INTRODUCTION

Streptococcus pneumoniae (pneumococcus) is a Gram-positive diplococcus responsible for a spectrum of clinical syndrome including non-invasive infections such as paranasal sinusitis, otitis media and lobar pneumonia as well as invasive diseases, such as bacteremic pneumonia and meningitis. Pneumococcus is the most common cause of community-acquired pneumonia (CAP) in both ambulatory and hospitalized patients worldwide.

DISEASE BURDEN

After nearly 7 decades of introduction of safe antibiotics, diseases caused by S. pneumoniae continue to cause substantial morbidity and mortality globally, particularly among children and elderly. In the United States, approximately 500,000 cases of pneumonia, 50,000 episodes of bacteremia and 3000 cases of bacterial meningitis are attributed to S. pneumoniae each year, with a case-fatality rate of 5-7%, 20% and 30% respectively. In Europe, the incidence of CAP due to S. pneumoniae appears to be higher than in other continents. In developing countries such as India, there are no population-based data on the burden of pneumococcal disease among adults; however, indirect evidence suggests a high burden of disease. The only available nationally representative data on pneumococcal infections in India come from the Invasive Bacterial Infection Surveillance (IBIS) study conducted by the International Clinical Epidemiology Network (INCLEN). In this prospective multicentre hospital surveillance, the pneumococcal pneumonia, bacteraemia, and meningitis were associated with case-fatality rates of 19%, 21%, and 34% respectively. Further, about one-third of the patients (103 of 314) with proven IPD were younger than 5 years; and about 23% (69 of 304) were older than 50 years. Serotype 1 was the most common followed by serotypes 6, 19, 7, 5, 15, 4, 29, 14, and 23, in the descending order. The sensitivity of conventionally employed techniques for the diagnosis of pneumococcal infection, such as culture and antigen detection, is known to be notoriously low, and hence the figures emerging from the studies grossly underestimate the true burden of pneumococcal disease. Rather, the proportion of pneumonia cases prevented by vaccination may present a better estimate of the true burden of the disease (vaccine probe concept).

RISK FACTORS

Age is the most important risk factor for pneumococcal infections. Highest incidence is among children less than 5 years and elderly. However, pneumococcal infection and IPD may be seen in other age groups, particularly in presence of risk factors. The list of risk factors is long and the common predisposing factors include presence of chronic respiratory diseases (chronic obstructive pulmonary disease, bronchiectasis, severe asthma), other chronic systemic diseases (diabetes mellitus, ischemic heart disease, heart failure, cirrhosis of liver, or chronic renal failure); hyposplenism (post-splenectomy, sickle cell disease, or congenital); human immunodeficiency virus infection or other immunodeficiency states (organ or bone marrow transplantation, alcoholism, haematological malignancies).

PNEUMOCOCCAL VACCINES

A century ago, in 1911, the first clinical trial of pneumococcal vaccine was conducted among mine
workers in South Africa by Sir Almroth Wright. After initial setbacks and subsequent availability of new antibiotics, the interest in prevention of pneumococcal disease waned. A renewed interest in 1970s spurred development of the current 23-valent pneumococcal polysaccharide vaccine (PPV23) in 1983. The vaccine is composed of the capsular polysaccharides of the 23 most prevalent serotypes, which account for approximately 90% of all pneumococcal infections. A significant breakthrough impacting the burden of pneumococcal disease came with the licensing of a protein conjugate heptavalent vaccine (PCV7) in the year 2000. Three pneumococcal conjugate vaccines covering 7, 10 and 13 serotypes (PCV7, 10 and 13) are available presently; however, they are not currently recommended for use in adults. Salient features of PPV23 are shown in Table 1.

Whilst PPV23 has the potential to prevent disease and death, the degree of protection afforded against various clinical endpoints and within different population groups remains debatable. Indeed, meta-analyses of the efficacy of PPV in adults have produced varied results depending on the trials included for the study. The testimonial to the fact is that more than 15 meta-analyses with conflicting results have been published so far on the efficacy of PPV in adults. Salient features of PPV23 are shown in Table 1.

RECOMMENDATIONS & GUIDELINES

Guidelines for PPV23 in adults have been in place in developed countries for more than a decade now. Current recommendations of the Advisory Committee on Immunization Practices (ACIP) of the Department of Health and Human services, the United States of America, call for universal vaccination at age 65. In addition, younger patients (19-64 years) with risk factors should receive the vaccination (Table 2). Compared with the 1997 ACIP recommendations, the new guidelines now include smoking and asthma as indications for which PPV23 vaccination is recommended.

The ACIP also recommends one time revaccination with PPV after 5 years in patients with chronic renal failure, nephrotic syndrome, functional or anatomic asplenia, and immunosuppressive conditions. It recommends revaccination of persons aged 65 years or more if they were vaccinated before 5 years or earlier and were under 65 years at the time of first PPV administration.

World Health Organization (WHO) in its position paper in 2008 observed that “in resource-limited settings where there are many competing health priorities, the evidence does not support routine immunization of the elderly and high-risk populations with PPV23.” Cochrane meta-analyses (2008) supported the use of PPV23 to prevent IPD in adults, particularly otherwise healthy adults, in developed and developing country settings. It did not support the routine use of the vaccine to prevent all-cause pneumonia or mortality.

In India, the Association of Physicians of India convened an Expert Group for formulating guidelines for adult immunization for Indian scenario in 2009. The group observed that the available evidence is insufficient to recommend routine use of PPV in adults. Although PPV is efficacious in preventing invasive pneumococcal disease among adults, routine PPV administrations to adults is not likely to be cost-effective in India. The group recommended vaccination in patients undergoing splenectomy (preferably at least 2 weeks prior to splenectomy) (Level IV, Grade C); and one-time revaccination after 5 years in these patients. The Expert Group also noted that
currently, there is no evidence to support the efficacy of PPV in preventing invasive pneumococcal disease in populations considered at high-risk, such as healthy elderly (aged 65 years and above); patients suffering from chronic organ failure; diabetes mellitus, nephrotic syndrome; or immunodeficiency (Level Ia; Grade A).

CURRENT EVIDENCE

After three decades of existence and more than a dozen meta-analyses and systematic reviews on the vaccine, the indications for administration remain an area of debate. This has resulted in multiple recommendations and guidelines for different resource-settings.7-9,11 The effectiveness of PPV against pneumococcal pneumonia, IPD and mortality is controversial and various systematic reviews and meta-analyses have reached to opposing conclusions with regards to various clinical end-points.

Multitude of problems contribute to the difficulty in measuring the efficacy of this vaccine, that includes the low frequency of the most specific outcome (IPD), the inconsistency of the diagnostic criteria for common outcomes (pneumococcal pneumonia), and the likelihood that efficacy may vary with age and the presence and severity of various underlying conditions associated with an increased risk of pneumococcal disease. Majority of observational trials have reported large protective effects in contrast to clinical trials.12-14 The conflicting results between observational studies and clinical trials illustrate the fallacy in interpretation of the results from studies at risk of bias. Further, many trials, particularly older research, do not adequately report study methodology.

Two comprehensive meta-analyses of the studies assessing PPV vaccine efficacy and effectiveness have been reported in the last 5-years.10,15 The meta-analysis for Cochrane Database of Systematic Reviews in 2008 included 15 randomized controlled trials and 7 nonrandomized studies involving 48,656 and 62,294 patients, respectively.10 The results indicated that the pneumococcal vaccine was strongly effective against invasive pneumococcal disease both in RCTs and non-RCTs (odds ratio 0.26, 95% CI 0.15-0.46 and 0.48, 95% CI 0.37-0.61, respectively). The vaccine also reduced the risk for pneumonia from any cause; however, there was significant heterogeneity between individual studies in this outcome precluding any definite conclusion regarding efficacy against pneumonia. The vaccine did not significantly reduce the risk for all-cause mortality (odds ratio 0.87, 95% CI 0.69-1.10).

On subgroup analyses, PPV was found to be protective against IPD (only one RCT) as well as all-cause pneumonia (four RCTs) among adults in low-income countries (odds ratio 0.26, CI 0.15-0.46 and 0.54, CI 0.43-0.67, respectively). However, there was no evidence for protection against IPD or all-cause pneumonia among adults with chronic diseases in high income countries (odds ratio 1.56, CI 0.35-0.94 and 0.97, CI 0.65-1.46, respectively).

In 2009, Huss et al. reported a systematic review and meta-analysis focused on randomized clinical trials taking the quality of trials into account.15 The study included 22 trials involving 1,015,07 participants. One third of research was completed in countries with a low median income, and nearly 60% of research focused on patients at high risk for pneumonia. One third of the trials were double-blind, and another third were open label. In studies reporting pneumonia outcomes, the diagnosis was most often confirmed with radiology and bacterial culture. The outcomes measures studied included pneumococcal pneumonia, any pneumonia, bronchitis, invasive pneumococcal disease, death from pneumonia, death from pneumococcal disease and overall mortality. The results of the meta-analysis indicated that the vaccine was effective in reducing the risk for presumptive pneumococcal pneumonia (relative risk 0.64, CI 0.43-0.96) and all-cause pneumonia (relative risk 0.73, CI 0.56-0.94). However, vaccination was not significantly effective in reducing the risk for bacteremia (0.90, CI 0.46-1.77), bronchitis (0.92, CI 0.76-1.12), death from pneumococcal infection (0.93, CI 0.29-3.05), or overall mortality (0.97, CI 0.87-1.09). The authors emphasized that among higher-quality trials, defined by being double-blind or having adequate concealment of treatment allocation, there was no significant benefit associated with the use of the vaccine. Further, the pneumococcal vaccine was not effective among those patients for whom it was intended, the elderly or chronically ill.

In a nutshell, the results of various studies are conflicting; however, it is generally agreed that vaccination does not protect from pneumonia or decrease all-cause mortality. Further, the previous reports of benefit in IPD are challenged by the results of the latest meta-analysis.

FUTURE DIRECTION

Research is needed in India to address the complete lack of population-based data on the risk of pneumococcal infections in adults, particularly high-risk groups. Further, continuous surveillance of the infecting serotypes is also required. More evidence is needed on the efficacy of PPV in high-risk populations such as HIV infected persons and those with chronic diseases living in developing countries such as India. More importantly, data on cost-effectiveness of PPV in the Indian setting are required to formulate any India-specific guidelines on pneumococcal vaccination.

The recent studies have fuelled scepticism about the effectiveness and efficacy of the PPV, especially in the elderly adults. The remarkable success of protein-conjugate vaccines among young children has renewed interest and hopes for possible use of these vaccines in adults. In contrast to the 23-valent non-conjugated vaccine, the conjugated vaccines
activate B- and T-cell leading to immune memory. They elicit strong adaptive and booster response. Although earlier PCV formulations did not consistently demonstrate higher antibody responses in older adults, compared with responses to PPV, the PCV7 formulation have shown such differences.\(^{16,17}\) The suggested advantages of PCVs in elderly adults are higher levels of protection against the vaccine serotypes and the ability to prolong the duration of protection by use of repeated vaccinations over time.\(^{16,17}\) Low serotype coverage is the major limitation of PCV. The 13-valent PCV, which offers greater serotype coverage than PCV7, is currently being evaluated in clinical trials in healthy adults.\(^{18,19}\) However, the phenomenon of serotype replacement in which decreases in disease due to vaccine-type *S. pneumoniae* are counterbalanced by increases in disease due to non-vaccine serotypes, may ultimately limit the protection offered by serotype-specific vaccines.\(^{17}\) Future vaccine development may include a number of protein-based pneumococcal vaccine candidates which offer the potential advantage of serotype-independent protection.\(^{20}\)

Although PPV23 vaccination is recommended for a large number of indications in the developed countries; the practice is poorly supported by existing evidence. Going forward, availability of better pneumococcal vaccine preparations or more evidence regarding the efficacy/cost-effectiveness of PPV will decide the future perspective of pneumococcal vaccination in adults.

**ACKNOWLEDGEMENTS**

MS is supported by the Scientists’ Pool Scheme of Scientific and Industrial Research (CSIR), Government of India.

**CONFLICTS OF INTEREST**

None

**REFERENCES**