Pneumococcal disease burden from an Indian perspective: Need for its prevention in pulmonology practice

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ABSTRACT

Globally, pneumococcal diseases are a significant public health concern. They are preventable and frequently occur among older adults. Major risk factors for the disease are extremes of age, alcohol intake, smoking, air pollution, and comorbid conditions (diabetes, chronic obstructive pulmonary disease, chronic kidney disease, liver disease, and heart disease). Risk factors, coupled with limited disease-burden data and the emergence of antibiotics resistance, are hindering the effective management of the disease in older adults. Various global guidelines recommend pneumococcal vaccines for the prevention of pneumococcal diseases, as they reduce disease burden, hospitalization, and mortality rates among patients with comorbid conditions. Besides being an integral part of childhood immunization, these vaccines are advocated by various Indian healthcare bodies/groups for older and younger adults with certain medical conditions. The article presents an overview of the closed-door discussion by the Indian pulmonary experts on the scientific evidence and clinical practice followed for the prevention of pneumococcal disease in India.

KEY WORDS: Chronic obstructive pulmonary disease, community-acquired pneumonia, comorbidity, mortality, pneumococcal conjugate vaccine, Streptococcus pneumoniae

INTRODUCTION

Pneumococcal diseases are a global health-care concern caused by the pathogen, Streptococcus pneumoniae (Pneumococcus); however, these diseases are preventable.1–3 Pneumococcal diseases are broadly classified into invasive and noninvasive forms. Invasive pneumococcal disease (IPD) is diagnosed when the pathogen is identified in normally sterile body fluids (cerebrospinal fluid, blood, and pericardial fluid) of an affected individual, for example, bacteremia, meningitis, etc. Non-IPD includes sinusitis, acute otitis media, and community-acquired pneumonia (CAP); the noninvasive form of pneumonia can change into...
the invasive form when coupled with bacteraemia.\textsuperscript{[11,4,5]} \textit{S. pneumoniae} exists in about 93 serotypes, characterized by a distinct polysaccharide capsule. Different serotypes present variations in colonizing and tissue invasiveness, thus leading to a difference in the biological behavior of the serotype. The pathogen colonizes the nasopharynx and through the transmission to the lower respiratory tract, leads to the development of pneumonia. Vaccination is used for disease prevention.\textsuperscript{[3-5]}

For this article, PubMed served as the primary electronic literature search engine. The international guidelines and Indian recommendations on pneumococcal disease prevention were also consulted. A thorough literature search was conducted to identify scientific literature written in English published between November 8, 1999 and November 9, 2018 using keywords antibiotics, comorbidity, consensus statement, COPD, epidemiology, for pneumococcal infections that were paired with terms such as \textit{S. pneumoniae}, herd immunity, immunogenicity, India, mortality, pneumococcal conjugate vaccine, pneumococcal polysaccharide vaccine, pollution, prevention, recommendations and guidelines, risk stacking, safety, and serotype.

In a pioneer attempt, we intend to summarize the scientific evidence on pneumococcal disease burden and its prevention through vaccination in India, discussed by a group of pulmonologists in a closed-door discussion. However, clinical judgment should rely upon the individual’s condition.

**BURDEN OF PNEUMOCOCCAL DISEASES**

According to the Global Burden of Disease (GBD) 2016 estimates, lower respiratory tract infections (LRI), defined as pneumonia or bronchiolitis, were the leading cause of mortality and morbidity worldwide. Approximately 2.38 million deaths resulted from LRI in 2016.\textsuperscript{[6]} \textit{S. pneumoniae} emerged as the leading cause of LRI morbidity and mortality globally, contributing to more deaths compared to all other etiologies combined in 2016 (1,189,937 deaths). The prevalence of LRI in all age groups was found to be highest in Sub-Saharan Africa, South Asia, and Southeast Asia.\textsuperscript{[7]} The number of deaths due to LRI among adults aged >70 years increased from 746,700 to 1,080,958 from the year 2000 to 2016.\textsuperscript{[8]} However, a reduction in mortality was observed in the under-5 year age group.\textsuperscript{[7]} In the 2017 GBD estimates, the incidence and mortality further registered substantial increases of about 26% and 33% among those aged 50–69 years and >70 years, respectively.\textsuperscript{[9]} According to the World Health Organization (WHO), IPD (e. g., meningitis, pneumonia, and sepsis) accounts for an estimated 600,000–800,000 cases of mortality among adults every year. The invasive form of the disease predominantly affects older adults with underlying comorbidities.\textsuperscript{[9,10]}

A recent population-based study conducted among American adults revealed the substantial burden of CAP in the country and estimated that >1.5 million adults are hospitalized annually due to the disease in the country. Of the hospitalized patients, an estimated 100,000 die during hospitalization, and approximately one out three patients die during subsequent years of hospitalization.\textsuperscript{[11]} Epidemiological studies from the European region conducted among the adult population reported the incidence rate of CAP in the range of 1.6–11.6/1000 individuals.\textsuperscript{[4]} Data available for the adult population report an IPD case fatality rate in the range of 26%–30% in the region.\textsuperscript{[9]} The WHO 2008 report revealed Asia to have the highest burden of pneumonia, with the Indian subcontinent contributing the largest share of the disease burden.\textsuperscript{[12]} Furthermore, results from an Indian prospective study revealed CAP to be the second-most common reason of death from infectious diseases in the region.\textsuperscript{[13]}

**EPIDEMIOLOGY OF PNEUMOCOCCAL DISEASES IN INDIA**

Various studies evaluating the clinical and bacteriological profiles for IPD across various parts of India showed the predominance of \textit{S. pneumoniae} in the region. Meningitis and pneumonia emerged as the most common clinical conditions and were found to have a high case fatality rate despite their treatment in hospital settings.\textsuperscript{[9,10,14-17]} A recent laboratory-based surveillance study on IPD conducted in a tertiary care setting among the adult population of India showed that \textit{S. pneumoniae}-positive cultures were characterized by serotype prevalence and antimicrobial resistance patterns.\textsuperscript{[18]} In line with the findings from the previous studies, pneumonia and meningitis were found to be the most common clinical conditions, accounting for 39% and 24.3% of total IPD cases, respectively.\textsuperscript{[18]} Furthermore, the highest IPD case fatality rates were observed for pneumococcal sepsicemia, with an unknown focus on infection, pneumonia, and meningitis.\textsuperscript{[18]} In contrast to previously reported findings, the most common serotypes found in the study were 1, 3, 5, 19F, 8, 14, 23F, 4, 19A, and 6B. These serotypes accounted for 54.9% of IPD cases, which shows a clear need for the addition of the 13-valent pneumococcal conjugate vaccine (PCV13) to cover all prevalent serotypes and provide the necessary protective serotype coverage in the country.\textsuperscript{[18]}

The study further noted an overall high resistance to erythromycin and co-trimoxazole antibiotics. Nonsusceptibility to penicillin and cefotaxime was observed for pneumococcal meningitis, thus making cephalosporin the drug of choice for the treatment of pneumococcal diseases.\textsuperscript{[18]} The susceptibility profiles of various antibiotics, over the study duration, are presented in Figure 1.\textsuperscript{[18]}

Other studies have also reported an overall high nonsusceptibility to co-trimoxazole and the slow
emergence of resistance to penicillin, tetracycline, and erythromycin.\textsuperscript{9,10.15,19}

**RISK FACTORS ASSOCIATED WITH HIGHER INCidence OF PNEUMOCOCCAL DISEASES**

Pneumococcal diseases are more prevalent in extremes of age, under-5 years, and older adults. With aging, complex changes in the immune system are seen in older adults (immunosenescence), which make them more vulnerable to pneumococcal and other infectious diseases.\textsuperscript{11} Moreover, compared to young adults, the aged adult population tends to have one or more chronic comorbidities that make the disease more severe.\textsuperscript{11}

In addition to age, an interplay of various risk factors places an individual at a higher risk of developing pneumococcal diseases. A case–control study by Jackson et al. conducted among immunocompetent older adults with CAP showed that factors such as low body weight, smoking, existing lung and heart diseases, and impaired body functions were independent risk factors for CAP.\textsuperscript{20} The study revealed that, if current smokers in the study stopped smoking, the burden of CAP would reduce by 2.4%. A systematic review including seven observational studies further highlighted smoking and intake of alcohol to be independent risk factors for IPD.\textsuperscript{21} The analysis indicated at least a two-times-higher risk for IPD among current smokers compared to nonsmokers.\textsuperscript{21} Alcohol intake was also a significant risk for IPD, with the risk of IPD ranging between 2.9 and 11.4 in adult individuals.\textsuperscript{21}

Environmental factors have a substantial impact on the pulmonary system. In a population-based study conducted among older adults, long-term exposure to pollutants (nitrogen dioxide and particulate matter) was found to be an independent risk factor for hospitalization due to CAP.\textsuperscript{22} Furthermore, in India, the detrimental impact of indoor pollution (biomass fuel combustion, tobacco smoke, and bioaerosols) cannot be ignored. Indoor pollutants aggravate lower respiratory tract ailments, further increasing the incidence of pneumonia among adults.\textsuperscript{23}

**EFFECT OF UNDERLYING COMORBID CONDITIONS**

A study by Jackson et al. revealed chronic cardiopulmonary disease to account for 42% of pneumonia cases in their study population.\textsuperscript{20} Furthermore, the severity of the underlying comorbid disease was found to be directly proportional to the risk of CAP among older adults.\textsuperscript{20} A nationwide cohort study based on a European registry assessed the 30-day mortality, hospitalization rate, and risk of subsequent hospitalization for COPD exacerbations with and without pneumonia in patients >40 years of age.\textsuperscript{24}

The study showed that around 36% of patients who were hospitalized for a first-time COPD exacerbation were diagnosed with pneumonia. This first-time pneumonia exacerbation further increased the hospitalization rate for successive COPD exacerbation and was associated with a high 30-day mortality rate among older adults.\textsuperscript{24} Similar findings were reflected in another prospective observational study, wherein mortality rates were found to be significantly higher for pneumonia-related exacerbations compared to pneumonia-unrelated exacerbations ($P < 0.001$).\textsuperscript{25}

A population-based study showed a significant association between asthma and the risk of IPD. Patients with asthma had a threefold increased risk of developing IPD, compared with patients without asthma.\textsuperscript{20} In another retrospective study, adults with asthma were found to have a six-fold higher risk of developing IPD and pneumococcal pneumonia compared to patients without asthma.\textsuperscript{27} A retrospective study by Shea et al. conducted in an adult population (>65 years) revealed that patients with asthma are at a 5.9- and 16.7-time higher risk of developing pneumococcal pneumonia and IPD, respectively, compared to healthy individuals.\textsuperscript{28}

While assessing the impact of various lung diseases on CAP outcomes, a Swiss case–control study conducted in an adult population showed a comparable occurrence rate of CAP complications in IPD patients and the control group; however, a significantly higher in-hospital mortality rate was observed among IPD patients compared to patients in the control group (16.3% vs. 6.8%).\textsuperscript{29}

In another retrospective, longitudinal American study, diabetic patients were found to be at higher risk of conditions, such as fibrosis, pneumonia, and COPD, compared to healthy individuals.\textsuperscript{30} The risk of pneumonia significantly increased with increasing HbA1c values.\textsuperscript{30} This rise in the risk of pneumococcal diseases in diabetic patients was due to the decrease in pulmonary function and immune response.\textsuperscript{30} A retrospective cohort study conducted among the Asian population highlighted CKD as another comorbid condition contributing to a higher risk of pneumonia. The study showed pneumonia incidence rates of 65.6 and 28.4/1000 person-years for patients with
and without CKD, respectively. The comorbid condition served as an independent contributor and increased the risk of both outpatient and inpatient pneumonia. The increased infection risk among CKD patients can be attributed to immune cell impairment (increased cytokines and neutrophil phagocytosis) observed in uremia. In a retrospective study by Shea et al., episodes of pneumococcal pneumonia and IPD were assessed for a duration of 1 year.

The study population consisted of healthy individuals, immunocompetent adults with chronic medical conditions (“at-risk” group), and immunocompromised adults (“high-risk” group). All-cause pneumonia rates were higher for the at-risk and high-risk populations when compared to healthy individuals across all age groups. In addition, all-cause pneumonia rates increased significantly with the accumulation of multiple risk factors/comorbidities (risk-stacking). The effect of various risk factors in the study is presented in Figure 2.

Findings from another retrospective study conducted among an adult population showed that individuals with two or more concurrent comorbid diseases had higher pneumococcal disease incidence rates compared to individuals with chronic high-risk conditions. In addition, the incidence rates of pneumococcal pneumonia, IPD, and all-cause pneumonia increased significantly with the accumulation of concurrent at-risk conditions. In a case–control American study conducted among unvaccinated adults (>50 years), the mortality rate increased with the stacking of risk factors (up to 6 factors), with each additional risk factor increasing the mortality rate by approximately 55%.

UNMET NEEDS AND TREATMENT CHALLENGES IN PNEUMOCOCCAL DISEASES

Prior to formulating policies on the management of a disease, a precise estimate of the disease burden and seroprevalence, as well as the antimicrobial susceptibility profile data for the region, is essential. Certainly, data on pneumococcal diseases in India are limited, especially for the older adult population. As the majority of CAP forms can be treated, accurate and timely diagnosis is required to optimize treatment. A sound understanding of causative pathogens is warranted. However, due to inadequate resources and the inconsistent quality of laboratory tests for disease-causing pathogens, diagnosis is a major challenge in the region. Advanced and speedy diagnostic tools will not only ensure selection of the correct treatment agent but will also ensure timely hospitalization in severe cases.

Apart from the challenges encountered in diagnosis, the prevalence of antibiotic-resistant strains of S. pneumoniae is increasing at an alarming rate in India proving to be the primary obstacle in the effective treatment of CAP. Despite resistance to penicillin being comparatively lower in India compared to the rest of the world, recent data indicate an increase in resistance to the treatment agent. In a surveillance study conducted over a period of 11 years in India, nonsusceptibility to penicillin among meningeal IPD cases was found to be 27.4%. Resistant strains lead to high rates of treatment failure, increase in the length of hospital stay, and increase in the risk of mortality among elderly individuals with underlying comorbid conditions. In the absence of new antibiotics, the treatment of pneumococcal diseases is a major challenge among older adults.

Against this backdrop, the prevention of risk factors assumes vital importance. The measures consist of reducing childhood wasting; lessening indoor and ambient air pollution; infection control practices; and attempts at mitigating the susceptibility to pneumococcal diseases by vaccination. Vaccination against pneumococcal diseases is a crucial preventive strategy and should be regarded as the key focus.

PNEUMOCOCCAL VACCINES IN PULMONARY PRACTICE

Pneumococcal vaccines vary based on the number of S. pneumoniae serotypes they contain and whether these serotypes are conjugated to a protein carrier or not. At present, two vaccines are used clinically and recommended globally: the previously introduced unconjugated 23-valent pneumococcal polysaccharide vaccine (PPSV23), introduced in 1983, and the recently introduced conjugated PCV13, introduced in 2009. The detailed characteristics of both vaccines are presented in Table 1.

WHAT DO THE VARIOUS PNEUMOCOCCAL VACCINES HAVE TO OFFER?

Vaccination has several benefits. In a population-based study conducted over a span of 2 years, CAP patients previously vaccinated with the PPSV23 were found to
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Table 1: Characteristics for pneumococcal vaccines

| Characteristics                          | PPSV23                                                                 | PCV13                                                                 |
|------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|
| Type of vaccine                          | Unconjugated capsular polysaccharide antigens                          | Capsular polysaccharides conjugated with a protein carrier             |
|                                          | Contains antigens from 23 common serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) | Contains antigens from 13 common serotypes (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) |
| Immune response                          | T‑cell-independent immune response (IgM antibody produced, response declines in 3-5 years, and no anamnestic response at revaccination) | T‑cell-dependent immune response (larger duration and boosting effect at revaccination) |
| Efficacy                                 | Considerable efficacy proven against IPD (50%‑70%) in immunocompetent elderly individuals | High efficacy (80%‑90%) against vaccine-type IPD proven in children |
|                                          | Unclear (null to small) efficacy against nonbacteremic pneumococcal pneumonia | At present, relatively small serotype coverage for IPD in the elderly (30%‑40%) |
|                                          | No efficacy demonstrated in reducing nasopharyngeal carriage           | Potential efficacy in reducing nasopharyngeal carriage                |
|                                          | No impact proved in reducing the overall pneumococcal disease burden    | Future reduction of vaccination impact in adults/elderly               |
|                                          |                                                                        | (because of indirect effects from the pediatric use of PCV13)          |

IPD: Invasive pneumococcal disease, IgM: Immunoglobulin M, PPSV23: 23-valent pneumococcal polysaccharide vaccine, PCV13: 13-valent pneumococcal conjugate vaccine

Table 1: Characteristics for pneumococcal vaccines

- **Type of vaccine**: PPSV23 contains unconjugated capsular polysaccharide antigens from 23 common serotypes, while PCV13 contains conjugated capsular polysaccharides with a protein carrier.
- **PPSV23**
  - Provides an initial immune response but response declines in 3-5 years, with no anamnestic effect occurring at revaccination.
  - Considerable efficacy proven against IPD in immunocompetent elderly individuals (50%-70%).
  - Unclear efficacy against nonbacteremic pneumococcal pneumonia.
  - No demonstrated efficacy in reducing nasopharyngeal carriage.
  - No impact on reducing overall pneumococcal disease burden.

- **PCV13**
  - Provides a T-cell-dependent immune response with larger duration and boosting effect at revaccination.
  - High efficacy (80%-90%) against vaccine-type IPD proven in children.
  - Potential efficacy in reducing nasopharyngeal carriage.
  - Future reduction of vaccination impact in adults/elderly due to indirect effects from pediatric use.

In a retrospective study conducted among elderly patients with COPD, vaccinated COPD patients had reduced hospitalization, lower mortality, and reduced direct medical care costs. The vaccine was associated with a 43% reduction in hospitalization for pneumonia.

**PLACE OF UNCONJUGATED AND CONJUGATED VACCINES IN THE WAKE OF EMERGING RECOMMENDATIONS**

Before discussing various recommendations and the schedule of pneumococcal immunization for adults in detail, it is pertinent to acknowledge the difference between the effectiveness of the PPSV23 and PCV13.

PPSV23 has been available for more than three decades and found to have a consistent protective effect against IPD and all-cause pneumonia among healthy adults. Evidence shows an effectiveness of 50%–80% against preventing IPD in adults with comorbid conditions. The vaccine has not shown risk reduction of CAP associated with seasonal influenza in adults. Furthermore, there is a dearth of robust evidence supporting protective effect of PPV23 in adults at highest risk of pneumococcal disease.

The key limitations associated with PPSV23 isolated us include the following: uncertain effectiveness for prevention against nonbacteremic pneumococcal pneumonia, hypo-responsiveness upon repeated administration, and a decrease in clinical protection with age (>65 years) in the adult population.

The PPSV23 is unable to provide long-lasting immunity to adult patients, with no anamnestic effect occurring postrevaccination. Immune response to the vaccine is also found to be specifically low in immunocompromised adults and adults with various underlying comorbid conditions.

According to a meta-analysis conducted by Huss et al., including 22 trials and assessing the clinical outcome of death and rates of pneumonia, little evidence was found in favor of the effectiveness of PPSV23 against pneumonia in elderly patients or adults with chronic illness.

The combined limitations of PPSV23 make the protection of the aging adult population from IPD a challenge.

PCV13, a relatively new vaccine, has proven its safety and efficacy in various clinical trials. In addition, it can address the unmet medical need of the PPSV23 by serving as a valuable pneumococcal vaccination option in older adults. The findings of the clinical trials summarized in Table 2 highlight how PCV13 exhibits a more robust or greater immune response compared to the PPSV23 in majority of shared pneumococcal serotypes.

The 5-year, randomized controlled, CAP Immunization Trial in Adults was a landmark study that highlighted the importance of PCV13 vaccine in adult immunization. The trial, conducted among > 80,000 adults (aged > 65 years), showed an efficacy of 46% (95% confidence interval [CI] 22%–63%) and 75% (95% CI 41%–91%) for PCV13 in relation to the prevention of vaccine-type pneumonia and IPD, respectively. The overall efficacy of PCV13 against pneumonia caused by S. pneumoniae was 31% (95% CI 10%–47%). The study helped in justifying the need for PCV13 in addition to the PPSV23 and served as the foundation for various recommendations for protecting the older adult population against pneumococcal diseases.

Findings from a study by Greenberg et al. conducted among treatment-naive adults revealed that an initial single dose of PCV13 amplifies the anti-pneumococcal response to subsequent administration of PPSV23 for many common vaccine serotypes. This occurs due to a recalled and augmented immune response by the conjugated PCV13.
Table 2: Effectiveness and safety profiles of pneumococcal vaccines

| Author              | Study population                     | Treatment/analysis (duration)                                                                 | Key finding/s                                                                 |
|--------------------|--------------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| McLaughlin et al.  | CAP patients aged ≥65 years           | Real-world observational analysis for PCV13                                               | The effectiveness of PCV13 against the vaccine-type CAP in adults              |
|                    |                                      |                                               | PCV13 effectiveness was 42.3% against VT-CAP in the age group with higher vaccine uptake |
| Prato et al.       | CAP patients aged ≥65 years           | Prospective, 2 years cohort study for PCV13                                               | PCV13 promisingly effective against all confirmed CAP                          |
| Solanki et al.     | Individuals aged 50-65 years          | Open-label, single-arm study for PCV13 (post hoc comparator studies enrolled PPSV23-naive adults aged 50-64 years) | PCV13 elicited a robust immune response                                        |
| Jackson et al.     | Age >70; previously vaccinated with PPSV23 at least 5 years earlier | Sequential vaccination separated by 1 year (study duration: 13 months): PPSV23→PCV13 PCV13→PCV13 | Safe and well tolerated in Indian adults aged 50-65 years                       |
| Jackson et al.     | Age 60-64 years, vaccine-naive        | Single dose of PCV13 versus PPSV23 (study duration: 12 months)                              | Group B had significantly higher OPA titers in 10 of 12 common serotypes      |
| Jackson et al.     | Vaccine-naive adults aged 60-64 years | Extension study (5 years) Repeat vaccination 4 years following initial vaccination: PCV13→PCV13 PCV13→PPSV23 PPSV23→PPSV23 | PCV13 had significantly higher 1-month postvaccination OPA titres in 8 of 12 common serotypes |
| Bonten et al.      | Adults aged >65 years                 | Randomized controlled trial PCV13 versus placebo (3 years)                                 | Repeat PCV13 had OPA titres significantly higher for 7 of 13 serotypes than after the initial vaccination |
| Greenberg et al.   | Vaccine-naive adults aged 60-64 years | Repeat vaccination 12 months following initial vaccination (3 arms): PCV13→PCV13 PCV13→PPSV23 PPSV23→PPSV23 | Repeat PPSV23 had OPA titres significantly lower for 9 of 13 serotypes than after the initial vaccination |

AE: Adverse event, CAP: Community-acquired pneumonia, OPA: Opsonophagocytic activity, PPSV23: 23-valent pneumococcal polysaccharide vaccine, PCV13: 13-valent pneumococcal conjugate vaccine, VT: Vaccine type, IPD: Invasive pneumococcal disease, →: Sequential vaccination, ↓: Decrease

vaccine when followed upon by sequential administration of PPSV23. On the contrary, an initial administration of PPSV23 before PCV13 results in a diminished response to subsequent administration of PCV13 for all the serotypes. The study helped in providing a reasonable rationale for the recommendation on first administering PCV13 followed by PPSV23.[56]

Furthermore, results from a double-blind, randomized trial evaluating the immunogenic response and safety profile of PCV13 coadministered with trivalent, inactivated influenza vaccine showed that both the vaccines could be safely coadministered in the adult population (>50 years).[57]

In light of increasing evidence that S. pneumoniae might be a coinfection or a follow-up infection to viral infections, it is pertinent to note that permissible immunogenic response and safety profile was shown by the coadministered PCV-13 and trivalent, inactivated influenza vaccine was demonstrated in older adults.[54,59]

The results from both the studies add value in a comprehensive immunization schema for older adults. As acceptable immunogenicity and tolerability profile are demonstrated by both the coadministered influenza vaccine and PCV, immunization for older adults becomes convenient with enhanced compliance.

PCV13 also has the potential to slow the rate of antibiotic resistance. The vaccine exerts this effect by slowing the spread of resistant pneumococcal serotypes (19A) and by preventing the disease in the first place, thereby eliminating the need for antibiotics.[40] A reduction in the rate of antibiotic-resistant infection among older adults was also observed in a laboratory-based study. The incidence rate of pneumococcal diseases caused by penicillin-resistant strains reduced to 8.4 from 16.4 cases/100,000. Furthermore, the rates of resistant pneumococcal disease caused by vaccine serotypes reduced by 87%.[60]

PCV13 immunization was also found to be relatively more cost-effective for immunocompromised individuals than the previously recommended vaccinations.[61] This benefit is especially noteworthy for developing nations such as India.

Hence, based on the overall scientific evidence for the PCV13 vaccine in the adult population, the Advisory Committee on Immunization Practices guidelines recommend administration of one dose of PCV13 in a sequential manner with the PPSV23 in high-risk individuals and all individuals aged >65 years (with or without risk conditions).[61]

Despite several limitations of PPSV23 vaccine in older adult, it is recommended along with PCV13 as a part of...
comprehensive immunization schema. It is sequentially administered after PCV13, in order to provide maximum coverage of disease-specific serotypes to healthy or at risk, immunocompromised older adults with underlying comorbid conditions.

**EVOLUTION OF GUIDELINES FROM A GLOBAL PERSPECTIVE**

Various guidelines have advocated the use of pneumococcal vaccines sequentially for preventing disease occurrence among older adults. The chronological evolution of pneumococcal vaccine recommendations from global advocacy groups is detailed in Table 3.\(^{62-65}\)

**WHERE DOES INDIA STAND WITH RESPECT TO PNEUMOCOCCAL DISEASE PREVENTION IN PULMONOLOGY PRACTICE?**

India has the highest mortality and morbidity due to IPD among adults aged >50 years.\(^{66}\) With the increase in the aging population and the rise in the incidence of comorbid conditions in the country, vaccination can play a crucial role in the prevention of pneumococcal diseases and in improving the quality of life of the at-risk population.\(^{66,67}\) Both PPSV23 and PCV13 are available in the country. At present, PCV13 is approved for use only in adults aged >50 years. Although the vaccines are recommended and advocated globally for the at-risk elderly population, their usage is suboptimal in the region and is majorly dependent on clinicians’ awareness of guidelines.\(^{66,67}\)

Hence, despite the increasing global clinical evidence on the benefits of these vaccines, India is lagging in implementing preventive steps for protecting its at-risk population from pneumococcal diseases.

In addition, there are several factors, leading to neglect of preventive care for the older population in the country. As with advancing age, the immunity is decreased, older adults are at higher risk of acquiring the pneumococcal infections. However, on the contrary, there is no defined immunization schedule for the older population in India.\(^{66}\) Furthermore, region specific evidence on modest coverage (57.9%) of *S. pneumoniae* serotypes by PPV23 vaccine in the adult population cannot be ignored.\(^{66}\)

In the light of the above discussion, it is crucial to set forth a comprehensive immunization schedule (PCV13/PPSV23) tailored to the Indian region, for protecting the elderly population of the country.

**GUIDELINES BY INDIAN BODIES FOR THE PREVENTION OF PNEUMOCOCCAL DISEASES**

Acknowledging the fact that adult immunization is as essential as childhood immunization, various Indian health-care groups, and bodies have proposed recommendations for pneumococcal vaccination among adults [Table 4].\(^{36,67,70,71}\)

Although the recommendations described above are put forward considering the global guideline and evidence perspective, it is pertinent to state that, these recommendations give due weightage to the current Indian clinical practice and consider the regulatory requirements in the country. In the absence of evidence-based India-specific guidelines for pneumococcal vaccination and scarcity of robust evidence for effectiveness and safety of pneumococcal vaccines in varied Indian population, the importance of these recommendations for limiting the consequences of pneumococcal disease in the region cannot be disregarded.

Furthermore, these recommendations will serve as an excellent base for structuring formal evidence-based guidelines by the pulmonary associations of the country.

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**Table 3: Chronological evolution of pneumococcal vaccine recommendations**

| Advocacy group/body | Recommendation/s |
|---------------------|------------------|
| NICE Guidelines for vaccination of COPD patients (NICE, UK 2010) | Pneumococcal vaccination and an annual influenza vaccination to be offered to all patients with COPD |
| ACIP, 2015 | Immune competent adults (≥65 years) | Never vaccinated with PCV13 or PPSV23 are recommended single-dose PCV13 followed by 1 dose of PPSV23 after a year |
| | Previously vaccinated with a dose of PPSV23 at ≥65 years are recommended PCV13 minimum a year after PPSV23 |
| | Previously vaccinated with a dose of PCV13 at age <65 years are recommended PPSV23 minimum a year after PCV13 |
| | PCV13 and PPSV23 recommended for all patients ≥65 years of age |
| | PPSV23 also recommended for younger COPD patients with significant comorbid conditions, including chronic heart or lung disease |
| GOLD, 2017 | PCV13 and PPSV23, recommended in patients with diabetes aged ≥65 years |
| ADA, 2017 | Recommend PCV23 and PCV13, routinely in patients with diabetes aged ≥65 years |

COPD: Chronic obstructive lung disease, PPV23: 23-valent pneumococcal polysaccharide vaccine, PCV13: 13-valent pneumococcal conjugate vaccine, NICE: National Institute for Health and Care Excellence, ACIPs: Advisory Committee on Immunization Practices, GOLD: Global Initiative for Chronic Obstructive Lung Disease, ADA: American Diabetes Association
Table 4: Pneumococcal immunization recommendations by various Indian groups

| Indian advocacy group/body | Recommendation/s |
|---------------------------|-------------------|
| API; 2014                 | PCV13 and PPSV23 recommended for all adults aged ≥65 years, as well as for diabetics, COPD, and smokers aged <65 years. A single dose of PPSV23 for adults <65 years with chronic heart (except hypertension)/loup/liver/ kidney disease, nephritic syndrome, diabetes, alcoholism, HIV infection, immunosuppressive conditions, anatomic/functional asplenia, or cochlear implant/CSF leak. |
| Geriatric Society of India (Indian Vaccine Advocacy Group; 2015) | PCV13 and PPSV23 for all adults aged ≥50 years and in those risk factors, such as chronic liver/kidney/ heart/lung conditions. |
| Indian Society of Nephrology (2016) | Patients with CKD, aged 19-64 years or ≥65 years: Are recommended single-dose PCV13 followed by 1 dose of PPSV23 ≥8 weeks and a single dose of PPSV23 ≥5 years later if they were never vaccinated or previously vaccinated with 1 dose PPSV23 ≥1 year ago, but never vaccinated with PCV13. Are recommended single-dose PCV13 if previously vaccinated with ≥1 dose of PCV13 (≥8 weeks ago), but never vaccinated with PPSV23. |
| Mass Gathering Advisory Board Consensus Recommendation (2016) | PCV13 might be recommended 4 weeks before undertaking Hajj. PPSV23 might be offered to patients on return from Hajj, depending on their risk status. The panel recommends: The use of PCV13 for adults ≥50 years followed by a dose of PPSV23 at least 1 year later (and at least 5 years after their previous PPSV23 dose) depending on the clinical judgment of the physician. PCV13 is available for vaccination of older adults and must be considered an important step for vaccinating older diabetes patients with age of ≥50 years. PPSV23 may be offered to immune-compromised patients with diabetes for additional coverage after PCV13. Repeated vaccination with PPSV23 must be avoided to prevent hyporesponsiveness. Clinical judgment in relation to individual subjects should be relied upon before these recommendations are put into practice. |
| Research Society for the Study of Diabetes in India (2016) | Are recommended single-dose PCV13 followed by 1 dose of PPSV23 ≥8 weeks and a single dose of PPSV23 ≥5 years later if they were never vaccinated or previously vaccinated with 1 dose PPSV23 ≥1 year ago, but never vaccinated with PCV13. PCV13 is available for vaccination of older adults and must be considered an important step for vaccinating older diabetes patients with age of ≥50 years. PPSV23 may be offered to immune-compromised patients with diabetes for additional coverage after PCV13. Repeated vaccination with PPSV23 must be avoided to prevent hyporesponsiveness. Clinical judgment in relation to individual subjects should be relied upon before these recommendations are put into practice. |

PCV: Pneumococcal conjugate vaccine, PPSV: Pneumococcal polysaccharide vaccine, HIV: Human immunodeficiency virus, API: Association of Physicians of India, CKD: Chronic kidney disease

FUTURE DIRECTIONS FOR PNEUMOCOCCAL DISEASE PREVENTION

Vaccination has an indisputable potential to reduce the global pneumococcal disease burden. Serotype-switching and replacement are significant causes of vaccine ineffectiveness. With >90 pneumococcal serotypes for the disease, the development of broad-spectrum vaccines covering the majority of serotypes would be a future direction for the effective prevention of pneumococcal diseases. In addition, the development of serotype-independent protein vaccines, which is still in the nascent stage and would further require the construction of a defined regulatory and licensing framework, is of paramount importance. Recent GBD data show a moderate reduction in mortality due to LRI among children aged <5 years, after the introduction of PCV in many countries. The finding, thus, suggests that a great deal of LRI burden could be averted by universal coverage of PCV.

SUMMARY AND CONCLUSION

Timely prevention is better than treatment for any disease; this is especially true for pneumococcal diseases. Pneumococcal diseases are a major challenge for developing countries such as India, which is already burdened with other communicable and noncommunicable diseases. Further, it is necessary to acknowledge that the presence of certain comorbid conditions places patients at high risk of developing pneumonia. Pneumococcal diseases can be prevented by offering effective vaccination. Pneumococcal vaccines have demonstrated safety and efficacy in various global clinical trials conducted among both children and adults. Consistent with global guideline recommendations, Indian health-care groups/bodies have recommended vaccination in diverse older adult population. However, pneumococcal vaccination usage is suboptimal in the region, which could be attributed to the absence of structured region-specific guidelines for the use of pneumococcal vaccine. This unmet need requires a primary address to not only reduce the burden of pneumococcal diseases, its associated mortality, its consequences on the Indian economy but also to empower the practicing clinicians in the country.

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There are no conflicts of interest.

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