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REVIEW

Review: Current and new generation pneumococcal vaccines

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Summary Pneumococcal polysaccharide vaccines (PPVs) and conjugate vaccines (PCVs), of which PPV23 and PCV13 are the current front runners, have had a significant, beneficial impact on public health. With regard to PPV23, there has been some debate, however, about its protective efficacy against all-cause pneumonia, as opposed to invasive pneumococcal disease, in high-risk cases. PCVs, on the other hand, have been included in many national immunisation programmes for prevention of severe pneumococcal disease in infants and young children, as well as for adults in various high-risk categories. Although innovative and effective, the protective efficacy of PCVs, the composition of which is based on the geographic prevalence and virulence of pneumococcal serotypes, is limited due to colonisation of the nasopharynx with non-vaccine serotypes. This phenomenon of serotype replacement has provided the impetus for development of new generation recombinant protein and whole cell pneumococcal vaccines with the potential to provide serotype-independent protection. In addition to an overview of the successes and limitations of PPVs and PCVs, this review is focused on emerging and pipeline protein-based and whole cell vaccines, preceded by a consideration of conserved pneumococcal virulence factors which are potential vaccine candidates.
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Streptococcus pneumoniae (pneumococcus) — the organism

The pneumococcus is a Gram-positive diplococcus, of which there are more than 90 serotypes known, not all of which are pathogenic in man.[1,2] The natural reservoir for the microorganism is the human nasopharynx, and nasopharyngeal carriage is not only an essential precursor of active infection, but also a source of transmission of the pneumococcus.[1–3] The organism has a myriad of virulence factors that allow it on one hand to successfully colonise the nasopharynx of the human host, evading the host's immune response, and on the other hand to cause active infection, including invasive disease.[1,2]

One of the most important virulence factors of the pneumococcus is its polysaccharide capsule.[1,2] Each of the serotypes has a chemically distinct polysaccharide capsule and the overall contribution of the capsule to virulence of the pneumococcus appears to vary with its composition.[1,3] The capsule is a primary virulence factor, enabling the organism to evade phagocytosis.[2,3] The serotype of the organism affects various aspects of pneumococcal disease pathogenesis, as well as likely susceptibility or resistance of the isolate to antimicrobial agents, and while serotypes differ in prevalence and in their tendency to cause either mucosal colonisation or invasive disease the most common serotypes associated with carriage or invasive disease are geographically fairly consistent.[3] Importantly, the capsular polysaccharides are immunogenic, inducing antibodies which are protective against pneumococcal infection, this being the basis of current vaccines.[4]

The burden of pneumococcal disease

It is clearly evident from a number of recent reviews that infections with *S. pneumoniae* (pneumococcus) continue to be associated with considerable morbidity and mortality worldwide, and that despite significant advances in medicine, a number of challenges remain with regard to diagnosis, treatment and prevention.[5–9]

The pneumococcus can cause non-invasive or invasive disease (organism isolated from a normally sterile body site)[5,8] and is a common cause of community-acquired pneumonia (CAP), meningitis and bacteraemia in both children and in adults.[10] With regard to all-cause CAP, it is clear that the pneumococcus is the most commonly isolated pathogen, irrespective of whether the infection is either mild enough to be treated at home or requires hospitalisation or even intensive care unit admission, also irrespective of the severity of infection such as assessed by the Pneumonia Severity Index (PSI).[8,11] However, in a meta-analysis of studies from Europe it is clear that there are regional differences in the prevalence of the pneumococcus as a cause of CAP, depending on both the treatment setting and diagnostic approach.[12] However, since the pneumococcus is the most important pathogen in most situations, the data on the epidemiology of CAP to a large extent mirrors that of pneumococcal pneumonia.[8]

A number of additional reviews confirm the enormous clinical and economic burden caused by CAP in North America, Europe, the Asia Pacific region, Latin America, and elsewhere,[2,13–15] with pneumococcal disease *per se* having been documented to carry high economic costs in the United States and in Europe.[8,16] There have certainly been changes in the epidemiology of invasive pneumococcal disease (IPD) in adults in the era of paediatric pneumococcal conjugate vaccines, with their use in children certainly having benefitted older adults (decreases in the incidence of IPD in adults $\geq$50 years of age), indirectly through herd protection, more so in healthier persons than in adults with certain comorbid conditions.[17]

Yet the true burden of pneumococcal pneumonia is likely to be considerably underestimated since many studies reporting on the incidence of pneumococcal disease report on invasive disease, given the difficulties in diagnosing non-invasive pneumococcal infections.[7] Said and colleagues conducted a systematic literature review of studies providing information on the performance of various laboratory tests used for detecting pneumococcal pneumonia (urine, sputum, blood culture).[7] The authors concluded that for every case of bacteraemic pneumococcal pneumonia there were likely to be at least 3 additional cases of non-invasive pneumococcal pneumonia. One additional factor that needs to be considered with regard to the burden of pneumococcal infections is the increasing occurrence of antimicrobial resistance, although there is some debate as to the true impact of resistance on outcome of infections with antibiotic-resistant serotypes, at least in the case of the beta-lactam agents commonly used.[2,6,18,19]

Risk factors for pneumococcal infection

The risk factors for pneumococcal infection, including CAP and IPD, have been well characterised and are extensively reviewed elsewhere.[2,8,10,11,20] Major risk factors include:

- demographic factors (age, gender)
- ethnic and socioeconomic factors
- living circumstances
- substance use (alcohol and smoking)
- comorbid medical conditions
- viral respiratory infections, especially influenza
- immunosuppression (including human immunodeficiency virus (HIV) infection and organ transplant recipients)
- various malignancies
- asplenia or splenic dysfunction (including sickle cell disease)
- certain medications

With regard to age as a risk factor, both the young and the elderly are at increased risk of pneumococcal infections and with the aging of the population in countries such as the United States, decision analytical models suggest that there is likely to be significant increases in pneumococcal pneumonia hospitalisations and costs into the future.[21] Clearly, many of the risk factors for infection are also risk factors for mortality, identifying those patients for whom pneumococcal vaccination is clearly beneficial.[22]

Mortality from pneumococcal infection

CAP and pneumococcal infections are associated with mortality, both short-term and long-term, which varies

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