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Vaccination in Adults with 23 valent Pneumococcal Polysaccharide Vaccine –ABC: Awareness, Benefits and Clinical Aspects

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ABSTRACT

Pneumococcus is an important cause of community acquired pneumonia and the commonest cause of community acquired bacterial pneumonia. It also causes invasive pneumococcal disease that increases hospitalization rates, economic burden, morbidity and mortality. Apart from children below 5 years, adults 65 years or more, and all adults with underlying medical conditions or immunodeficiency are at increased risk of pneumococcal infection. For these adult groups pneumococcal vaccination that includes the 23-valent polysaccharide vaccine (PPSV23) is recommended that has shown to reduce risk of severe pneumococcal pneumonia, invasive pneumococcal disease, hospitalization rates, and mortality. However, awareness and practical implementation of adult pneumococcal vaccination is concerningly low. Surveys, awareness programs, and counseling, at the community level, as well as with physicians in primary care, have shown significant improvements in adult pneumococcal vaccination rates.

Key words Pneumococcal vaccination, 23-valent polysaccharide vaccine, pneumococcal pneumonia, invasive pneumococcal disease, adult vaccination

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INTRODUCTION

Introduction and Epidemiology

Streptococcus pneumoniae, or Pneumococci, which are the common causative organisms of bacterial pneumonia, have their reservoir in the nasopharynx, and also cause otitis, sinusitis and nasopharyngitis. The bacteria spreads by the saliva or mucus from an infected person to people in close contact, by coughing or sneezing.[1] Invasive pneumococcal disease (IPD) most commonly manifests as meningitis or sepsis.

The global pneumonia burden is 400-450 million per year, with children constituting 150-160 million.[2] The global incidence of CAP (community acquired pneumonia) is 1.5 to 14 per 1000 person-years.[3] Hospitalizations rate in CAP is around 20-30% increasing with age to 67–75% in ≥ 65 years.[4] The case fatality rate ranges from 2 -20% reaching up to 50% in ICU patients and varies between healthcare settings, region, patient categories and age. Pneumonia is a major cause (4th leading cause) of death among all age groups, resulting in 3-4 million annual deaths.[5] India contributes about 23% of global pneumonia burden and 36% of WHO regional burden in patients under 5 years.[6,7] India's CAP burden is between 2-12 cases per 1000 person-years, with around 40-45 million CAP cases, and around 4-5 million CABP (community acquired bacterial pneumonia) annual cases. The reported case fatalities are 14%-30% in all CAP patients and 47% in severe/hospitalized CAP.[7]

Pneumococcus is the most common organism present in 10-40% of CAP and 70-80% of CABP, and is the leading cause of LRTI (lower respiratory tract infection) related morbidity and mortality.[3,6,7] The incidence rates of adult pneumococcal disease in India in 2018 were found to be 31.3%, 22.7%, and 13.9% among adults with CAP aged ≥60 years, 44–60 years, and 18–44 years.[8] Pneumococcal infections cause more than 1.5 million annual deaths worldwide, with majority of deaths occuring in developing countries.[9] Even in developed countries, invasive pneumococcal disease carries high mortality in certain population groups (like elderly people especially those living in institutions, and patients with comorbidities and immunodeficiencies). The mortality rates for pneumococcal disease varies from 5-10% in pneumonia to 15-20% in IPD.[1] Antibiotic resistance is a major hurdle in management of pneumococcal disease, and multidrug resistance is seen in one third of the S. pneumoniae isolates.[10]

Clinical Aspects and Risk Factors

The populations identified at high risk of pneumococcal disease include persons ≥ 65 years of age (responsible for 50% of hospitalizations), and young children (kills > 300,000 children under 5 years worldwide every year with most of these deaths occuring in developing countries). In adults, lifestyle issues like cigarette smoking, high alcohol intake, crowded living conditions and comorbidities like diabetes, lung diseases (COPD), as well as heart, liver and kidney disease, or chronic organ failure, are the recognized risk factors. People with asplenia, and cochlear implants or organ transplants, and conditions or therapies causing immunodeficiency, are also at higher risk.[1,11]

Diabetes

Pneumonia is the second most common cause of hospitalization in diabetic patients. *Streptococcus pneumoniae* is among the most commonly identified pathogens for pneumonia in diabetic patients. Diabetic patients >18 years are 3 times likely to contract pneumonia when compared with healthy people of the same age group, while diabetic patients >65 years are 3 times more likely to contract pneumonia compared with younger patients. Incidence of hospitalization due to pneumonia in adult diabetic patients compared with healthy adults is also 3-4 times higher.[12,13] Diabetes is not only associated with a higher risk of pneumococcal pneumonia but reported to have 3.5 times increased risk of invasive pneumococcal disease (IPD).[14] Among people with diabetes, death rates (mortality) for pneumococcal infection range from 21 to 36%.[15] A study reported CAP mortality rates of 17%, 23%, and 34% in non-diabetics, prediabetics and diabetics respectively (Figure 1a).[16]

COPD and Asthma

COPD and asthma (particularly asthma COPD overlap syndrome - ACOS) are risk factors for CAP especially in the elderly> 65 years. *S. pneumoniae* is the most common cause of CAP in patients with COPD and accounts for up to 43% of CAP cases.[17,18] The risk of contracting pneumococcal pneumonia is 7-8 times higher for COPD, and 6 times higher with asthma. Patients of COPD have 8 times higher risk of

hospitalization due to pneumococcal pneumonia than controls.[17] The relative risk (adjusted for age, race and other co-morbidities) of IPD, and mortality in IPD, is significantly higher in patients with COPD, as compared to otherwise healthy adults, around 5.6 and 2.8 times respectively (Figure 2a).[18] Risk factors in COPD patients for pneumonia include elderly, and presence of emphysema (lung involvement), low FEV1<60% and high BMI>22.

Diabetes as a comorbidity increases risk of COPD hospitalizations. The risk of pneumonia is higher for COPD- diabetic patients with or without complications compared with COPD without diabetes.[19] The risk of developing respiratory failure, kidney failure, and stroke is higher in COPD patients with diabetes as compared to COPD without diabetes.

Chronic Kidney Disease

Chronic kidney disease (CKD) is an independent risk factor for pneumonia with 1.97 times higher risk overall, 1.4 times higher risk for outpatient pneumonia and 2.17 times higher risk for inpatient pneumonia compared with patients without CKD.[20,21] CKD patients on dialysis have 16 times higher mortality rates due to respiratory infections compared to the general population. Community-acquired pneumonia in both dialysis patients and kidney transplant recipients is mainly caused by pneumococcus.

A study showed that the incidence rate of pneumonia in CKD compared to individuals without CKD (age/gender matched over 4 years from insurance database) was 65.6 and 28.4 per 1000 person-years respectively in patients with and without CKD, with the hospitalization rates going up to 43.3 per 1000 person-years in those with CKD compared to 16.6 per 1000 person-years in those without CKD (Figure 3a).[22] The overall incidence rate ratio of end stage renal disease (ESRD) in patients hospitalized was 23% higher in those with pneumococcal pneumonia than in those without (5.26 vs. 3.10 per 1000 person–years).[23]

COVID

Reports show that bacterial co-infection is also predominant in COVID-19 patients (COVID-19 associated secondary/co-infection prevalence is up to 45%). In the COVID pandemic, *S. pneumoniae* has been seen to be the most common coinfecting pathogen. Half of the COVID-19 mortality cases showed co-infection, and pneumonia-related COVID-19 mortality in patients >65 years was 23%. The weakening of immune function caused by COVID-19 remains a high-risk factor for pneumococcal infection. Pneumococcal disease and COVID-19 also have similar risk factors, and underlying medical conditions with COVID-19 and pneumococcal diseases increase the risk for severe illness at any age. COVID-19 is now considered a primary risk factor for pneumococcal pneumonia and invasive pneumococcal disease.[24]

Benefits of Pneumococcal Vaccination in Adults

The benefits of pneumococcal vaccination in adults have been well studied and documented. A retrospective study analysis of 450 adults > 50 years of age showed a 32% reduction in pneumococcal infections in the population that had received the pneumococcal vaccine in the preceding year.[25] In another large study, pneumococcal vaccine recipients were less likely to die of any cause during hospitalization than those with no record of vaccination (OR 0.5), even after adjustment for comorbid illnesses, age, smoking, other vaccines like flu and missing vaccination data.[26] Vaccination also lowered the risk of respiratory failure (adjusted OR, 0.67) and other complications, and reduced median length of hospital stay by 2 days, compared with those not vaccinated (P<.001). In-hospital survival was also seen to be higher at 2 months in those vaccinated as compared to unvaccinated (around 80% vs 50% respectively).[27]

Pneumococcal Polysaccharide Vaccine

Pneumococcus has many serotypes, identified by its capsular antigens: 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15,17F, 18C, 19A, 19F, 20, 22F, 23F, 33F serotypes that cause 90% of pneumococcal disease. The available vaccines in India include the 13-valent conjugate (PCV) and 23-valent polysaccharide (PPSV) vaccine. Adult pneumococcal vaccination with 23-valent pneumococcal polysaccharide vaccine has seen to significantly reduce IPD incidence by up to 80%.[28] In India currently two 23-valent pneumococcal polysaccharide vaccine (PPSV23) are approved and available: PNEUMOVAX®23 (Merck Sharp & Dohme Corp) and VAXIMUNE®23 (G.C. Chemie Pharmie Ltd).

Recommendations

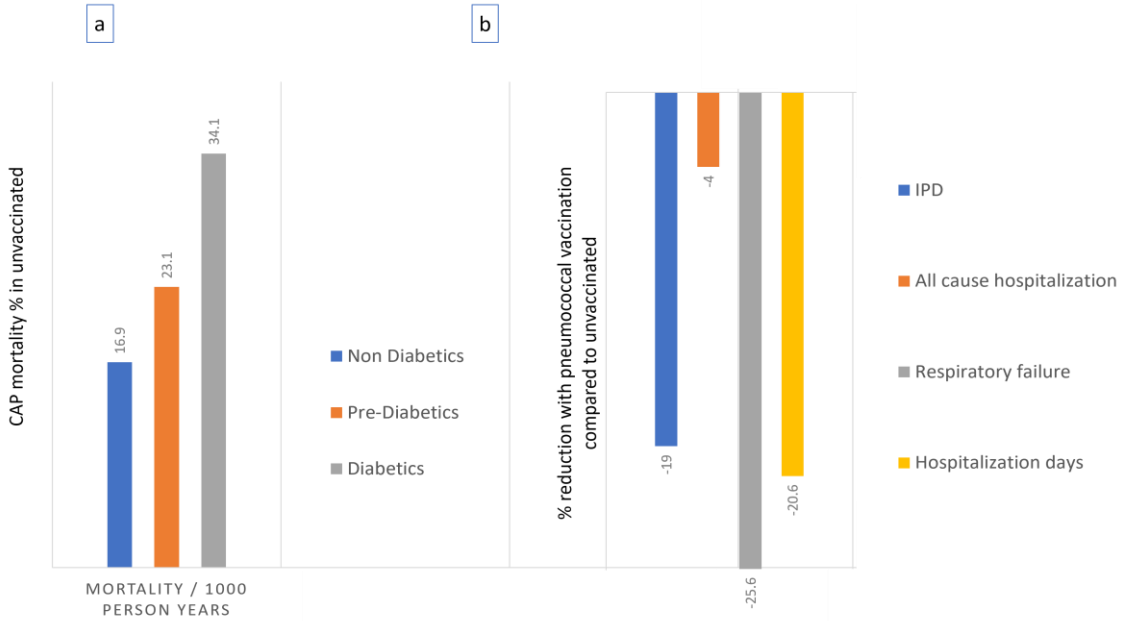
Currently, the Centers for Disease Control and Prevention - Advisory Committee on Immunization Practices (CDC-ACIP) advises high-risk patients who have not received prior immunization or whose prior vaccination status is unknown, that is all persons ≥ 65 years of age, and persons 2-64 years with underlying medical or immunocompromised conditions to receive pneumococcal vaccination.[29] Medical conditions include diabetes mellitus, chronic cardiovascular, pulmonary or liver disease, alcoholism, chronic renal failure, cerebrospinal fluid leaks, functional or anatomic asplenia and cochlear implants. Immunodeficient conditions mentioned are HIV + infection, leukemia, Hodgkin's disease/lymphoma, multiple myeloma, generalized malignancy, nephrotic syndrome, immunosuppressive chemotherapy, organ or bone marrow transplant, and sickle cell disease. The CDC-ACIP recommends using both PCV13 and PPSV23 with a gap of one year between the two irrespective of which is given first. The minimum interval can be reduced to 8 weeks, considered in adults with immunocompromising condition for giving PCV13 followed by PPSV23. Repeat dose of PPSV23 is not to be considered before 5 years of completion after previous dose.

The Indian consensus-based recommendations on pneumococcal vaccination for adult from the Clinical Practice Guidelines by the Indian Chest Society recommends 1 dose of PPSV23 in all healthy adults aged 65 or more. In this age group, for those with medical or immunocompromising conditions, recommendations to give either 1 dose PPSV23 or the same after a dose of PCV13, is to be considered on a case-to-case basis.[8] For adults <65 years with medical and/or immunocompromising conditions listed above, PCV13 should be given followed by PPSV23 after a year, and after minimum 8 weeks in those immunocompromised.

Diabetes

A study in diabetics showed that 23-valent pneumococcal polysaccharide vaccine (PPSV23) vaccinated group had reduced risks of IPD by 19%, reduced hospitalization rate by 20% with shortened length of hospitalization, and reduced respiratory failure rate by 25% (Figure 1b).[30] A study found the efficacy of PPV23 was found to be 84% in diabetic patients, and did not decline with increasing post-vaccination interval.[31] PPSV23 vaccination was effective in prevention of pneumococcal disease and reduction of medical utilization in diabetic especially in elderly aged 75 years and more. For adults with diabetes, the ADA recommends one dose of PPSV23 with another dose at ≥65 years of age, 5 years after the 1st dose.[32]

Figure 1: Pneumonia and Diabetes. (a) CAP mortality in unvaccinated.[16] (b) Clinical Benefit with Pneumococcal vaccination.[30]



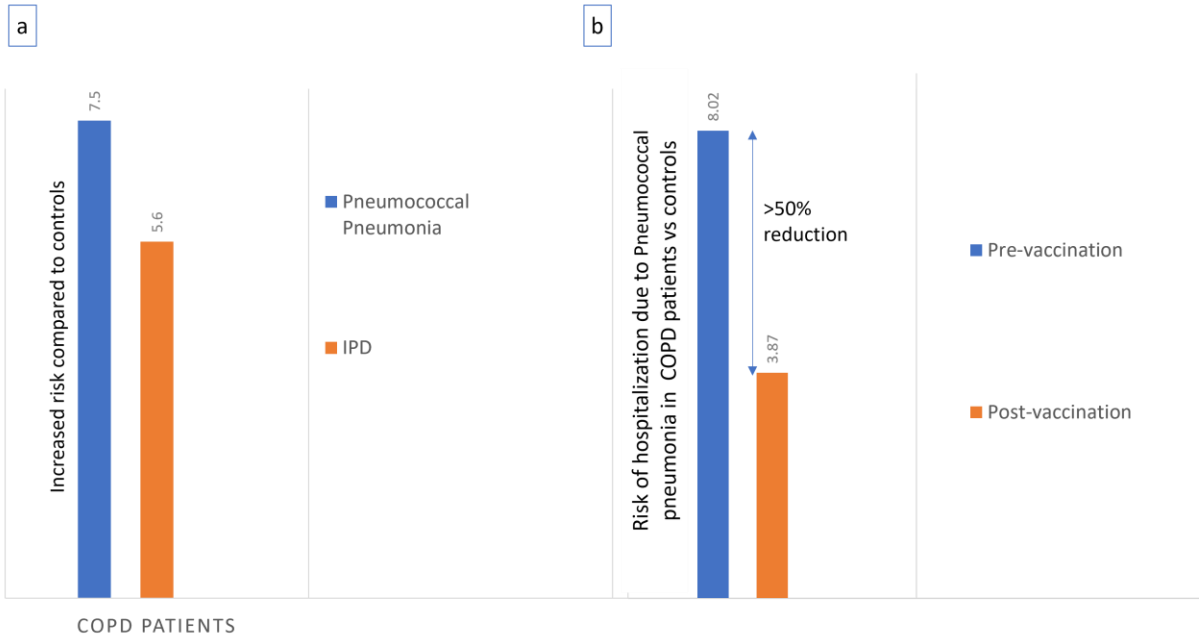
CAP – Community Acquired Pneumonia; IPD – Invasive Pneumococcal Disease

COPD

Patients with COPD and high risk for pneumonia, that is elderly, and presence of emphysema (lung involvement), low FEV1<60% and high BMI>22 is a very important group to be vaccinated. Vaccinated COPD patients with PPSV23 had a frequency of pneumonia of 28.4/1000 patient-years, while unvaccinated patients had a frequency of 62.4/1000 patient-years (p= 0.151) in a study.[33] Pneumococcal vaccination provides significant protection against CAP, decreases incidence of LRTI in COPD patients, reduces likelihood of a COPD exacerbation, and reduces hospitalization due to pneumococcal pneumonia. Risk of hospitalization due to pneumococcal pneumonia in COPD patients was 8 times the normal (control) pre-vaccination versus 3.7 times normal post-vaccination (Figure 2b).[34]

PPSV23 has been shown to reduce the incidence of community-acquired pneumonia in COPD patients <65 years, with FEV1< 40% predicted, or those with comorbidities (especially cardiac).[35] Patients of COPD with diabetes should be a high priority group for pneumococcal vaccination.

Figure 2: Pneumonia and COPD. (a) Increased Risk Compared to Controls.[18] (b) Hospitalization Risk Reduction with Pneumococcal vaccination[34]

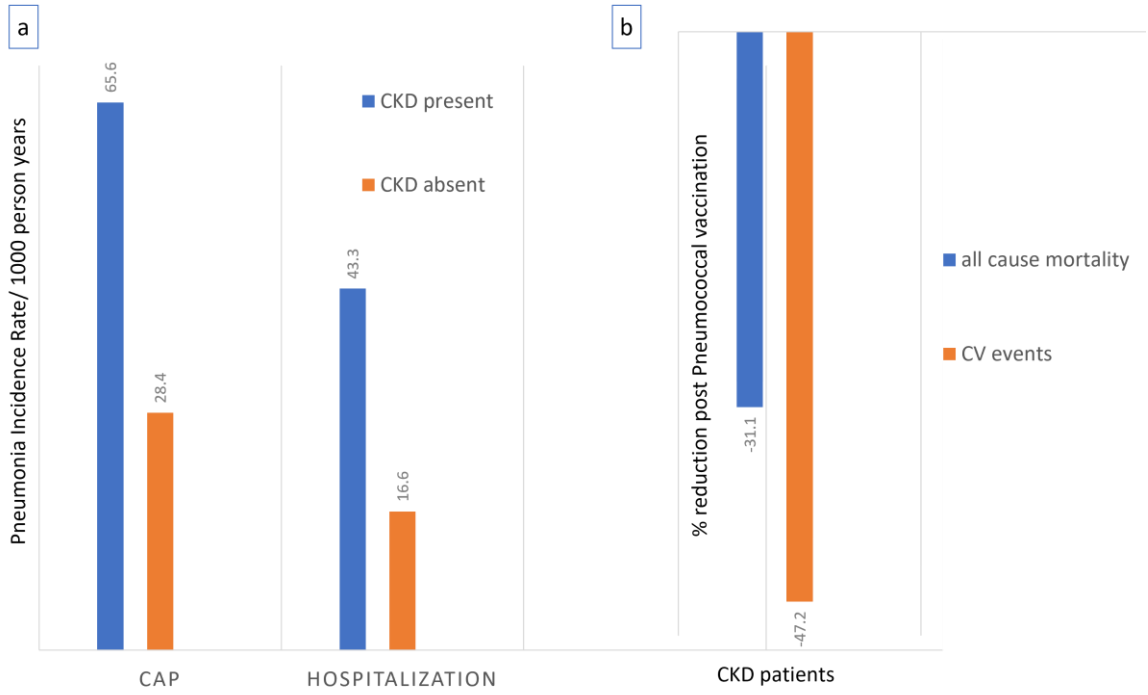


COPD – Chronic Obstructive Pulmonary Disease; IPD – Invasive Pneumococcal Disease

CKD

Pneumococcal vaccination is beneficial in CKD patients on dialysis, and has been seen to reduce all-cause mortality and cardiovascular events by around 31% and 42% respectively (Figure 3b).[36] In a population-based study of >27,000 patients aged ≥60 years, pneumococcal vaccination was associated with around 35% reduction in the adjusted risk of ischemic stroke.[37] In a large meta-analysis of >230,000 patients, pneumococcal vaccination was associated with significant reduction in the risk of acute coronary syndrome (ACS) events in patients aged ≥65 years.[38]

Figure 3: Pneumonia and CKD. (a) Increased Risk Compared to Controls.[22] (b) Cardiovascular and Mortality Risk Reduction with Pneumococcal vaccination[36]



CAP – Community Acquired Pneumonia; CKD – Chronic Kidney Disease; CV - Cardiovascular

Awareness and Implementation

While childhood immunization is well structured at the pediatrician and community level, adult vaccination awareness and implementation is often far below the required level. Pneumococcal vaccination is part of pediatric immunization programs in many countries including India. However adult pneumococcal vaccination in the elderly and mentioned high risk groups continues to be low. The national longitudinal ageing study in India, a national household survey conducted during 2017–2018. found the coverage of each of the studied vaccinations (flu, pneumococcal, typhoid and hepatitis B) >45 years was less than 2%, with pneumococcal vaccination standing at 0.6%.[39] Overall vaccine uptake was higher among respondents with cardiovascular disease, diabetes or lung disease than those without any of these. Uptake of influenza vaccine was higher among those with lung disease, while hepatitis B vaccine uptake was higher among those with cardiovascular disease or diabetes. Male sex, urban residence, wealthier household, more years of schooling, existing medical conditions and sedentary behaviors were significant predictors of vaccine uptake.

The lower rates of vaccination urge the necessity of nationwide vaccination strategies targeting these high-risk populations. Longer diabetes duration, higher education level, and older age were the common independent associates of having vaccination for both types of diabetes patients. The percentage of people with type II diabetes taking the flu and pneumococcal vaccine is around 21% and 7% respectively.[40]

In a survey in Ankara, Turkey in 200 people 65 years and older,2.5% people interviewed had received the pneumococcal vaccine.[41] It was seen that 59.8% who completed the questionnaire during a phone call and 81.6% who completed the questionnaire during a face-to-face interview went ahead and received the pneumococcal vaccine. As a result, the rates of pneumococcal vaccination increased from 2.5% before the study to 73.5% after the awareness and knowledge was imparted. This immensely stresses the importance of awareness and counseling in the community for improving adult immunization rates. In 2013, a large recent

retrospective cohort study across 255, 330 adults, aged 19-64, newly diagnosed with chronic (i.e. diabetes, chronic heart, lung, or liver disease, alcohol or tobacco dependence) or immunocompromising (i.e. cancer, chronic renal disease, organ transplant, HIV/AIDS, and asplenia) conditions, was conducted. Adults were followed up until the time of pneumococcal vaccination, death, or end of 2019, whichever came first. The study found that pneumococcal vaccination remains low and most adults diagnosed with underlying medical conditions are unvaccinated.[42] Vaccination rate increased from 6.0% to 21% among adults with 1 and 5-year follow-up respectively, after diagnosis of a medical condition. It took around 2.4 years for adults to receive vaccination after initial diagnosis.

Adults aged 50–64, 35–49 (relative to 19–34) years or those receiving flu vaccine, were more likely to receive pneumococcal vaccination.[42] Adults with HIV were more likely and those with other conditions were less likely to be vaccinated than those with diabetes.[42] Adults being diagnosed by other health providers were less likely to be vaccinated than those diagnosed by primary care providers, the latter emphasizing the importance of raising awareness with general and family physicians to aid counselling the elderly>65 years and those diagnosed with medical conditions to take the dose of PPSV23.[42]

Conclusion

Adult pneumococcal vaccination with 23-valent polysaccharide vaccine is recommended in all healthy adults 65 years or more, and adults with underlying medical conditions or immunodeficiency, with the latter group also to receive a preceding dose of PCV13 under advice. Such vaccination can help reduce risk of invasive pneumococcal disease and severe pneumonia in these high-risk groups, as well as its accompanying hospitalization, morbidity, and mortality. Low community awareness and lack of practical implementation of adult vaccination programs are the hurdles to be addressed. Certain conditions like diabetes, chronic kidney disease, and COPD, though common in the community, present with significant gaps not only in pneumococcal vaccination rates, but also in time to vaccination post diagnosis. Awareness programs at the level of the community as well as primary care physicians can help immensely in furthering adult pneumococcal vaccination implementation and its clinical benefits.

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