Table 3 shows the indications for the pneumococcal vaccine in adults.

The fact that PPSV23 is a polysaccharide vaccine has not shown with certainty its efficacy in preventing non-invasive forms of the disease [8]. Although different studies including a meta-analysis provided evidence that supports that PPSV23 would prevent invasive pneumococcal disease (IPD) in adults [9], non-invasive disease is not prevented by this vaccine, which is why the evidence is not clear regarding patients with chronic diseases. The vaccine is recommended in adults to prevent IPD [10].

In 2015, Bonten et al. published a double-blind, placebo-controlled, randomized study in which 84,496 subjects older than 65 years were randomly assigned to receive a single dose of PCV13 or placebo [11]. It was shown in the vaccinated subjects 45.6% fewer first episodes of CAP due to a serotype present in the vaccine compared to placebo ($p < 0.001$); 45.0% fewer episodes of non-bacteremic/non-invasive CAP due to a serotype present in the vaccine ($p = 0.007$) and 75.0% fewer first-episode IPD ($p < 0.001$). Throughout the world, national and continental scientific societies have developed guidelines for vaccination against pneumococcus for adults that contain both types of available vaccines. The Argentine Association of Respiratory Medicine designed a sequential scheme that is shown in figure 3 [12].

PERTUSSIS

Despite the existence of a vaccine to prevent it, whooping cough is a disease that is still present, mainly affecting young infants with high morbidity and mortality. But it also affects

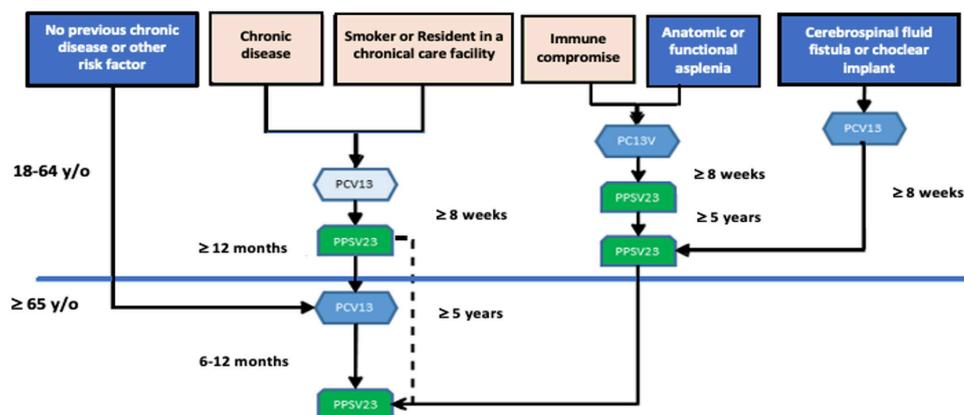


Figure 3 | Pneumococcal vaccination schedule in adults [11]

Includes immunodeficiencies (types T, B and Complement), HIV infection, chronic renal failure, nephrotic syndrome, leukemia, lymphoma, malignant disease, transplant, iatrogenic immunosuppression (includes radiotherapy and corticosteroids)
 Administering PCV13 to patients with chronic lung disease and/or smokers, older than 65 years, followed by the application of PPSV23 could provide better immunogenicity for vaccine serotypes in this age group.

adolescents and adults who have lost the effect of the initial vaccination; this second group has become the main reservoir and source of transmission of *Bordetella pertussis* to infants.

The new pertussis vaccines, formulated for this age group, have a good immunogenicity and safety profile and their efficacy reaches 92%. Currently, few countries have in their calendar the application of the acellular pertussis vaccine once in life in adults at the time of the application of the double bacterial vaccine (tetanus-diphtheria), replacing the latter in this case by the triple bacterial (tetanus-diphtheria-acellular pertussis).

The universal use of this vaccine could contribute to the control of whooping cough in the most susceptible groups. In those countries where this vaccine is not included in the schedule for adults, it is usually prescribed as an indication, at least in pregnant women between weeks 27 to 36 of their pregnancy and in health personnel, to reduce the potential contagion to infants [13].

SARS-COV-2

The appearance of the new coronavirus inaugurated a new era in vaccination against pneumonia-producing diseases. At the end of 2021, there are more than 10 widely distributed vaccines that have shown their efficacy and safety to control infection by the SARS-CoV-2 coronavirus, which have been developed in a very short time, so much so that they required urgent authorization for their use (Emergency Use Authorization, EUA), without having complied with the usual periods that regulatory agencies require for other vaccine developments. The platforms used have been messenger RNA: Moderna and Pfizer BioNTech; Viral vector (Adenovirus): AstraZeneca-Oxford, Janssen, Gamaleya and Cansino; Inactivated virus: Sinovac, Sinopharm Wuhan and Sinopharm Beijing.

Phase 3 randomized controlled clinical trials (RCCTs) reported an efficacy between 50 and 95% against symptomatic COVID-19, which enabled the use by the regulatory agencies (CDC, EMEA, etc) for vaccines that successfully passed phase 3 [14].

New studies may find differences in E with respect to RCCT (factors such as cold chain, interval between doses, circulating variants or incomplete vaccination).

Most of these vaccines were originally designed for 2 doses 3 to 12 weeks apart. The application of booster doses, initially to additional populations (e.g., children, pregnant women, the elderly, immunocompromised) and most likely extended to the rest of the population, became apparent after the appearance of new variants that began to show a loss of effectiveness, are approved based on their immunogenicity.

Further studies of efficacy will be necessary to confirm the inferences from the immunological data.

FUTURE DEVELOPMENTS

The future will be oriented in several objectives. About the

flu vaccine, for many years the need to develop a "Universal" vaccine has been raised that is not aware of the viral "shift" or "drift" that forces us to be aware of the evolution of the virus to develop vaccines annually that require revaccination [13]. Regarding pneumococcus, the appearance of conjugate vaccines capable of preventing the development of invasive and non-invasive pneumococcal disease markedly changed the mortality attributable to this bacterium. However, this remarkable effect partially reduced its potential impact due to the appearance of serotypes absent in the PCV13 vaccine. This obstacle will be quickly resolved by the development of new vaccines such as PCV20, already approved by the FDA in the United States, which will possibly eliminate the need for sequential schemes [15,16]. As pointed out in the introduction, there are many viruses that are responsible for CAP in adults, which have not yet been considered. However, researchers are developing vaccines for other viruses, such as metapneumovirus and respiratory syncytial virus, which, although not yet available, they have posed problems of great magnitude, surely as pathogens or co-pathogens they are collaborating in morbidity and mortality, particularly in those over 60 years of age and in those with comorbidities, and in the future, we will also see new developments appear in this field.

CONFLICTS OF INTEREST

The author declares no conflicts of interest

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