

Systematic Review

Globally Increasing Prevalence of *Streptococcus pneumoniae* in Pneumonia, Bloodstream Infection, Meningitis, Otitis Media and Sinusitis: Review and Rationale for PCV-13 in Egypt

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Abstract

Objective: *Streptococcus pneumoniae* or *pneumococcus* is an opportunistic colonizer of the upper respiratory tract and can lead to so-called invasive pneumococcal disease (IPD), including meningitis, bacteremia, and pneumonia. Involving around 100 serotypes with limited cross-protection and variation with age and ambient conditions, vulnerable groups include children under 2, the elderly, and the immuno-compromised. While being a primary cause of pneumonia, it has gradually emerged as a leading cause of bacterial meningitis in Egypt and elsewhere. Integrating the pneumococcal conjugate vaccine (PCV-13) into the national immunization program of Egypt has become a necessity to prevent IPD.

Methods: A focused review of English-language publications illustrating the epidemiology and increasing burden of IPD was conducted for the last 20 years. The review covered both global and local pneumonia, bloodstream infection and meningitis in children and adults.

Results: Currently, 75% of countries (147/195) have implemented PCV into their immunization programs, while many non-implementing are from Africa that contains about 20% of the world's population. Gaps in Africa's vaccine manufacturing capacity have been exposed during COVID-19 pandemic and warranted a presidential directive in Egypt to establish a vaccine manufacturing capacity for local and regional needs at the Vaccine and Biotechnology City (VBC). The pneumococcal conjugate vaccine (PCV-13) will be the first launch to mitigate the burden and risks of IPD.

Conclusion: Serotype coverage of PCV-13 in Egyptian meningitis cases rose from 30% in 2003 to 90% in 2024. National implementation of the vaccine is essential to address this etiological shift and reduce IPD incidence, mortality, antibiotic consumption, and associated healthcare costs. Serotype replacement; a crucial phenomenon seen after the introduction of the pneumococcal vaccine will be monitored.

Keywords: *Streptococcus pneumoniae*, invasive pneumococcal disease, community-acquired pneumonia, PCV-13, meningitis

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1 INTRODUCTION

Streptococcus pneumoniae (Pneumococcus) is a common inhabitant of the human respiratory tract that can be isolated from the nasopharynx in 5% to 90% of healthy individuals. This wide range of prevalence depends on the age of the subject and life settings, including the geographic location, contacts and underlying immunological conditions.

For instance, pneumococcal carriage in the throat and nasopharynx of school-age children may range from 20% to 60% and decreases to 5%-10% in adults - particularly those not living with children. However, the rates may rise up again to 50-60% during military service^[1].

As an opportunistic microorganism, *S. pneumoniae* can cause life-threatening infections upon invading normally

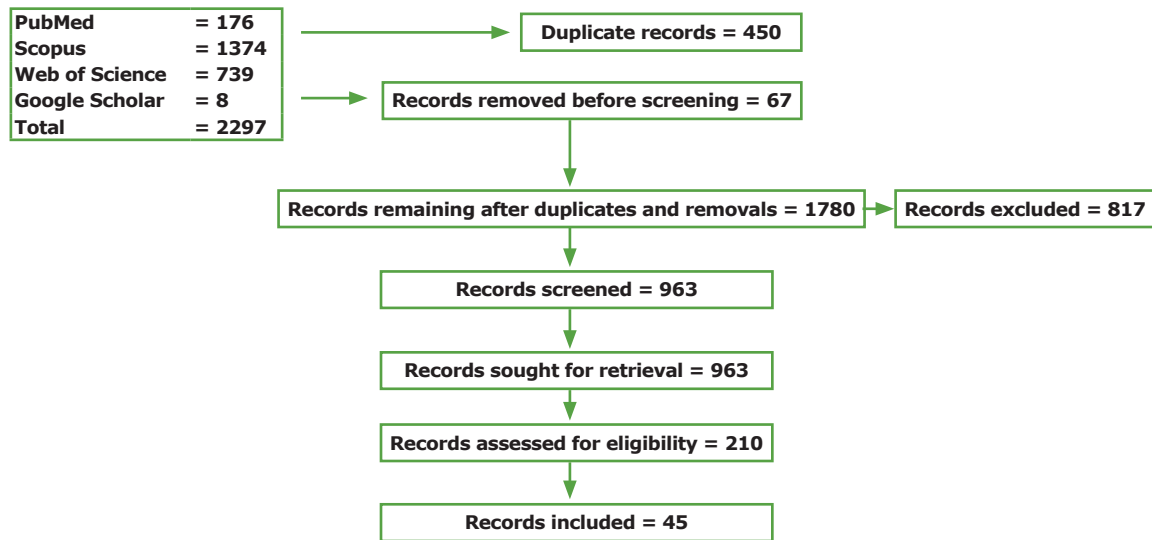


Figure 1. PRISMA Flow Chart for Records Identified in This Study.

sterile sites of the body, such as the bloodstream and central nervous system, resulting in conditions like bacteremia with pneumonia or meningitis. These are collectively termed invasive pneumococcal diseases (IPD)^[1], whereas pneumonia without bacteremia, bronchitis, otitis media, and sinusitis are considered non-invasive infections.

The polysaccharide capsule of *S. pneumoniae* is the key virulence factor, primarily by enabling evasion of phagocytosis and contributing to resistance against certain antibiotics^[2]. To date, approximately 100 encapsulated serotypes have been identified, with 23 of the most clinically relevant serotypes being targeted partially or totally by the available capsular-based vaccines^[1,3].

However, 3-19% of invasive disease cases have been attributed to non-encapsulated *S. pneumoniae* strains (NESp), particularly among infants, immunocompromised individuals, and the elderly^[4]. These non-encapsulated strains exhibit high rates of genetic recombination to produce alternative surface proteins that replace the capsular polysaccharides and confer multidrug resistance. Some NESp strains may also show multilocus sequence types [STs], like ST344 and ST448 that can harbor genetic loci to facilitate pneumococcal colonization as in otitis media^[5,6].

The purpose of this review is to underscore the rising global burden of infections caused by *S. pneumoniae* and the changes that led to making it a major cause of meningitis cases compared to meningococci and other bacterial species. Current literature shows a compelling argument for introducing the PCV-13 vaccine into Egypt's national immunization program for protection against IPD. Despite the high implication of pneumococci in meningitis cases and other forms of IPD, the vaccine is used at a small scale and has not yet been integrated into the routine public health policy. Evidence-based health benefits of a nationwide use of PCV-13 and cost-effectiveness are

reviewed, with insights for policymakers and investors to support this essential public health decision.

2 METHODS

Peer-reviewed articles were retrieved from PubMed, Scopus, Web of Science, and Google Scholar, covering studies mainly published during the last two decades. Keywords used in the search included "*Streptococcus pneumoniae*" and "Egypt", "Invasive pneumococcal disease" and "IPD" and "Middle East", "Bloodstream Infection" and "*S. pneumoniae*" and "Middle East", "Community-acquired pneumonia" and "CAP" and ", "Bacterial Meningitis" and "*S. pneumoniae*" and "Egypt", "Otitis media" and "*S. pneumoniae*", "Sinusitis" and "*S. pneumoniae*", "PCV-13 Vaccine" and "Egypt", "Vaccine Cost Effectiveness" and "Egypt".

A PRISMA chart was drawn (Figure 1) to show that studies were selected based on predefined eligibility criteria that considered the tangible role of *S. pneumoniae* in the global epidemiology and increasing burden of IPD, with a particular reference to Egypt and the nearby countries. Inclusion and exclusion standards were applied during screening to ensure relevance. Excluded records were those addressing molecular structures of *S. pneumoniae*, individual case studies, improper bacterial identification or serotyping, lack of laboratory data or data collected from non-sterile sites or data from non-human origin. A total of 41 articles were included in the study.

The quality of included studies was critically appraised to ensure consistency, validity, reliability, and the overall strength of the evidence.

3 RESULTS

3.1 Data Selection

Selection of data was based on the flow chart depicted in Figure 1. The data show a paucity of literature in relation

to otitis media and sinusitis caused by *S. pneumoniae* due to difficulties in confirming the presence of the organism in the middle-ear fluid (obtained through tympanocentesis) or sinus aspirates. The methods are invasive and not routinely performed in clinical practice. In addition, otitis media and sinusitis were often complicated by the presence of other bacterial pathogens, making the attribution of the disease solely to pneumococcus challenging.

Meanwhile, bloodstream infection is usually manifested as a fever, mostly associated with pneumonia or meningitis. However, it was hard to detect *S. pneumoniae* from blood culture.

In previous publications, the authors of this review and others have declared difficulties in the isolation of *S. pneumoniae* from blood cultures of septicemic patients, despite the inoculation of the recommended blood volumes into BACTEC culture bottles and patient declaration of no antibiotic intake prior to providing the sample^[7-9]. Detection of other bacteria from blood was more frequent compared to *S. pneumoniae*, which was mainly identified by PCR from both blood and the cerebrospinal fluid (CSF) or by culture from the CSF only^[7,8].

3.2 Community-Acquired Pneumonia (CAP) and Global Burden

This infection is typically contracted outside the hospital settings and has been diagnosed in an estimated 152 million children under 5 each year, with 10-20 million of those cases requiring hospitalization^[10,11]. In contrast, nosocomial pneumonia, also known as healthcare-associated pneumonia or atypical CAP is largely caused by different types of antibiotic-resistant bacteria, including *Klebsiella pneumoniae*, methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter* species^[11]. All have demonstrated significant global morbidity and mortality rates. Accurate diagnosis of these infections is imperative for proper management and therapy.

Globally, the World Health Organization (WHO) estimated that pneumonia, which is a severe form of acute lower respiratory infection, accounted for 3 million deaths annually in 2019^[12], with 14% of those deaths occurring in children under 5 years of age. This rate translates to 740,180 child deaths, making pneumonia the single largest infectious cause of death in children under five^[12].

In a 4-year study published in Egypt in 2015, Draz et al.^[13] found that the incidence of IPD (pneumonia and meningitis) among hospitalized children averaged 18.2/100,000 or around one half of non-IPD incidence (36.4/100,000). Per definition, this is the number of newly diagnosed cases within a specific population in one year.

Infants < 1 year were significantly more vulnerable to *S. pneumoniae* infection than those between 1 and 5 years

of age (annual rate: 110.5/100,000 and 21.6/100,000, respectively). The overall pneumococcal annual case fatality was 33.3%, being higher in IPD (75%) than in non-IPD (12.5%) cases. An increasing trend of pneumococcal detection rate was observed during the study period ($P < 0.0001$). The results were comparable to those reported from the United Arab Emirates and the Kingdom of Saudi Arabia before the introduction of pneumococcal vaccines^[13].

3.3 Pneumococcal Disease in Egypt

Again, these values were confirmed among Egyptian children in 2020. The incidence of pneumonia in children under 5 years of age was 0.11-0.20 episodes per child/year. Knowing that children under 5 years in Egypt represent about 13.4% of the total population, it follows that about 20 million cases of childhood pneumonia occur each year. Ten percent of these cases are expected to be hospitalized and may show up to 19% mortality^[14].

Another study estimated that the prevalence of CAP among children in the Delta region of Egypt was around 1.96%, being more severe in 71.8% of them compared to atypical CAP^[11]. Also, El-Beleidy and coworkers^[15] claimed that *S. pneumoniae* was the most common cause of IPD, acute mastoiditis and severe complications of acute otitis media in children between 9 months and 11 years old. Approximately 30% of the Egyptian children were carriers of antibiotic-resistant *S. pneumoniae* strains in the nasopharynx, rendering the treatment of pneumococcal disease a growing global challenge and suggesting the implementation of PCV-13 into the national immunization program.

Predominant serotypes associated with penicillin resistance were 6B, 1, 19A, 23F, and 6A^[15]. Other *S. pneumoniae* isolates that showed high resistance to sulfamethoxazole-trimethoprim, tetracyclines, erythromycin, and clindamycin included 9V and 19F^[8,15], all of which would be covered by PCV13. Multidrug-resistant serotypes in Egypt showing resistance to ≥ 3 antimicrobial agents were identified in 41% of the isolates; including serotypes 23F, 6B, and 6A^[15].

However, along with the temporal differences observed in the proportions and serotype distribution of *S. pneumoniae*^[9], higher susceptibility rates were reported in Egypt around 2020, increasing from 27.4% to 32.7% for penicillin, 64.5% to 72.7% for clindamycin, 50% to 55.5% for erythromycin and 3.3% to 45.5% for sulfamethoxazole/trimethoprim^[16]. Meanwhile, the susceptibility to ceftriaxone decreased from 99.8% to 54.5% in association with the higher use in the country^[16]. In countries that did not introduce PCV yet, penicillin resistance was high in Algeria and Tunisia up to 70%, but relatively less in Iraq and Iran (range 16% and 50%). More than 90% of *S. pneumoniae* isolates within these countries were sensitive to ceftriaxone/cefotaxime. However, penicillin resistance

Table 1. Pneumococcal Serotypes Involved in 7 Vaccines Based on Stela and Minter and Capeding et al. ^[20,21]

Pneumococcal Serotypes	PCV-7	PCV-10	PCV-11	PCV-13	PCV-15	PCV-20	PPSV-23
1		✓	✓	✓	✓	✓	✓
2							✓
3			✓	✓	✓	✓	✓
4	✓	✓	✓	✓	✓	✓	✓
5		✓	✓	✓	✓	✓	✓
6A				✓	✓	✓	
6B	✓	✓	✓	✓	✓	✓	✓
7F		✓	✓	✓	✓	✓	✓
8							✓
9N							✓
9V	✓	✓	✓	✓	✓	✓	✓
10A						✓	✓
11A						✓	✓
12F						✓	✓
14	✓	✓	✓	✓	✓	✓	✓
15B						✓	✓
17F							✓
18C	✓	✓	✓	✓	✓	✓	✓
19A				✓	✓	✓	✓
19F	✓	✓	✓	✓	✓	✓	✓
20							✓
22F					✓	✓	✓
23F	✓	✓	✓	✓	✓	✓	✓
33F					✓	✓	✓

Table 2. Main Pneumococcal Serotypes Associated with Invasive Disease and Risk of Death (Adapted from Darkwah et al. ^[22]**)**

Clinical Association	Pneumococcal Serotypes
Highly invasive pneumococcal disease	1, 2, 4, 5, 7F, 8, 9, 12F, 14, 16, 18C, 19A
Less invasive disease	3, 6A, 6B, 11A, 15B/C, 19, 23F
More associated with pneumonia	1, 3
More associated with meningitis	6, 10, 23
More associated with high risk of death	3, 6A, 11A, 15A, 19F, 31
Associated with lower risk of death	1, 5, 7F, 8

post PCV13 introduction decreased between 10-25% in Kuwait, Lebanon, Morocco, Saudi Arabia and Turkey. On the contrary, a notable rise in erythromycin non-susceptibility from 23% to 40%, was observed ^[17].

3.4 Pneumococcal Serotypes and Vaccine Coverage

Since around 100 *S. pneumoniae* serotypes have been implicated in IPD due to significant antigenic variation and differences in distribution by age and geographic location. In Lebanon, vaccine coverage depended on the product used and was estimated to be 41.4%, 53.9%, and 67.2% for PCV-7, PCV-10, and PCV-13, respectively. However, for the age groups <2, 2–5, and >60 years, PCV-13 coverage

was 63%, 80%, and 68%, respectively, demarking the superiority of the PCV-13 for all age groups compared to the other vaccines ^[18]. In a more recent study conducted in Spain, higher valency pneumococcal conjugate vaccines (PCVs) showed a higher potential to reduce the CAP burden due to the evolution and distribution of more serotypes that are contained in the 20-valent PCV ^[19]. However, cost-effectiveness studies should be conducted before the use of high valency vaccines, particularly in middle- or low-income countries that have not introduced PCVs.

Table 1 illustrates the different serotypes of *S. pneumoniae* that are currently involved in the available vaccines, based on Stela and Minter (2023) and Capeding et.al. (2003) ^[20,21], while Table 2 shows the main pneumococcal serotypes associated

with invasive disease and risk of death (adapted from Darkwah et al.^[22]).

Among adults in the Middle East and North Africa, including Egypt, Lebanon and other Middle Eastern countries, the burden of CAP-IPD presented a considerable challenge, particularly among those with underlying health conditions or low income. If pediatric vaccination programs have lowered the overall burden of many vaccine-preventable diseases, adults have shown at least 30% increase in the burden of CAP-IPD disease, mainly due to lower vaccination uptake and the global ageing^[23]. Consequently, addressing IPD prevention in adults is necessary to minimize potential severity and impact on the public health^[18,23].

In the developed European countries that implemented pneumococcal vaccination policies, serotypes of PCV-20 vaccine were detected in 23.9% of adult CAP patients in Spain, with 68.4% of these patients diagnosed by chest X-ray or culture^[19]. In Italy, CAP associated serotypes in adults were represented in the PCV-13, PCV-15 and PCV-20 at 3.3, 4.4 and 7.5%, respectively, although coverage in children was higher^[24]. These observations suggest the need for developing new pneumococcal vaccines with expanded serotype coverage^[25].

In the United States, *S. pneumoniae* was detected in 10.2% of the hospitalized adult CAP patients, including 3.0% with serotypes covered by PCV-13, 3.9% by PCV-15, and 5.7% by PCV-20. Overall, PCV-13 has been successfully endorsed for more than a decade for older adults and individuals with pneumococcal lower respiratory tract infection or immunocompromising conditions^[26]. So, pneumococcal vaccines with broader serotype coverage were advocated to help prevent a significant residual burden of CAP caused by serotypes not included in the currently available PCV-13, PCV15, or PCV20 based on data from Europe and the USA^[24-26].

Having briefly summarized the current situation of community-acquired pneumonia, the other, most serious infection caused by *S. pneumoniae* is bacterial meningitis, which has globally affected over 1.2 million cases and 300,000 deaths in 2021^[27]. In the United States alone, the organism was responsible for more than 50% of meningitis infections in 2017^[1] and was the main cause of the disease (59%) between 2008 and 2023, leading to mortalities up to 11% (573/5,028)^[26]. This is in agreement with Koelman and coworkers who reported the association of *S. pneumoniae* with 70% of bacterial meningitis cases in Europe and Northern America in 2020^[28].

3.5 Meningitis and Pneumococcal Vaccines

Meningitis is the inflammation of the meninges and subarachnoid space and may extend to the brain cortex and parenchyma. Infection may be contracted from the community (community-acquired bacterial meningitis)

or from the hospital as a complication of invasive procedures^[29]. Sequels of this infection may include hearing loss, developmental delays, and death, especially in vulnerable populations like young children and the elderly.

In the UK, pneumococcal meningitis was reported at a lower prevalence than the United States, although *S. pneumoniae* was still the leading cause of infection, having been identified in 19.9% of the cases followed by *Neisseria meningitidis* (12.2%) then other less prevalent bacterial species^[30]. This change in the pattern of causative agents may be attributed to the widespread use of vaccines against meningococcal serotypes and *Haemophilus influenzae* type b, permitting the selection of *S. pneumoniae* as the foremost cause of meningitis^[31]. Pneumococcal serotypes that are commonly involved in meningitis cases and included in the available vaccines are shown in Table 2.

In Egypt, *S. pneumoniae* was recovered from 42% (354/843) of CSF cultures between 1998 and 2004, followed by *Haemophilus influenzae* serotype b (20%), *Neisseria meningitidis* (17%), *Mycobacterium tuberculosis* (17%) and other bacteria (6%)^[8]. Further, 6% of the culture negative specimens were also positive for *S. pneumoniae* by PCR^[8].

Serotyping of *S. pneumoniae* during several years in Egypt showed that 29 and 42% of the isolates were covered by the 7- and 11-valent conjugate vaccines, respectively. Among children <2 years, the coverage was 38% and 56% using the 7- and 11-valent vaccines, respectively. The data also indicated the emergence of multidrug resistant isolates^[8,9], but the relatively low representation of local serotypes (less or around 50%) in the available vaccines discouraged their use in the country^[8,9]. These findings were also supported by those of Sheded et al.^[32] who added that vaccine serotype representation and treatment modalities should be monitored in Egypt before vaccine introduction.

More recently, Al-Kersh et al.^[33] confirmed the rising role of *S. pneumoniae* in bacterial meningitis during sentinel surveillance studies (2016-2023) in Egypt and other countries in the MENA region. The organism was detected in 90% of the CSF samples using culture or PCR, while *N. meningitidis* and *H. influenzae* (serotype b and non-b) were found in 5 and 1% of the samples, respectively. The data showed that the 11-valent conjugate vaccine could cover 76% of the identified *S. pneumoniae* serotypes, highlighting a considerable change in the pattern of bacterial causes of meningitis in Egypt during the last two decades.

The serotype coverage increased from 42% to 76% may be due to microbial shifts^[31], not to mention the potential methodological differences between laboratories or the limited number of patients enrolled in each study. Underestimates may have been obtained in earlier studies because of limitations in culture or PCR detection systems at the laboratories. However, the data suggests the need for introducing pneumococcal vaccines in the country, not only because of CAP infection but

Country / Region	2025	2024	2023	2022	2021	2020	2019	2018	2017	2016	2015	2014	2013	2012	2011	2010
Algeria	Yes															
Egypt														No		
Jordan	Yes													No		
Lebanon	Yes															
Morocco	Yes															
Qatar	Yes															
Saudi Arabia	Yes															
Tunisia	Yes															

Figure 2. Countries Introducing PCV-13 in the MENA Region Based on the Latest WHO Data. [Introduction of PCV \(Pneumococcal conjugate vaccine\)](#)

also for preventing meningitis as a significant public health problem of endemic nature, with severe complications and high mortality rate.

3.6 Cost-Effectiveness Studies and Impact of PCV-13 in Egypt

However, before investing in the procurement or local production of vaccines, WHO and the Centers for Disease Control and Prevention, USA, have recommended conducting cost-effectiveness evaluations^[34,35]. Using the influenza vaccine as a model to compare vaccine-related costs and benefits (disease or death prevented) against no intervention, a negative net cost indicated that vaccination saved more than the spent^[34]. In Colombia, for instance, conceptual estimates showed that PCV-13 vaccine introduction would significantly reduce cases of pneumococcal diseases such as bacteremia, meningitis, and CAP over a five-year period. The financial burden of not vaccinating was higher than PCV-13 cost during that period based on trends of *S. pneumoniae* serotype surveillance in children^[36].

An in-Silico model was developed for the introduction of PCV-13 vaccine in India in 2018, since cost-effectiveness reports from high-income countries were not readily comparable due to differences in the prevalence of pneumococcal serotypes, socioeconomic standards, targeted populations and available health systems. The model utilized a simulated population of about 25,000 people in 4,300 households. Assuming about 77% vaccination coverage, as in DPT vaccine, PCV-13 was expected to reduce huge medical treatment expenses, prevent thousands of deaths per year, and support the life of poor families^[37]. Those results were consonant with others from China^[38], Portugal^[39] and Philippines^[40].

3.7 Vaccine Introduction: Evidence and Considerations

Figure 2 demonstrates the countries that have introduced

PCV-13 into the MENA region. Many countries have introduced it more than 10 years ago, while Jordan introduced in 2025 and Egypt is still considering. The most common serotypes of *S. pneumoniae* identified from the Nasopharynx and IPD cases among Egyptian children^[16] showed an estimated vaccine coverage of 77.6% for PCV-13. Mathematically, the coverage reached similar levels with PCV-15 (79.2%) and was higher with both PCV-20 and PCV-23 (87.9% and 91.2%, respectively) (Table 3). Higher valency vaccines resulted in a broader serotype coverage, but cost-effectiveness studies must be considered particularly in countries that have not introduced PCVs before. The WHO does not provide recommendations on the efficacy of such vaccines, but rather requires prequalification and evidence of safety, immunogenicity, and protection in clinical trials. Earlier, both PCV-10 and PCV-13 have shown 48-74% reduction of infection among susceptible subjects and infection due to non-vaccine-type serotypes was minimal^[41].

At present, Egypt is considering the introduction of PCV-13 in the routine childhood immunization program, given the latest surveillance findings and significant shifts in meningitis causative agents, not to mention the high CAP rates. The vaccine could be regarded as a life saver at this stage to reduce the burden of these infections and improve their prognosis, complications and mortalities. It will also reduce the increasing antimicrobial resistance among IPD cases. Many countries in the Middle East have introduced this vaccine into their National Immunization Programs, including Bahrain, Kuwait, Qatar, Saudi Arabia, UAE, Oman, Jordan, Lebanon, Algeria, and Morocco. Some of these countries were shown in Figure 2.

A cost-utility analysis (CUA) conducted in Egypt in 2022 has shown large incremental cost-effectiveness ratios from both government and patient perspectives for both PCV-13 and PCV-10 compared to no program per quality-adjusted life year (QALY), respectively. QALY is a measure of how many years of healthy life is gained from

Table 3. Common Serotypes of *S. pneumoniae* in Egypt and Estimated Coverage by Different PCV Formulations (Adapted from El-Kholy et al.^[16])

Vaccine	Included Serotypes Found in Dataset	Estimated Coverage (%)
PCV13	1, 3, 4, 5, 6A/B, 7F, 9V, 14, 18C, 19A, 19F, 23F	77.6%
PCV15	PCV13 + 22F + 33F	79.2%
PCV20	PCV15 + 8, 10A, 11A, 12F, 15B	87.9%
PPSV23 (PPV23)	PCV20 + 2, 9N, 17F (20 not detected)	91.2%

a treatment or intervention. However, the impacts of PCV-13 vaccine utilization were much higher than those of PCV-10 as per CUA and CBA parameters^[42]. Also, cost-benefit analysis (CBA) indicated that rates of return from PCV-13 and PCV-10 reached 488% and 164%, respectively, compared to no program. PCV-13 vaccine seems to offer a highly recommended, cost-effective intervention in Egypt to induce a significant reduction in pneumococcal disease and deaths^[42].

As of December 2021, 147 countries (14 with PCV-13, 26 with PCV-10, and 7 with PCV-10 & PCV-13) have introduced these vaccines into their national immunization programs and prevented an estimated number of 250,000 deaths in children from 2000 to 2015, thanks to the financial support of the Global Alliance for Vaccines and Immunization (GAVI) offered for 60 of those countries^[43].

Since Africa accounts for around 20% of the world's population, with many of its countries suffering from economic difficulties, the European Union, the GAVI Vaccine Alliance and Africa Centers for Disease Control and Prevention [Africa CDC] are working together to support a sustained growth of drug and vaccine manufacture capacities in the continent. The Vaccine and Biotechnology City (VBC) is highly committed to manufacturing PCV-13 and other vaccines for the prevention of infectious diseases and developing solutions to improve the health outlook in the region and Africa.

4 DISCUSSION

This literature review examined studies published over the past twenty years regarding the worldwide prevalence of infections caused by *S. pneumoniae* and their effects on Egypt and its neighboring countries. Although *S. pneumoniae* may be regarded as a normal inhabitant of the nasopharynx, it can cause serious conditions by invading the sterile sites of the body, leading to bacteremia with pneumonia or bacteremia with meningitis. Pneumonia without bacteremia, bronchitis, otitis media, and sinusitis are considered non-invasive infections. Out of 2,297 records fetched from PubMed, Scopus, Web of Science and Google Scholar, 963 records were screened and 210 were assessed for eligibility.

Limited literature was found on otitis media and sinusitis caused by *S. pneumoniae*, probably due to their classification as non-invasive conditions, possible presence

of mixed bacterial infections, harshness of sampling techniques and uncommon clinical practice. Meanwhile, bloodstream infections caused by *S. pneumoniae* were also hard to detect by bacterial culture alone. This observation has been attributed to the prior use of antibiotics, low bacterial count outside the bacteremic phase and the presence of an autolysin that can kill the bacteria during the stationary growth phase. Among patients admitted to hospitals with CAP, only 7-13% of adults and 1-5% of children were reported to show positive blood cultures, particularly among severe cases^[44]. PCR was more sensitive but not commonly used in developing countries and peripheral laboratories^[7-9].

Diagnosis of the etiological agents of IPD is essential for the management of all cases, a challenging requirement, especially in children due to difficulties in specimen collection, potential contamination and misleading results^[44].

4.1 Burden of CAP

According to numerous research that looked into the epidemiology of IPD in hospital-based surveillance settings, the infection affects 152 million children under the age of five annually, with 10-20 million of those cases necessitating hospitalization^[10,11]. Also, based on WHO reports, pneumonia caused 3 million fatalities per year in 2019, with 14% of those deaths occurring in children under the age of five^[12]. This suggests pneumonia as the leading infectious cause of death for children under five, accounting for 740,180 fatalities^[12].

In 2020, the incidence of pneumonia in Egyptian children under five years old was 0.11-0.20 episodes per child/year, or around 20 million cases, with hospitalization rates of 10% and mortality rates of up to 19%^[14]. However, it is challenging to vaccinate against such infections due to the involvement and distribution of more than 100 *S. pneumoniae* serotypes that may or may not be cross reactive in IPD. *S. pneumoniae* was shown to undergo significant antigenic variation by subject age and geographic location^[16,19]. Because of this, there are several types of pneumococcal vaccines that are currently available and endow variable protective coverage depending on the involved serotypes. For instance, in 2012, the protective coverage reached 41.4%, 53.9%, and 67.2% in Lebanon for PCV-7, PCV-10, and PCV-13, respectively^[18]. Since PCVs only target a fraction of those numerous pneumococcal serotypes, serotype replacement; a crucial phenomenon

seen after the introduction of the pneumococcal vaccine must be monitored.

Nevertheless, a fraction of IPD (3-19%) was caused by NESp, particularly among infants, immunocompromised individuals, and the elderly^[4]. Although historically considered less virulent than encapsulated strains, accumulating evidence indicates that NESp can effectively colonize the nasopharynx, contribute to mucosal infections such as otitis media and conjunctivitis, and, less commonly, cause invasive disease. Their pathogenicity has been linked to alternative surface virulence factors, including pneumococcal surface protein K (PspK), as well as enhanced genetic adaptability and antimicrobial resistance potential^[4-6].

In Egypt, surveillance studies have primarily focused on capsular serotype distribution and consequently, reliable estimates of the proportion of pneumococcal disease attributable to NESp are currently unavailable. This represents an important knowledge gap and highlights the need for future molecular surveillance efforts.

It has been well documented that the immunological suppression of serotypes induced by one vaccine creates an ecological niche in the nasopharynx for non-vaccine serotypes that can then increase in carriage and disease incidence. In the developed European countries, serotypes of PCV-20 vaccine were only detected in 23.9% of adult CAP patients in Spain,^[19] and were represented in the PCV-13, PCV-15 and PCV-20 at 3.3%, 4.4% and 7.5%^[19]. These observations were due to serotype replacement and suggest the need for using pneumococcal vaccines of expanded serotype coverage^[25]. The same observation was reported in the United States with the detection of *S. pneumoniae* in 10.2% of the hospitalized adult CAP patients, including 3.0% with serotypes covered by PCV-13, 3.9% by PCV-15, and 5.7% by PCV-20^[25].

4.2 Pneumococcal Meningitis

According to the latest findings, there has been more than 1.2 million meningitis cases, with 300,000 deaths worldwide in 2021^[27]. The bacterium caused over 50% of meningitis infections in the United States alone in 2017^[1], and between 2008 and 2023, it was the primary cause of meningitis (59%), resulting in deaths of up to 11% (573/5,028)^[45]. In Europe and North America, *S. pneumoniae* was also the most common cause of meningitis^[28], followed by *Neisseria meningitidis* and other less common bacterial species^[30]. The regular use of meningococcal vaccinations may be the cause of the shift in the pattern of causative agents from *N. meningitidis* as a predominant causative agent to *S. pneumoniae* and other organisms^[31].

Likewise, in Egypt, the rising role of *S. pneumoniae* in bacterial meningitis has been confirmed over the years (2016-2023)^[33]. Although the organism was detected in

90% of the CSF samples, *N. meningitidis* and *H. influenzae* (serotype b and non-b) were only found in 5 and 1% of the samples, respectively. The data suggests the need for introducing pneumococcal vaccines in the country, not only because of CAP infection but also for preventing meningitis as a significant public health problem of endemic nature, with severe complications and high mortality rate.

4.3 Use of PCV-13 in the MENA Region and Efficacy

Overall, the most common serotypes of *S. pneumoniae* have been recently identified from the Nasopharynx and IPD in Egyptian children by El-Kholy et al.^[16], 2020. The estimated coverage percent by the different PCVs was found to be 77.6%, 79.2%, 87.9% and 91.2% for PCV-13, 15, 20 and 23, respectively (Table 3). It was clear that vaccines with higher valency resulted in broader serotype coverage, given laboratory monitoring and cost effectiveness considerations. However, the coverage provided by PCV-13 appears satisfactory (77.6%), since Egypt has not introduced this vaccine yet (Figure 2).

In addition, WHO did not define a single "accepted efficacy level" that every PCV must achieve. Instead, they rely on prequalification and evidence that a vaccine is safe, immunogenic, and provides protection using clinical effectiveness data. The global impact of 10- and 13-valent PCVs on pneumococcal meningitis has been studied in all ages in the PSERENADE project, and the results were published in 2025 showing 48-74% reduction of infection among susceptible subjects. Also, disease due to non-vaccine-type serotypes was minimal^[41].

4.4 Cost-Effectiveness

Studies from middle income countries found that PCV-13 vaccine introduction could significantly reduce IPD and the financial burden of its management^[36]. One study postulated that if PCV-13 covered 77% of a population, similar to DPT, it can highly reduce medical treatment expenses, prevent thousands of deaths per year, and support the life of poor families^[37]. Those results were consonant with other countries^[38,40].

So far, 147 countries have introduced the pneumococcal vaccines into their national immunization programs, preventing an estimated number of 250,000 deaths in children from 2000 to 2015 and a higher number may have been achieved in recent years^[43]. Hopefully, Egypt will join these countries soon, since the European Union, the GAVI Vaccine Alliance and Africa Centers for Disease Control and Prevention (Africa CDC) are fostering a growing program for the use and manufacture of vaccines in the continent. The Vaccines and Biotechnology City (VBC) plays part of this big plan along with other partners.

5 CONCLUSION

Pneumococcal disease represents a substantial public

health problem for children in Egypt and elsewhere. Available data suggest the use of relevant pneumococcal vaccines to reduce the burden of infection. A national vaccination strategy to reduce the disease burden among Egyptian children at high cost-effectiveness is necessary to protect the population against the deleterious effects of IPD.

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Ethical Statement

Not applicable.

Conflicts of Interest

The authors declared no conflict of interest.

Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Author Contribution

Wasfy MO and Elsayed M contributed equally to the conception, execution, data analysis, and preparation of this manuscript. Wasfy MO performed the final revisions and edits. Both authors reviewed and approved the final version of the manuscript.

Abbreviation List

CAP, Community-acquired pneumonia
CBA, Cost-benefit analysis
CSF, Cerebrospinal fluid
CUA, Cost-utility analysis
GAVI, Global Alliance for Vaccines and Immunization
ICERs, Incremental cost-effectiveness ratios
IPD, Invasive pneumococcal disease
NESp, Non-encapsulated *S. pneumoniae* strains
PCVs, Pneumococcal conjugate vaccines
QALY, Quality-adjusted life year
WHO, World Health Organization

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