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INFECTIOUS DISEASE

Pneumococcal Vaccination of Adults in Italy: What Strategies?

ELVIRA MASSARO[1], GIOVANNI GABUTTI[2]
[1] ASL3 Healthcare System of the Liguria Region, Genoa, Italy;
[2] Italian Society of Hygiene, Preventive Medicine, and Public Health (SItI), Cogorno (Ge), Italy; Adult Immunization Board (AIB)

Keywords

Pneumococcal Vaccination • *Streptococcus pneumoniae* • Invasive Pneumococcal Disease • Epidemiological Surveillance

Summary

S. pneumoniae has been classified by the World Health Organization (WHO) as one of the 12 priority pathogens with the greatest global health impact. Although many individuals (approximately 20–30% of adults and nearly 40–50% of children) may carry the bacterium asymptomatically, certain groups are considered at higher risk of disease (non-invasive illnesses and invasive diseases). These include young children, the elderly and individuals who are immunocompromised or affected by pre-existing medical conditions.

Italian surveillance data show a significant increase in Invasive Pneumococcal Disease (IPD) incidence in 2023 in comparison with 2021 and 2022, rising from 0.84 cases per 100,000 population in 2021 to 3.02 in 2023. The highest rates were observed in children under 1 year of age [10.41/100,000 (2023)] and in adults aged 65 and over (7.45/100,000 in 2023 compared with 2.11 in 2021 and 4.49 in 2022).

Surveillance systems and epidemiological studies on the global distribution of the different pneumococcal serotypes associated with disease continue to be essential to determining which serotypes to include in new vaccines, in order to produce preparations capable of preventing an increasing number of cases, hospitalizations, sequelae and deaths.

A milestone in pneumococcal vaccination was the development of conjugate vaccines (PCVs), which started in the 2000s. The first PCV, which covered seven serotypes (PCV7: 4, 6B, 9V, 14, 18C, 19F, and 23F), was introduced in Italy in 2005 for the pediatric population. The introduction of this vaccination strategy leading to a significant reduction in disease among children and an overall decline in the pneumococcal disease burden across all age-groups. However, an increase in disease caused by serotypes not included in PCV7 was observed. This phenomenon, named serotype replacement, led to the development of higher-valency conjugate vaccines. In 2010, the 13-valent pneumococcal vaccine (PCV13) and 10-valent pneumococcal vaccine (PCV10) were approved. However, the phenomenon of serotype replacement continued to be observed, and consequently, the need for broader-spectrum vaccines remained a public health priority.

In 2021 and 2022 PCV15 (serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) and PCV20 (serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F) were authorized for immunization in individuals aged ≥18 years, respectively. In March 2025, the use of a new 21-valent pneumococcal vaccine was approved (serotypes: 3, 6A, 7F, 19A, 22F, 33F, 8, 10A, 11A, 12F, 9N, 17F, 20, 15A, 15C, 16F, 23A, 23B, 24F, 31 and 35B) and it included some serotypes particularly aggressive or emerging.

Maximizing the effectiveness of a vaccination program in combating diseases related to S. pneumoniae is based on the integration of three key elements: epidemiological need, immunological need and vaccine compliance.

From an epidemiological perspective, the 2023 specific data analysis reveals that, out of 1,783 cases, 734 involved individuals over the age of 64 (41.2%). The estimated global coverage with the PCV20 vaccine would be 63.6%, while with the PCV21 vaccine it would be 76.4%. The specific analysis of the most recent available data (1st half of 2024) reveals that a total of 1,152 cases were reported, 58.4% of which occurred in individuals over 64. If only the data referring to subjects over the age of 64 are analyzed, the estimated coverage becomes 72.1% for PCV20 and 79.2% for PCV21.

From an immunological standpoint, the vaccine of choice should induce an immune response that is at least non-inferior to the comparator, and ideally, more robust and long-lasting.

Regarding compliance, all possible strategies must be activated in order to raise public awareness of the risks of pneumococcal disease and the benefits of vaccination, so as to increase coverage rates.

A thorough analysis of epidemiological and clinical data, combined with an assessment of the economic and social impact, is crucial to guiding vaccination policies and supporting efficient decision-making in order to protect the health of the entire population.

Introduction

Streptococcus pneumoniae (*S. pneumoniae*), a Gram-positive bacterium, causes a wide spectrum of diseases, ranging from non-invasive illnesses such as bronchitis, non-bacteremic pneumonia, sinusitis and otitis media, to invasive diseases, including bacteremia, septicemia, osteomyelitis, pneumonia and meningitis [1].

S. pneumoniae is able to colonize the nasopharynx, resulting in a carrier state, which involves approximately 20–30% of adults and nearly 40-50% of children [2].

Among its essential structural components, phosphorylcholine – part of the bacterial cell wall – plays a key role in the colonization of the upper respiratory tract, owing to its ability to bind specific receptors on human epithelial cells [3, 4].

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Under normal conditions, colonization does not progress to clinically apparent disease. Progression to invasive disease requires the local activation of proinflammatory mediators, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF) [5]. This inflammatory response induces both quantitative and qualitative changes in the receptors present on epithelial and endothelial cells. Choline in the bacterial cell wall has a high affinity for the platelet-activating factor receptor, whose expression is increased during inflammation [6]. Interaction with this receptor facilitates bacterial internalization and promotes transcellular passage across epithelial and vascular barriers, allowing *S. pneumoniae* to invade deeper tissues [7].

Another key factor in the pathogenesis of pneumococcal disease is pneumolysin, a cytotoxin capable of forming pores in eukaryotic cell membranes and interfering with complement activation, thereby contributing to immune evasion and tissue damage [6, 7].

Although many individuals may carry the bacterium asymptomatically, certain groups are considered at higher risk of disease. These include young children, the elderly and individuals who are immunocompromised or affected by pre-existing medical conditions. Among these, diabetes mellitus, chronic lung disease, liver disease, chronic kidney disease and sickle cell anemia are major risk factors. Recent studies have also identified additional predisposing conditions, such as sarcoidosis, inflammatory polyarthropathies, systemic connective tissue diseases and various neurological disorders, highlighting the complexity of individual susceptibility profiles [8]. Furthermore, concurrent viral infections can predispose individuals to invasive pneumococcal disease [9]. Other contextual and behavioral factors – such as the winter season, tobacco smoking and chronic alcohol consumption – also constitute risk factors for the development of invasive pneumococcal disease [8].

To date, the polysaccharide capsule surrounding the cell wall is widely recognized as the main virulence factor of *S. pneumoniae*. The structural composition of the capsule enables the bacterium to evade opsonization and phagocytosis [10]. Analysis of the capsule's polysaccharides has led to the identification of over 100 different *S. pneumoniae* serotypes. However, it is important to note that only a subset of these serotypes is responsible for the majority of invasive clinical cases [11]. Disease-causing serotypes differ not only in their structural characteristics but also in their associated disease severity, lethality, invasiveness, antibiotic susceptibility and distribution across age-groups and geographic regions [12, 13].

The Burden of *Streptococcus pneumoniae* Disease in Adults: A Major Public Health Concern

Despite significant progress in diagnostic and therapeutic pathways, infections caused by *S. pneumoniae* remain associated with high morbidity and mortality rates, particularly among vulnerable populations such as children, the elderly and individuals with compromised immune systems [14]. Indeed, *S. pneumoniae* has been classified by the World Health Organization (WHO) as one of the 12 priority pathogens with the greatest global health impact [3].

In 2021, *S. pneumoniae* was responsible for the majority of lower respiratory tract infection (LRTI)-related cases and deaths (excluding SARS-CoV-2), with an estimated 97 million cases and 505,000 deaths globally. Of these, the largest number occurred in children under the age of 5 years, and in adults over 70 years old [15, 16].

According to data from the European Centre for Disease Prevention and Control (ECDC), in 2022 the incidence rate of invasive pneumococcal disease (IPD) in Europe was 5.11 cases per 100,000 population, with the highest rates being observed in individuals over 64 years of age and in children under 4 years (13.42 and 12.49 cases per 100,000 population, respectively). Clinically, the most common presentations were bacteremic pneumonia (41.2%) and septicemia (37.7%), followed by meningitis (13.8%). Overall case fatality rates were 17.1% among those over 65 and 10.9% among individuals aged 45–64 [17].

Italian surveillance data show a significant increase in IPD incidence in 2023 in comparison with 2021 and 2022, rising from 0.84 cases per 100,000 population in 2021 (500 cases) to 3.02 in 2023 (1,783 cases). The highest rates were observed in children under 1 year of age [10.41/100,000 (2023), exceeding the pre-pandemic value of 6.50 in 2019] and in adults aged 65 and over (7.45/100,000 in 2023 compared with 2.11 in 2021 and 4.49 in 2022). This increase was probably attributable, at least in part, to improved diagnostic techniques and growing awareness of IPD in Public Health Surveillance. Most notifications occurred during the winter months, confirming the established seasonal pattern. The most frequently reported clinical manifestations were sepsis and bacteremia (37–55% of cases), followed by pneumonia associated with sepsis/bacteremia (25-36%) and meningitis, with or without sepsis/bacteremia (18-25%) [15]. The interim report for the first six months of 2024 cited a total of 1,152 IPD cases, 673 of which occurred in individuals over 64 years of age [18].

S. pneumoniae infections, especially in the elderly, are often responsible for a large number of community-acquired pneumonia (CAP) cases, making them the leading cause of hospital admissions among individuals aged > 65 years – approximately 2,000 admissions per 100,000 per year in the developed countries [19]. Moreover, beyond the disease burden directly caused by the infection, pneumococcal CAP in the elderly is frequently complicated by cardiovascular events, which further increase its clinical, economic and social impact [14, 20, 21].

In high-income countries, *S. pneumoniae* remains responsible for up to 50% of CAP cases, with in-hospital mortality reaching as high as 40% among older adults [22].

In Italy, CAP has a significant clinical and economic impact, with a hospitalization rate of 31.8% among adults, and *S. pneumoniae* remains the main etiological agent [23]. A large study conducted in four Italian regions between 2017 and 2020 found that, among 1,155 individuals aged ≥ 65 years hospitalized for CAP, 13.1% had an infection caused by *S. pneumoniae*. The most frequently detected serotypes were: 3 (2.0%), 8 (1.7%), 22F (0.8%), 11A (0.7%) and 9N (0.6%). Moreover, the study showed that highly invasive serotypes (1, 5, 7F and 8) accounted for 2.1% of cases. Serotypes included in the conjugate vaccines PCV15 and PCV20 were present in 4.4% and 7.5%, respectively, of CAP cases [24].

Serotype 3 plays a significant role in clinical manifestations and is associated with more severe disease [22, 25]. In recent years, this serotype has become one of the most commonly identified causes of interstitial lung disease in most Western countries [24, 26]. Its increased circulation is probably due to several factors: the current conjugate pneumococcal vaccines (PCVs) for adults appear to have limited efficacy against this serotype, whose polysaccharide capsule is thicker and lacks a covalent bond to the peptidoglycan layer. This characteristic renders the capsule more resistant to immune attack, as it reduces opsonophagocytic killing, thereby facilitating persistence and transmission.

Surveillance Systems: The Importance of Continuous Monitoring

Communicable diseases continue to constitute a public health priority, owing to their significant clinical, economic and epidemiological impact. In this context, epidemiological and laboratory surveillance plays a central role, as it allows the systematic and integrated collection of essential data that can guide public health decision-making, support efforts to combat respiratory infections and aid the development of new vaccines. It also plays a key role in both global and local health security. By definition, infectious disease surveillance involves the continuous and systematic collection of information regarding the distribution of diseases and associated risk factors, as well as the analysis of temporal, spatial and demographic trends, with the aim of informing effective prevention and control measures [27].

Recently, the World Health Organization (WHO), through the publication of the *Global Strategy on Comprehensive Vaccine-Preventable Disease Surveillance (2021–2030)*, has emphasized the need to develop more comprehensive and integrated national and regional surveillance systems capable of monitoring the full spectrum of the infectious diseases that are most relevant in various geographical contexts. This integrated approach not only supports efforts to achieve the elimination and eradication goals set out in the *Immunization Agenda 2030*, but also constitutes an essential tool for strengthening vaccination programs [28].

In the United States, following the release of the report *Addressing Emerging Infectious Disease Threats: A Prevention Strategy for the United States* [29], the Emerging Infections Program (EIP) was established a network of state health departments coordinated by the Centers for Disease Control and Prevention (CDC). The aim of this network is to detect emerging pathogens, conduct research based on laboratory and epidemiological data, and implement projects supporting public health protection and prevention efforts [30].

In 1995, the Active Bacterial Core Surveillance (ABCs) system was launched – a surveillance network created under the CDC's EIP to monitor and estimate the burden of invasive bacterial infections of public health relevance [31]. Initially composed of four sites (California, Connecticut, Oregon and Minnesota), the ABCs network expanded in 2003 to include Georgia, Maryland, New York, Tennessee, Colorado and New Mexico, thus comprising a total of 10 sites. The network ensures case monitoring through the systematic verification of clinical and laboratory data in collaboration with the CDC, state health departments and universities [32].

The need to establish an active surveillance network arose alongside the development of the 13-valent PCV, as it was crucial to have a system capable of determining baseline IPD rates, monitoring circulating serotypes and assessing vaccine effectiveness. Indeed, evidence gathered through the ABCs network revealed a significant reduction in IPD incidence in children, due to the introduction of the 7-valent PCV (PCV7), as well as in adults, due to herd protection. However, it also showed an increase in cases caused by *S. pneumoniae* serotypes not included in the commercial vaccines [31].

In Europe, the first *S. pneumoniae* surveillance systems date back to the 1990s, when the growing availability of vaccines – initially polysaccharide-based and later conjugate vaccines – highlighted the need for standardized data on disease incidence and serotype distribution, in order to measure vaccine impact and guide immunization strategies. With the introduction of the PCV7 conjugate vaccine, several European countries established dedicated surveillance systems or strengthened existing ones.

The ECDC implemented the TESSy surveillance, which was designed for the collection, analysis and sharing of epidemiological data across the European Union and the European Economic Area. This system integrates demographic, clinical and laboratory data, enabling time-trend analyses of cases and comparisons between member states, with the aims of monitoring incidence, evaluating the impact of vaccination programs, identifying emerging trends and supporting evidence-based policy decisions.

In Italy, a surveillance system for Invasive Bacterial Diseases (MIB), coordinated by the Istituto Superiore di Sanità (ISS), has been in place since 2007. The aim of this surveillance is to monitor the temporal and spatial trends of these diseases, describe the frequency of cases

by pathogen (*Neisseria meningitidis*, *S. pneumoniae* and *Haemophilus influenzae*) and serotype, and estimate the proportion of cases preventable through vaccination, in order to improve prevention and control strategies [15].

Pneumococcal Vaccines: Epidemiological Evolution, Serotype Variation and New Opportunities

Surveillance systems and epidemiological studies on the global distribution of the different pneumococcal serotypes associated with disease continue to be essential to determining which serotypes to include in new vaccines, in order to produce preparations capable of preventing an increasing number of cases, hospitalizations, sequelae and deaths [33].

The development of the first generation of pneumococcal polysaccharide vaccines using purified capsular polysaccharides dates back to the 1950s. The non-conjugate polysaccharide vaccines elicit a short-lived immune response, with a significant decline in immunity 6–24 months after vaccination. Indeed, these vaccines primarily induce a B cell-mediated immune response without involving T cells [34-36].

The first second-generation pneumococcal polysaccharide vaccine was the 14-valent PPSV14, licensed in the United States in 1977. It was later superseded by PPSV23, which contains the serotypes most commonly associated with invasive pneumococcal disease (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F) [35]. PPSV23 is indicated for active immunization from 2 years of age, is administered in a single dose and is used sequentially after a conjugate vaccine, with revaccination being possible after five years [37].

A milestone in pneumococcal vaccination was the development of conjugate vaccines (PCVs), which started in the 2000s. These vaccines are based on mechanisms similar to those of conjugated Hib vaccines, which used carrier proteins such as diphtheria toxoid (PRP-D), meningococcal outer membrane protein (PRP-OMP) and tetanus toxoid (PRP-T) [34]. The covalent conjugation of capsular polysaccharides with a carrier protein has been shown to elicit a T cell-dependent adaptive immune response and induce B memory cells, resulting in immunological memory. This antigenic shift renders these vaccines much more immunogenic in both adults and infants [38, 39].

The first PCV, which covered seven serotypes (PCV7: 4, 6B, 9V, 14, 18C, 19F, and 23F), was introduced in the United States in 2000 and in Europe in 2001. In Italy, vaccination with PCV7 was included in the National Immunization Prevention Plan (PNPV) in 2005 for the pediatric population [40].

The introduction of pediatric vaccination with PCV7 effectively generated long-lasting immunity in vaccinated infants and reduced nasopharyngeal carriage of the seven most virulent *S. pneumoniae* serotypes – leading to a significant reduction in disease among children and an overall decline in the pneumococcal disease burden across all age-groups [39, 41, 42].

In parallel with the reduction in IPD cases caused by vaccine-targeted serotypes, however, an increase in disease caused by serotypes not included in PCV7 was observed [43]. This phenomenon, named serotype replacement, *i.e.* a relative increase in cases of disease due to serotypes not included in the commercially available vaccine, led to the development of higher-valency conjugate vaccines. In 2010, the 13-valent pneumococcal conjugate vaccine (PCV13) was approved. In addition to the serotypes in PCV7, it covers serotypes 1, 3, 5, 6A, 7F and 19A. Initially indicated only for children, it was later approved for adults over 50 years of age [44]. Around the same time, a 10-valent conjugate vaccine was also approved for the pediatric population [45].

In high-income countries, the introduction of PCV10 and PCV13 conjugate vaccines has led to two significant trends: on one hand, a considerable decrease in invasive and non-invasive disease caused by vaccine-included serotypes; on the other, the phenomenon of serotype replacement [35]. This epidemiological phenomenon has generated the need to develop conjugate vaccines that contain an ever-greater number of serotypes, in order to broaden protection against pneumococcal disease.

In 2021, the European Medicines Agency (EMA) authorized PCV15, a conjugated and adsorbed polysaccharide vaccine containing the serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F. Initially used for the active immunization of adults aged ≥18 years, in October 2022 it was also authorized for use in individuals from six weeks of age. For those over 18 years, a single dose is administered, and it is important to note that the product's Summary of Product Characteristics (SmPC) indicates co-administration with the seasonal quadrivalent (inactivated, split virion) influenza vaccine, thus providing an important contribution to vaccination strategies [46].

In February 2022, in Europe (in May 2022 in Italy), the 20-valent conjugated adsorbed vaccine (serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F) was authorized for immunization in individuals aged ≥18 years. Later, PCV20 also obtained authorization for pediatric use (March 2024) according to a 3 + 1 schedule. In adults and the elderly, PCV20 may be co-administered with the seasonal influenza vaccine [47].

The systematic review by Teixeira et al. examined 118 studies published between 2010 and 2022 in 33 European countries, and showed that the serotypes covered only by PCV20 (8, 10A, 11A, 12F, 15B, 22F and 33F) have become increasingly prevalent among adults since the introduction of PCV13, causing both invasive and non-invasive pneumococcal disease [12].

A recent cost-effectiveness study used a Markov model to evaluate the implementation of PCV20 in the Italian adult vaccination strategy. Assuming vaccination of 100% of cohorts aged 65 to 74 years, immunization with PCV20, in comparison with PCV13, proved to

be dominant (lower cost and a better health outcome), yielding an estimated reduction of 1,208 deaths; 1,171 cases of bacteremia (excluding meningitis); 227 cases of meningitis; 9,845 hospitalized cases of non-bacteremic pneumonia, and 21,058 non-hospitalized cases; the total gain was of 6,581.6 life-years and 4,734.0 QALYs (Quality Adjusted Life Year). Comparison with PCV15 showed an ICER (Incremental Cost-Effectiveness Ratio) of €66 per life-year gained and €91 per QALY. The authors concluded that vaccination of the elderly population with PCV20 was a sustainable and efficient investment [48].

In March 2025, in Europe and subsequently in Italy (May 2025), the use of a new 21-valent pneumococcal conjugate polysaccharide vaccine, conjugated to the CRM197 carrier protein, was approved [49]. The vaccine protects against 21 serotypes (3, 6A, 7F, 19A, 22F, 33F, 8, 10A, 11A, 12F, 9N, 17F, 20, 15A, 15C, 16F, 23A, 23B, 24F, 31 and 35B), some of which are particularly aggressive or emerging. Administered in a single dose, it is indicated for active immunization against invasive disease and pulmonary infection caused by *S. pneumoniae* in individuals aged 18 years or older.

Clinical trials conducted in adults have evaluated its effectiveness against invasive pneumococcal disease and pulmonary infection, as well as its immunogenicity. The double-blind, randomized STRIDE 3 trial included pneumococcal vaccine-naïve adults aged 18 years and older, with or without stable chronic medical conditions [50]. Participants were divided into two cohorts: the first included individuals aged 50 and older, who were randomized 1:1 to receive either PCV21 or PCV20. The second cohort comprised participants aged 18 to 49 years, randomized 2:1.

Serotype-specific opsonophagocytic activity (OPA) and IgG responses were measured on Day 1 and Day 30 post-vaccination. PCV21 displayed non-inferior OPA levels in comparison with PCV20 for the ten shared serotypes and met superiority criteria for 10 of the 11 serotypes included only in PCV21 (with the exception of serotype 15C). Although superiority was not reached for 15C, robust immune responses were observed. Additionally, PCV21 elicited a cross-reactive immune response to serotype 15B, probably due to structural similarity between 15B and 15C. PCV21 was generally well tolerated, with a safety profile similar to PCV20, and showed a greater response toward serotypes 3 and 8. Furthermore, the most commonly reported adverse events were mild and short-lasting (less than 3 days) pain at the injection site and headache [50].

In another Phase III randomized controlled trial (STRIDE-6), the safety, tolerability and immunogenicity of the PCV21 were evaluated in adults aged 50 years and older. The study included 717 previously vaccinated adults, who were divided into three cohorts on the basis of their prior vaccination history:

- Cohort 1: individuals previously vaccinated with PPSV23, randomized 2:1 to receive PCV21 or PCV15.
- Cohort 2: individuals previously vaccinated with PCV13, randomized 2:1 to receive PCV21 or PPSV23.
- Cohort 3: individuals with mixed vaccination history received open-label PCV21.

Immunogenicity was assessed 30 days post-vaccination in terms of geometric mean titers (GMTs) of OPA and geometric mean concentrations (GMCs) of IgG for all serotypes included in V116. Safety was monitored by recording the proportion of participants reporting adverse events.

PCV21 was found to be immunogenic against all 21 serotypes included, with immune responses generally comparable to those elicited by the other vaccines used in the study. Thirty days after vaccination, OPA GMTs against shared serotypes were generally similar between PCV21 and PCV15 (Cohort 1), and between PCV15 and PPSV23 (Cohort 2). The most frequently reported adverse events were injection site pain and fatigue, usually mild to moderate in intensity and lasting no longer than 3 days [51].

It is also noteworthy that PCV21 includes emerging and hard-to-control serotypes, including 9N, 15C, 16F, 17F, 20A, 23A, 23B, 24F, 31 and 35B. Notably, serotype 15C is capable of eliciting a cross-reactive immune response against the deOAc15B polysaccharide, owing to structural similarity, thereby providing protection against serotype 15B.

Table I provides a summary of the evolution of pneumococcal vaccines.

Figure 1 illustrates the evolution of third-generation pneumococcal vaccines.

Pneumococcal Vaccination of Adults in Italy: Where Do We Stand?

Recent demographic projections for Italy indicate an ongoing transition marked by progressive population aging. Indeed, it is estimated that, by 2050, individuals aged 65 and over will constitute 34.6% of the total population, compared with the current 24.3% [52]. In this context, it is clear that Public Health must pay particular attention to this population group, in order to implement vaccination programs capable of reducing the disease burden due to preventable infectious illnesses.

With regard to invasive pneumococcal disease (IPD) in Italy, among adults over the age of 64, the incidence increased in 2023, reaching 7.45 cases per 100,000 inhabitants, compared with 2.11 in 2021 and 4.49 in 2022 [15].

Pneumococcal vaccination with conjugate vaccines for adults and the elderly began to be offered in 2015 in certain Italian Regions, with a gradual rollout. The 2017-2019 PNPV recommended free pneumococcal vaccination for all individuals aged ≥65 years; this consisted of the administration of PCV13, followed, after at least two months, by a dose of 23-valent polysaccharide vaccine (PPSV23) in a sequential schedule. Vaccination was also recommended for all individuals at higher risk of severe pneumococcal infections and complications due to

Tab. I. Pneumococcal vaccines: the evolution.

FIRST GENERATION
1911: whole-cell vaccine
1930: vaccine serotypes combined with live attenuated bacteria
Mid-1930s: multivalent vaccines containing partially purified capsular material
Late 1940s: multivalent polysaccharide vaccines
Early 1950s: first generation of pneumococcal polysaccharide vaccines introduced into the market
SECOND GENERATION
Unconjugated polysaccharide vaccines
1977: 14-valent vaccine approved in the USA
1983: 23-valent vaccine (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 11F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F) approved in the USA
Conjugated polysaccharide vaccines
2000: 7-valent vaccine (PCV-7) (4, 6B, 9V, 14, 18C, 19F, 23F) approved in the USA and shortly afterwards in Europe (2001)
THIRD GENERATION
Conjugated polysaccharide vaccines with expanded antigenic coverage
2009-2010: approval of the 10-valent vaccine (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F) and the 13-valent vaccine (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F)
December 2021 (European approval) - March 2021 (Italian approval): 15-valent vaccine (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) approved for adults ≥ 18 years.
February 2022 (European approval) - May 2022 (Italian approval): 20-valent vaccine for individuals ≥18 years.
March 2025 (European approval) - May 2025 (Italian approval): 21-valent vaccine (3, 6A, 7F, 19A, 22F, 33F, 8, 10A, 11A, 12F, 9N, 17F, 20, 15A, 15C, 16F, 23A, 23B, 24F, 31 and 35B) approved for individuals aged ≥ 18 years.

Fig. 1. Evolution of third-generation pneumococcal vaccine.

* For PCV21, a cross-reactive immune response was observed *versus* serotype 15B; this was elicited by serotype 15C, which is structurally similar to serotype 15B.

specific clinical conditions or chronic comorbidities [53]. The 2023–2025 PNPV reinforces previous recommendations, reaffirming the need to ensure free pneumococcal vaccination for the cohort of 65-year-olds and for frail patients of any age [54]. It should be noted that the right to free vaccination is maintained for life.

Regarding at-risk adults and older individuals, vaccination with a single dose of PCV is recommended starting from the cohort of 65-year-olds. The offer should eventually be supplemented with a sequential vaccination schedule (PCV/PPSV) depending on the type of PCV used.

For these categories, a minimum coverage target of 75% and an optimal target of 95% has been established, in line with the standards already defined for other adult vaccinations. The stated objective is to harmonize vaccination uptake across the country, reduce regional inequalities and ensure adequate protection for the most vulnerable segments of the population [54].

A cross-sectional study conducted as part of the OBVIOUS project and published in 2024 analyzed pneumococcal vaccination coverage in Italy and the barriers limiting uptake. Conducted in 2022 on a representative sample of adults, the survey revealed that coverage among high-risk adults remained unsatisfactory: only 39.5% of eligible individuals had been vaccinated, with even lower rates among those aged ≥65 years (33.7%). Slightly higher rates were recorded among patients with chronic conditions such as diabetes, cardiovascular or respiratory diseases, but coverage still fell well below the ≥75% target set by the national program [55].

Another retrospective study, published in 2024 and conducted in the Province of Viterbo (Lazio Region, Italy), investigated the rate of completion of the sequential pneumococcal vaccination schedule among 65-year-olds. Coverage was extremely low, with only 2.32% of individuals completing the schedule within two years of turning 65, reaching a peak of just 3.27% in 2020 [56].

Finally, a study conducted during the 2023–2024 vaccination season at the geriatric outpatient clinic of the University of Palermo involved 76 frail elderly patients, who were primarily affected by cognitive or endocrine disorders such as diabetes and osteoporosis. The aim was to assess the feasibility and impact of a proactive

vaccination strategy by directly offering influenza and pneumococcal vaccines at the clinic. Vaccination coverage proved encouraging: 46.05% of patients received only the pneumococcal vaccine, 28.95% received both vaccines (influenza + pneumococcus), and 25% received only the influenza vaccine [57].
However, it is important to note that the available data on pneumococcal vaccination coverage in adults and the elderly come only from local or regional studies, making it difficult to assess whether the coverage targets set by the PNPV and the Essential Levels of Care (LEA) have been achieved.

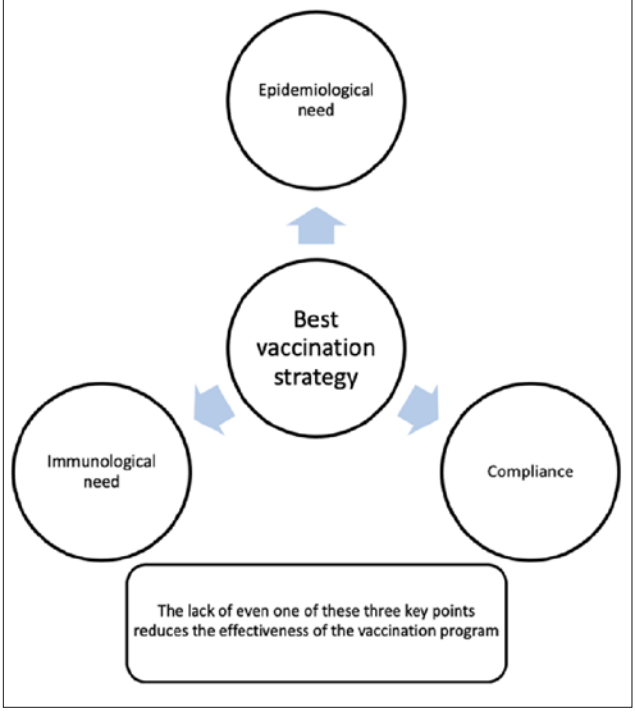
Key Elements for Choosing the Best Vaccination Strategy

Maximizing the effectiveness of a vaccination program in combating diseases related to *S. pneumoniae* is based on the integration of three key elements (Fig. 2):
- Epidemiological need;
- Immunological need;
- Vaccine compliance.

Epidemiological Need

The concept of epidemiological need is fundamental to defining vaccination strategies, as it is linked to ensuring that a vaccine effectively addresses the needs of a given population at a specific point in time, taking into account continuously evolving demographic characteristics. In the case of pneumococcus, the high antigenic variability (over 100 serotypes identified), the dynamics of serotype replacement induced by the selective pressures of conjugate vaccines, and the heterogeneity of the population groups affected require continuous surveillance and regular updating of preventive strategies [11-13, 58]. Over the years, serotype replacement has profoundly changed the epidemiology of IPD and CAP, particularly in the adult and elderly populations [58].
In the United States, after the introduction of PCV13, the incidence of IPD cases caused by vaccine serotypes in adults sharply decreased, displaying a 70% reduction in those aged ≥65 years. However, since 2014, no further reductions have been recorded, and during the 2018–2020 period, serotypes covered by PCV20 and PCV21 accounted for 54% and 85% of IPD cases in the elderly, respectively. In Canada, the most prevalent serotype among individuals aged ≥65 years in 2022 was serotype 3 (13.3%), followed by 22F (9.9%) and 9N (6.7%), with PCV20 coverage at 58.5% [59].
According to data from the ECDC, in 2022, cases due to serotypes not included in PCV13 showed higher incidence rates in individuals aged >64 years and children under 4 years old than in other population groups, with rates of 4.32 and 4.66 per 100,000 inhabitants, respectively [17]. In recent years, European epidemiological surveillance has revealed that certain serotypes continue to play a predominant role in causing invasive disease and CAP [12]. In particular, serotype 3 remains one of the main causes of IPD and CAP in adults and the elderly [60].
Data from various European and North American contexts report a considerable portion of cases caused by serotype 3 (between 12% and 19%) in subjects aged over 50 [12]. A systematic review analyzed data from primary studies conducted between 1984 and 2020 in order to gather information on the distribution of serotypes involved in pneumococcal pneumonia in adults and the elderly, while also considering the vaccination strategies in place during the studies. In all the publications, serotype 3 was the most common (11.9% of total isolates), with a growing percentage with increasing age (18.9% in those over 50). The authors reported that the prevalence of serotype 3 remained high even after the introduction of PCV10/PCV13 vaccination [60].
The persistence of this serotype, even though it was included in earlier-generation conjugate vaccines (PCV13), may be explained by its particular ability to evade the antibody response, a feature which contributes to its greater invasiveness and clinical severity, with significantly higher fatality rates than those of other serotypes [61].
At the same time, serotypes 22F and 33F have shown increasing epidemiological importance, emerging as frequent causes of invasive disease in adults. Indeed, a 2023 systematic review documented that serotype 22F accounted for approximately 6-7% of IPD cases not covered by PCV13 in adults, ranking among the most common serotypes alongside 8, 12F and 19A [62]. These findings are consistent with observations from European surveillance systems, which confirm the rising incidence

Fig. 2. Key elements for choosing the best vaccination strategy.



Tab. II. Serotypes identified in cases of invasive pneumococcal disease reported to the Italian MIB surveillance system that are common to both PCV20 and PCV21 vaccines [15, 18].

Serotype	2021	2022	2023	2024 (1st semester)	Total
3	41	171	336	183	731
6A	1	3	3	4	11
7F	2	5	8	7	22
8	52	137	191	118	498
10A	9	18	31	13	71
11A	8	18	29	13	68
12F	3	1	10	16	30
15B*	5	6	14	14	39
19A	11	43	57	42	153
22F	5	13	51	74	143
33F	0	4	9	9	22
Total	137	419	739	493	**1788**

* Serotype included in PCV20. For PCV21, a cross-reactive immune response was observed; this was elicited by serotype 15C, which is structurally similar to serotype 15B.

Tab. III. Serotypes identified in cases of invasive pneumococcal disease reported to the Italian MIB surveillance system that are exclusive to PCV20 [15, 18].

Serotype	2021	2022	2023	2024 (1st semester)	Total
1	4	2	8	7	21
4	2	2	8	6	18
5	1	1	1	0	3
6B	1	4	3	0	8
9V	1	1	3	1	6
14	5	15	17	22	59
18C	0	0	2	3	5
19F	7	21	34	18	80
23F	0	2	6	7	15
Total	21	48	82	64	**215**

Tab. IV. Serotypes identified in cases of invasive pneumococcal disease reported to the Italian MIB surveillance system that are exclusive to PCV21 [15, 18].

Serotypes	2021	2022	2023	2024 (1st semester)	Total
9N	7	21	42	19	89
15A	8	13	30	9	60
15C	1	1	11	16	19
16F	2	3	3	5	13
17F	1	6	8	1	16
20	5	4	9	9	27
23A	13	22	30	31	96
23B	7	24	29	15	75
24F	1	10	22	6	39
31	2	8	13	19	42
35B	0	3	11	3	17
Total	47	115	208	123	**493**

of 22F and, to a lesser extent, 33F as causal agents of IPD in individuals aged ≥65 years [62].

In Italy, the ISS reported that in 2023, 58% of IPD cases were covered by PCV20, compared with only 40% covered by PCV13. Among subjects aged ≥65, serotype 8 was the most frequent (15% of isolates), followed by 3, 22F and 33F. This indicates a mismatch between the vaccine used and the actual burden of disease [15].

An analysis of the data from the Surveillance System for Invasive Bacterial Diseases for the period 2021–2024 (first half) reveals the most frequently detected serotypes and allows us to compare them with recent conjugate vaccine formulations currently available for the adult/elderly population (PCV20 and PCV21).

Table II lists the *S. pneumoniae* serotypes detected by invasive bacterial disease surveillance in Italy during 2021–2024 (first half) [15, 18] that are common to both PCV20 and PCV21 vaccines.

As shown in Table II, a significant proportion of cases could potentially be prevented through the use of one of the latest-generation vaccines.

Surveillance data from 2021–2024 (first half) prompt further considerations.

Tables III and IV report the cases that could potentially be prevented by the exclusive use of PCV20 and PCV21, respectively.

As shown in Table IV, the new PCV21 vaccine has been specifically developed to include emerging serotypes of significant epidemiological and clinical relevance.

The 2023 specific analysis reveals that, out of 1,783 cases, 734 involved individuals over the age of 64 (41.2%). The estimated coverage with the PCV20 vaccine would be 63.6%, while with the PCV21 vaccine it would be 76.4%.

The specific analysis of the most recent available data on invasive disease cases (1st half of 2024) reveals that a total of 1,152 cases were reported, 58.4% of which occurred in individuals over 64. If only the data referring to subjects over the age of 64 are analyzed, the estimated coverage becomes 68.1% for PCV20 and 78.7% for PCV21.

The epidemiological need is conditioned not only by the age of the population but also by its vulnerability. Patients with immunodeficiencies, asplenia, HIV, or those who have undergone solid organ or hematopoietic transplants have a risk of invasive pneumococcal disease (IPD) that is 5 to 20 times higher than that of the general population [63]. Indeed, 30-day mortality in cases of pneumococcal bacteremia among immunocompromised patients can exceed 25%, as opposed to 10–15% in the general population [64]. The 2023-2025 National Immunization Plan (PNPV) therefore explicitly includes vulnerable individuals among the priority groups for vaccination, regardless of age, setting a minimum coverage target of 75% [54]. This measure addresses a clear epidemiological need to protect the groups at highest risk, in whom the expected benefit is greatest in terms of reducing hospitalizations and mortality. In summary, the persistence of serotype 3 and the emergence of new serotypes highlight the importance of ongoing epidemiological surveillance and the continuous updating of vaccination strategies. The inclusion of emerging serotypes in next-generation vaccines is a crucial step in further reducing the burden of pneumococcal disease among adults and the elderly

– populations that are particularly vulnerable to this disease and its complications.

Immunological Need

Immunogenicity constitutes the second pillar underpinning efforts to achieve "better protection". The vaccine of choice must induce an antibody response that is at least non-inferior to that of the reference comparator, thereby ensuring a comparable or superior efficacy profile across the age-groups and risk categories targeted by the vaccination program.

PCVs (pneumococcal conjugate vaccines) were developed to overcome the limitations of purified capsular polysaccharides, which elicit a T-cell–independent immune response that is poorly effective in young children and incapable of generating immunological memory [65]. The addition of a protein carrier (*e.g.,* CRM197, a non-toxic mutant of diphtheria toxin) converts the polysaccharide antigen into a T-cell–dependent immunogen that is capable of stimulating helper T cells, generating memory B cells and ensuring a stronger anamnestic response. This mechanism enhances long-lasting protection and reduces nasopharyngeal carriage, leading to herd immunity [66].

The introduction of PCV13 in children, and later also in the adult/elderly population, marked a turning point. However, as cases of IPD caused by vaccine-included serotypes declined, an increase in disease caused by non-vaccine serotypes was observed.

Another phenomenon emerged during the PCV13 vaccination campaigns; protection against serotype 3 proved to be suboptimal, with immunity waning over time. Several studies have documented lower antibody titers and lesser clinical effectiveness against this serotype, which remains a leading cause of CAP and invasive pneumococcal disease (IPD) in adults [24]. These findings have highlighted two critical aspects of immunogenicity; it must be evaluated not only in quantitative terms (antibody titers), but also in qualitative terms (opsonophagocytic activity and duration of protection).

The main correlate of protection against IPD is OPA (opsonophagocytic activity), which measures the ability of antibodies to mediate phagocytosis and bacterial killing. OPA titers ≥1:8 are generally considered protective, although the exact threshold may vary by serotype [67]. Capsular IgG antibodies (measured by enzyme-linked immunosorbent assay - ELISA) are useful, but not always predictive of protection. For example, serotype 3 can induce high IgG levels with low opsonophagocytic activity, which explains the suboptimal protection observed [68].

The two most recent conjugate vaccines currently available for the adult/elderly population (PCV21 and PCV20) meet the non-inferiority criteria for shared serotypes (*vs*. PCV13) and display superiority for the additional ones — reinforcing the rationale for their adoption. It should be noted, however, that in the non-inferiority study of PCV20 vs PPSV23, PCV20 did not meet the non-inferiority criterion for serotype 8 [47].

Compliance Need

The parameter associated with adherence to the vaccination program plays a crucial role.

To achieve a significant public health benefit, it is essential to reach and maintain vaccination coverage levels in line with the targets set by the National Immunization Plan, *i.e.* 75% or higher in adults and the elderly.

With regard to pneumococcal vaccination, "compliance" goes beyond individual adherence to recommendations: it is a key element of Public Health. Indeed, it reflects the system's ability to translate epidemiological needs and the immunological potential of vaccines into real, sufficiently high coverage rates capable of generating a collective impact. Compliance is therefore not only a responsibility of individual citizens but also of health institutions, which must ensure that vaccination pathways are accessible, free of charge and actively promoted.

In this context, strategic planning must include multiple actions implemented through a multidimensional approach. Desirable measures include:

- Integrating vaccination pathways into both primary care and specialist care settings;
- Strengthening the active role of general practitioners and medical specialists;
- Launching information campaigns to raise public awareness of pneumococcal risks and the benefits of vaccination, also by enlisting the support of patient associations;
- Enhancing training programs for healthcare professionals;
- Improving digital systems for tracking vaccination coverage.

In summary, adequate professional training, proper public awareness, efficient local health service organization, and continuous monitoring of coverage rates are key means of ensuring broad and equitable protection.

These efforts will help reduce the clinical, social and economic burden of pneumococcal diseases, especially in the context of Italy's aging population.

Conclusions

Infections caused by *Streptococcus pneumoniae* constitute a significant public health challenge both globally and locally, as they are associated with a substantial burden of morbidity and mortality in the general population – particularly among young children and the elderly.

Patients over the age of 65 are especially vulnerable to pneumococcal diseases, owing to age-related changes in the immune system and a higher prevalence of chronic conditions. Therefore, they are a primary target for vaccination programs.

The emergence of serotypes that are poorly covered by current vaccines, combined with the significant incidence and severity of disease, calls for a reassessment

of the adequacy of existing vaccination strategies, especially in adults. A dynamic vaccination strategy is required – one that can adapt to serotype replacement, a phenomenon driven by the very vaccination campaigns themselves [69].

From an epidemiological perspective, it is essential that the vaccine of choice provides broad and optimal protection against the serotypes most responsible for disease in the target population, in alignment with surveillance data.

From an immunological standpoint, the vaccine chioce should induce an immune response that is at least non-inferior to the comparator, and ideally, more robust and long-lasting.

Regarding compliance, all possible strategies must be activated in order to raise public awareness of the risks of pneumococcal disease and the benefits of vaccination, so as to increase coverage rates.

The absence of even one of the three above-mentioned pillars – epidemiological need, immunological strength and compliance – reduces the overall impact of the vaccination strategy and may have consequences both on the incidence of pneumococcal diseases and on the associated economic and social burden.

A thorough analysis of epidemiological and clinical data, combined with an assessment of the economic and social impact, is crucial to guiding vaccination policies and supporting efficient decision-making in order to protect the health of the entire population. An additional factor that makes the strengthening of vaccination campaigns even more urgent is the fight against antimicrobial resistance. Indeed, a major contributor to the significant burden of pneumococcal disease is growing resistance to the commonly used antibiotic therapies – such as beta-lactams and macrolides – with resistance rates exceeding 20% in Southern Europe [70-72].

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Conflict of Interest statement

The authors declare that they have no conflicts of interest in relation to this manuscript.

Authors' contributions

The authors contributed equally to the entire drafting of the manuscript.

References

[1] Drijkoningen JJ, Rohde GG. Pneumococcal infection in adults: burden of disease. Clin Microbiol Infect 2014;20(Suppl 5):45-51. https://doi.org/10.1111/1469-0691.12461.

[2] Bogaert D, van Belkum A, Sluijter M, Luijendijk A, de Groot R, Rümke HC, Verbrugh HA, Hermans PW. Colonisation by Streptococcus pneumoniae and Staphylococcus aureus in healthy children. Lancet 2004;363:1871-2. https://doi.org/10.1016/S0140-6736(04)16357-5.

[3] Weiser JN, Ferreira DM, Paton JC. Streptococcus pneumoniae: transmission, colonization and invasion. Nat Rev Microbiol. 2018;16:355-67. https://doi.org/10.1038/s41579-018-0001-8.

[4] Paton JC, Trappetti C. Streptococcus pneumoniae Capsular Polysaccharide. Microbiol Spectr 2019;7:10.1128/microbiolspec.gpp3-0019-2018. https://doi.org/10.1128/microbiolspec.GPP3-0019-2018.

[5] Bogaert D, De Groot R, Hermans PW. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. Lancet Infect Dis 2004;4:144-54. https://doi.org/10.1016/S1473-3099(04)00938-7.

[6] Tuomanen EI. The biology of pneumococcal infection. Pediatr Res 1997;42:253-8. https://doi.org/10.1203/00006450-199709000-0000.

[7] Van der Poll T, Opal SM. Pathogenesis, treatment, and prevention of pneumococcal pneumonia. Lancet 2009;374:1543-56. https://doi.org/10.1016/S0140-6736(09)61114-4.

[8] Naucler P, Galanis I, Petropoulos A, Granath F, Morfeldt E, Örtqvist Å, Henriques-Normark B. Chronic Disease and Immunosuppression Increase the Risk for Nonvaccine Serotype Pneumococcal Disease: A Nationwide Population-based Study. Clin Infect Dis 2022;74:1338-49. https://doi.org/10.1093/cid/ciab651.

[9] Mina MJ, Klugman KP. The role of influenza in the severity and transmission of respiratory bacterial disease. Lancet Respir Med 2014;2:750-63. https://doi.org/10.1016/S2213-2600(14)70131-6.

[10] Calabrò GE, Vitale F, Rizzo C, Pugliese A, Boccalini S, Bechini A, Panatto D, Amicizia D, Domnich A, Amodio E, Costantino C, DI Pietro ML, Salvati C, D'Ambrosio F, Orsini F, Maida A, Dominici A, Clemente D, Cecci M, Pellacchia A, DI Serafino F, Bakker K, Malik TM, Sharomi O, Belluzzo M, Leonforte F, Zagra L, LA Gatta E, Petrella L, Bonanni P, DE Waure C. Il nuovo vaccino coniugato antipneumococcico 15-valente per la prevenzione delle infezioni da S. pneumoniae in età pediatrica: una valutazione di HTA [The new 15-valent pneumococcal conjugate vaccine for the prevention of S. pneumoniae infections in pediatric age: a Health Technology Assessment]. J Prev Med Hyg 2023;64(1 Suppl 1):E1-E160. Italian. https://doi.org/10.15167/2421-4248/jpmh2023.64.1s1.

[11] Narciso AR, Dookie R, Nannapaneni P, Normark S, Henriques-Normark B. Streptococcus pneumoniae epidemiology, pathogenesis and control. Nat Rev Microbiol 2025;23:256-71. https://doi.org/10.1038/s41579-024-01116-z.

[12] Teixeira R, Kossyvaki V, Galvez P, Méndez C. Pneumococcal Serotype Evolution and Burden in European Adults in the Last Decade: A Systematic Review. Microorganisms 2023;11:1376. https://doi.org/10.3390/microorganisms11061376.

[13] Blasi F, Mantero M, Santus P, Tarsia P. Understanding the burden of pneumococcal disease in adults. Clin Microbiol Infect 2012;18(Suppl 5):7-14. https://doi.org/10.1111/j.1469-0691.2012.03937.x.

[14] Cheong D, Song JY. Pneumococcal disease burden in high-risk older adults: Exploring impact of comorbidities, long-term care facilities, antibiotic resistance, and immunization policies through a narrative literature review. Hum Vaccin Immunother 2024;20:2429235. https://doi.org/10.1080/21645515.2024.2429235.

[15] Fazio C, Camilli R, Giufré M, Urciuoli R, Boros S, Neri A, Del Grosso M, Vacca P, Giancristofaro S, Siddu A, Orioli R, Maraglino F, Pezzotti P, D'Ancona F, Palamara AT, Stefanelli P. Sorveglianza nazionale delle malattie batteriche invasive. Dati 2021-2023. Roma: Istituto Superiore di Sanità 2024. (Rapporti ISS Sorveglianza RIS-2/2024). Available at https://www.epi-

centro.iss.it/meningite/pdf/RIS%202-2024.pdf (Accessed on: 1 Sept 2025).

[16] GBD 2021 Lower Respiratory Infections and Antimicrobial Resistance Collaborators. Global, regional, and national incidence and mortality burden of non-COVID-19 lower respiratory infections and aetiologies, 1990-2021: a systematic analysis from the Global Burden of Disease Study 2021. Lancet Infect Dis 2024;24:974-1002. https://doi.org/10.1016/S1473-3099(24)00176-2.

[17] European Centre for Disease Prevention and Control. Invasive pneumococcal disease – annual epidemiological report for 2022. Available at: https://www.ecdc.europa.eu/en/publications-data/invasive-pneumococcal-disease-annual-epidemiological-report-2022 (Accessed on: 18 Aug 2025).

[18] Sorveglianza nazionale delle malattie batteriche invasive. Report ad interim – 01/01/2024 – 30/06/2024. Available at https://www.iss.it/documents/20126/9311018/Rapporto+ad+interim+MaBI-primo+semestre+2024.pdf/1093ea94-5ade-e56a-c61c-398b527bd83c?t=1739223411169 (Accessed on: 1 Sep 2025).

[19] Shoar, S., Musher, D.M. Etiology of community-acquired pneumonia in adults: a systematic review. Pneumonia 2020;12:11 https://doi.org/10.1186/s41479-020-00074-3.

[20] Anderson R, Feldman C. The Global Burden of Community-Acquired Pneumonia in Adults, Encompassing Invasive Pneumococcal Disease and the Prevalence of Its Associated Cardiovascular Events, with a Focus on Pneumolysin and Macrolide Antibiotics in Pathogenesis and Therapy. Int J Mol Sci 2023;24:11038. https://doi.org/10.3390/ijms241311038.

[21] Anderson R, Nel JG, Feldman C. Multifaceted Role of Pneumolysin in the Pathogenesis of Myocardial Injury in Community-Acquired Pneumonia. Int J Mol Sci 2018;19:1147. https://doi.org/10.3390/ijms19041147.

[22] Izurieta P, Borys D. Serotype distribution of invasive and non-invasive pneumococcal disease in adults ≥65 years of age following the introduction of 10- and 13-valent pneumococcal conjugate vaccines in infant national immunization programs: a systematic literature review. Front Public Health 2025;13:1544331. https://doi.org/10.3389/fpubh.2025.1544331.

[23] Viegi G, Pistelli R, Cazzola M, Falcone F, Cerveri I, Rossi A, Ugo Di Maria G. Epidemiological survey on incidence and treatment of community acquired pneumonia in Italy. Respir Med 2006;100:46-55. https://doi.org/10.1016/j.rmed.2005.04.013.

[24] Orsi A, Domnich A, Mosca S, Ogliastro M, Sticchi L, Prato R, Fortunato F, Martinelli D, Tramuto F, Costantino C, Restivo V, Baldo V, Baldovin T, Begier E, Theilacker C, Montuori EA, Beavon R, Gessner B, Icardi G. Prevalence of Pneumococcal Serotypes in Community-Acquired Pneumonia among Older Adults in Italy: A Multicenter Cohort Study. Microorganisms 2022;11:70. https://doi.org/10.3390/microorganisms11010070.

[25] Lodi L, Catamerò F, Sarli WM, Moriondo M, Nieddu F, Ferraro E, Citera F, Astorino V, Giovannini M, Voarino M, Pelosi C, Quaranta F, Lippi F, Canessa C, Ricci S, Azzari C. Serotype 3 invasive pneumococcal disease in Tuscany across the eras of conjugate vaccines (2005-2024) and anthropic-driven respiratory virus fluctuations. Hum Vaccin Immunother 2025;21:2510005. https://doi.org/10.1080/21645515.2025.2510005.

[26] Yildirim I, Lapidot R, Shaik-Dasthagirisaheb YB, Hinderstein S, Lee H, Klevens M, Grant L, Arguedas Mohs AG, Cane A, Madoff L, Johnson H, Ivanof C, Burns M, Pelton S. Invasive Pneumococcal Disease After 2 Decades of Pneumococcal Conjugate Vaccine Use. Pediatrics 2024;153:e2023063039. https://doi.org/10.1542/peds.2023-063039.

[27] Thurmond MC. Conceptual foundations for infectious disease surveillance. J Vet Diagn Invest 2003;15:501-14. https://doi.org/10.1177/104063870301500601.

[28] World Health Organization. Immunization Agenda 2030: A global strategy to leave no one behind. Available at: https://www.who.int/teams/immunization-vaccines-and-biologicals/strategies/ia2030 (Assessed on: 1 Sep 2025).

[29] Centers for Disease Control and Prevention. Addressing emerging infectious disease threats: a prevention strategy for the United States. Atlanta: U.S. Department of Health and Human Services, Public Health Service 1994 (Assessed on: 1 Sep 2025).

[30] Pinner RW, Rebmann CA, Schuchat A, Hughes JM. Disease surveillance and the academic, clinical, and public health communities. Emerg Infect Dis 2003;9:781-7. https://doi.org/10.3201/eid0907.030083.

[31] Langley G, Schaffner W, Farley MM, Lynfield R, Bennett NM, Reingold AL, et al. Twenty Years of Active Bacterial Core Surveillance. Emerg Infect Dis 2015;21:1520-8. https://doi.org/10.3201/eid2109.141333.

[32] Centers for disease control and Prevention-CDC-Active Bacterial Core surveillance (ABCs). Available at http://cdc.gov/abcs/index.html (Accessed on: 8 Aug 2025).

[33] Said MA, Johnson HL, Nonyane BA, Deloria-Knoll M, O'Brien KL; AGEDD Adult Pneumococcal Burden Study Team; Andreo F, Beovic B, Blanco S, Boersma WG, Boulware DR, Butler JC, Carratalà J, Chang FY, Charles PG, Diaz AA, Domínguez J, Ehara N, Endeman H, Falcó V, Falguera M, Fukushima K, Garcia-Vidal C, Genne D, Guchev IA, Gutierrez F, Hernes SS, Hoepelman AI, Hohenthal U, Johansson N, Kolek V, Kozlov RS, Lauderdale TL, Mareković I, Masiá M, Matta MA, Miró Ò, Murdoch DR, Nuermberger E, Paolini R, Perelló R, Snijders D, Plečko V, Sordé R, Strålin K, van der Eerden MM, Vila-Corcoles A, Watt JP. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. PLoS One 2013;8:e60273. https://doi.org/10.1371/journal.pone.0060273.

[34] Icardi G, Sticchi L, Bagnasco A, Iudici R, Durando P. Pneumococcal vaccination in adults: rationale, state of the art and perspectives. J Prev Med Hyg 2012;53:78-84.

[35] Maeda H, Morimoto K. Global distribution and characteristics of pneumococcal serotypes in adults. Hum Vaccin Immunother 2025;21:2469424. https://doi.org/10.1080/21645515.2025.2469424.

[36] Ozisik L. The New Era of Pneumococcal Vaccination in Adults: What Is Next? Vaccines (Basel) 2025;13:498. https://doi.org/10.3390/vaccines13050498.

[37] Agenzia Italiana per il Farmaco. Pneumovax. Riassunto delle caratteristiche del prodotto. Available at: https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_001117_034933_RCP.pdf&sys=m0b1l3 (Accessed on: 7 Aug 2025).

[38] Avci FY. Novel strategies for development of next-generation glycoconjugate vaccines. Curr Top Med Chem 2013;13:2535-40. https://doi.org/10.2174/15680266113136660180.

[39] Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, Reingold A, Cieslak PR, Pilishvili T, Jackson D, Facklam RR, Jorgensen JH, Schuchat A; Active Bacterial Core Surveillance of the Emerging Infections Program Network. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med 2003;348:1737-46. https://doi.org/10.1056/NEJMoa022823.

[40] Piano Nazionale Vaccini 2005-2007. Available at: https://www.salute.gov.it/portale/documentazione/p6_2_2_1.jsp?id=543&lingua=italiano (Accessed on: 7 Sep 2025).

[41] Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. Lancet Infect Dis 2011;11:760-8. https://doi.org/10.1016/S1473-3099(11)70090-1.

[42] Fitzwater SP, Chandran A, Santosham M, Johnson HL. The worldwide impact of the seven-valent pneumococcal conjugate vaccine. Pediatr Infect Dis J 2012;31:501-8. https://doi.org/10.1097/INF.0b013e31824de9f6.

[43] Balsells E, Guillot L, Nair H, Kyaw MH. Serotype distribution of Streptococcus pneumoniae causing invasive disease in children in the post-PCV era: A systematic review and meta-analysis. PLoS One 2017;12:e0177113. https://doi.org/10.1371/journal.pone.0177113.

[44] Riassunto delle caratteristiche del prodotto. Vaccino pneumococcico polisaccaridico coniugato, (13valente adsorbito). Available at https://ec.europa.eu/health/documents/community-register/2009/2009120968908/anx_68908_it.pdf (Accessed on: 4 Sep 2025).

[45] Riassunto delle caratteristiche del prodotto. Vaccino pneumococcico polisaccaridico coniugato (adsorbito) 10-valente. Available at https://ec.europa.eu/health/documents/community-register/2016/20160502134848/anx_134848_it.pdf (Accessed on: 4 Sep 2025).

[46] Riassunto delle caratteristiche del prodotto. Vaccino pneumococcico polisaccaridico coniugato (15-valente, adsorbito). Available at https://ec.europa.eu/health/documents/community-register/2022/20221021157327/anx_157327_it.pdf (Accessed on: 4 Sep 2025).

[47] Riassunto delle caratteristiche nel prodotto - Vaccino pneumococcico polisaccaridico coniugato (20-valente, adsorbito). Available at https://www.ema.europa.eu/it/documents/product-information/prevenar-20-epar-product-information_it.pdf (Accessed on: 4 Sep 2025).

[48] Polistena B, Icardi G, Orsi A, Spandonaro F, Di Virgilio R, d'Angela D. Cost-Effectiveness of Vaccination with the 20-Valent Pneumococcal Conjugate Vaccine in the Italian Adult Population. Vaccines (Basel) 2022;10:2032. https://doi.org/10.3390/vaccines10122032.

[49] Riassunto delle caratteristiche del prodotto. Pneumococcal polysaccharide conjugate vaccine (21-valent). Availale at https://www.ema.europa.eu/en/medicines/human/EPAR/capvaxive#product-info (Accessed on: 4 Sep 2025).

[50] Platt HL, Bruno C, Buntinx E, Pelayo E, Garcia-Huidobro D, Barranco-Santana EA, Sjoberg F, Song JY, Grijalva CG, Orenstein WA, Morgan L, Fernsler D, Xu W, Waleed M, Li J, Buchwald UK; STRIDE-3 Study Group. Safety, tolerability, and immunogenicity of an adult pneumococcal conjugate vaccine, V116 (STRIDE-3): a randomised, double-blind, active comparator controlled, international phase 3 trial. Lancet Infect Dis 2024;24:1141-50. https://doi.org/10.1016/S1473-3099(24)00344-X.

[51] Scott P, Haranaka M, Choi JH, Stacey H, Dionne M, Greenberg D, Grijalva CG, Orenstein WA, Fernsler D, Gallagher N, Zeng T, Li J, Platt HL; STRIDE-6 Study Group. A Phase 3 Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-Experienced Adults 50 Years of Age or Older (STRIDE-6). Clin Infect Dis 2024;79:1366-74. https://doi.org/10.1093/cid/ciae383.

[52] ISTAT. Previsioni della popolazione residente e delle famiglie – Base 2024. 2025. Available at: https://www.istat.it/wp-content/uploads/2025/07/Report_Previsioni-della-popolazione-residente-e-delle-famiglie_Base-Base-112024.pdf (Accessed on: 1 Sep 2025).

[53] Ministero della Salute. Piano Nazionale Prevenzione Vaccinale 2017–2019. Available at https://www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf (Accessed on: 1 Sep 2025).

[54] Ministero della Salute. Piano Nazionale Prevenzione Vaccinale 2023-2025. Available at: https://www.quotidianosanita.it/allegati/allegato1679488094.pdf (Accessed on: 5 Sep 2025).

[55] Di Valerio Z, La Fauci G, Scognamiglio F, Salussolia A, Montalti M, Capodici A, Fantini MP, Odone A, Costantino C, Soldà G, Larson HJ, Leask J, Lenzi J, Gori D; OBVIOUS board. Pneumococcal vaccine uptake among high-risk adults and children in Italy: results from the OBVIOUS project survey. BMC Public Health 2024;24:736. https://doi.org/10.1186/s12889-024-18216-3.

[56] Bongiovanni A, Santolini G, Vairo F, Corea F, Aquilani S, de Waure C. Analysis of Sequential Pneumococcal Vaccination Coverage in the Elderly Resident Population of the Viterbo Local Health Authority from 2018 to 2023. Vaccines (Basel) 2025;13:807. https://doi.org/10.3390/vaccines13080807.

[57] Veronese N, Ragusa FS, Titone PR, Vernuccio L, Catanese G, Randazzo MA, Palermo M, Di Bella G, Mansueto P, Dominguez LJ, Barbagallo M. Management of the vaccination campaign in a population of frail older outpatients affected by cognitive or endocrinological conditions: a pilot study in Italy. Aging Clin Exp Res 2024;36:179. https://doi.org/10.1007/s40520-024-02824-5.

[58] Weinberger DM, Malley R, Lipsitch M. Serotype replacement in disease after pneumococcal vaccination. Lancet 2011;378:1962-73. https://doi.org/10.1016/S0140-6736(10)62225-8.

[59] Maeda H, Morimoto K. Global distribution and characteristics of pneumococcal serotypes in adults. Hum Vaccin Immunother 2025;21:2469424. https://doi.org/10.1080/21645515.2025.2469424.

[60] Mrabt F, Guedes S. Systematic review on serotypes distribution of pneumococcal pneumonia in adults and the elderly. BMC Public Health 2025;25:1194. https://doi.org/10.1186/s12889-025-22164-x.

[61] Ciruela P, Izquierdo C, Broner S, Muñoz-Almagro C, Hernández S, Ardanuy C, Pallarés R, Domínguez A, Jané M; Catalan Working Group on Invasive Pneumococcal Disease. The changing epidemiology of invasive pneumococcal disease after PCV13 vaccination in a country with intermediate vaccination coverage. Vaccine 2018;36:7744-52. https://doi.org/10.1016/j.vaccine.2018.05.026.

[62] Méroc E, Fletcher MA, Hanquet G, Slack MPE, Baay M, Hayford K, Gessner BD, Grant LR. Correction: Méroc et al. Systematic Literature Review of the Epidemiological Characteristics of Pneumococcal Disease Caused by the Additional Serotypes Covered by the 20-Valent Pneumococcal Conjugate Vaccine. Microorganisms 2023, 11, 1816. Microorganisms 2025 31;13:793. https://doi.org/10.3390/microorganisms13040793. Erratum for: Microorganisms 2023;11:1816. https://doi.org/10.3390/microorganisms11071816.

[63] Kobayashi M, Farrar JL, Gierke R, Britton A, Childs L, Leidner AJ, Campos-Outcalt D, Morgan RL, Long SS, Talbot HK, Poehling KA, Pilishvili T. 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. MMWR Morb Mortal Wkly Rep 2022;71:109-17. https://doi.org/10.15585/mmwr.mm7104a1.

[64] Navarro-Torné A, Montuori EA, Kossyvaki V, Méndez C. Burden of pneumococcal disease among adults in Southern Europe (Spain, Portugal, Italy, and Greece): a systematic review and meta-analysis. Hum Vaccin Immunother 2021;17:3670-86. https://doi.org/10.1080/21645515.2021.1923348.

[65] Pletz MW, Maus U, Krug N, Welte T, Lode H. Pneumococcal vaccines: mechanism of action, impact on epidemiology and adaption of the species. Int J Antimicrob Agents 2008;32:199-206. https://doi.org/10.1016/j.ijantimicag.2008.01.021.

[66] Feemster K, Buchwald UK, Banniettis N, Joyce JG, Velentgas P, Chapman TJ, Yildirim I. Immunogenicity of Current and Next-Generation Pneumococcal Conjugate Vaccines in Children: Current Challenges and Upcoming Opportunities. Open Forum Infect Dis 2024;11:ofae220. https://doi.org/10.1093/ofid/ofae220. Erratum in: Open Forum Infect Dis 2024;11:ofae440. https://doi.org/10.1093/ofid/ofae440.

[67] Ganaie FA, Nahm MH. Approaches to assess new pneumococcal vaccines for immunogenicity, development and licensure. Hum Vaccin Immunother 2025;21:2545032. https://doi.org/10.1080/21645515.2025.2545032.

[68] Duke JA, Avci FY. Emerging vaccine strategies against the incessant pneumococcal disease. NPJ Vaccines 2023;8:122. https://doi.org/10.1038/s41541-023-00715-w.

[69] Weinberger DM, Malley R, Lipsitch M. Serotype replacement in disease after pneumococcal vaccination. Lancet 2011;378:1962-73. https://doi.org/10.1016/S0140-6736(10)62225-8.

[70] Wang JL, Lai CC, Ko WC, Hsueh PR. Global trends in non-susceptibility rates of Streptococcus pneumoniae isolates to ceftriaxone: Data from the antimicrobial testing leadership and surveillance (ATLAS) programme, 2016-21. Int J Antimicrob Agents 2024;63:107072. https://doi.org/10.1016/j.ijantimicag.2023.107072.

[71] Li L, Ma J, Yu Z, Li M, Zhang W, Sun H. Epidemiological characteristics and antibiotic resistance mechanisms of Streptococcus pneumoniae: An updated review. Microbiol Res 2023;266:127221. https://doi.org/10.1016/j.micres.2022.127221.

[72] Ozisik L. The New Era of Pneumococcal Vaccination in Adults: What Is Next? Vaccines (Basel) 2025;13:498. https://doi.org/10.3390/vaccines13050498.

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Correspondence: Elvira Massaro, MD, ASL3 Healthcare System of the Liguria Region, Genoa, Italy. E-mail: elvira.massaro@edu.unige.it.

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