

Pneumococcal disease: Epidemiology and new vaccines

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ABSTRACT

Streptococcus pneumoniae causes invasive and noninvasive infections. Among infectious diseases, invasive pneumococcal disease (IPD) is a leading cause of morbidity and mortality in children and adults. Community acquired pneumonia in adults is the main presentation of non-IPD and is the most common infectious source of IPD. The incidence, severity and mortality of pneumococcal disease vary widely depending on several factors, some are host related, and others are organism related. After introduction of the vaccine, rates of pneumococcal disease caused by vaccine serotypes have dramatically decreased among vaccinated children, nonvaccinated children, and adults. However, incidents of pneumococcal disease due to new emerging nonvaccine serotypes and antimicrobial resistance have increased. Continuous monitoring and surveillance studies focused on the clinical and molecular epidemiology of pneumococcal disease will be required to understand the impact of the new vaccines and possible alteration in the pattern of disease presentation.

Key words: Pneumococcal disease, pneumococcus, *Streptococcus pneumoniae*

INTRODUCTION

Pneumococcal disease is a major public health problem worldwide. The clinical spectrum of pneumococcal infections ranges from acute otitis media to pneumonia and invasive pneumococcal disease (IPD) such as meningitis and septicemia. Currently, 93 serotypes and 46 serogroups have been documented, and the last serotypes reported are serotype 6C, 6D and 11E.^[1-3] Approximately, 10 serogroups are responsible for most of the pneumococcal infections. The disease most frequently affects individuals at extremes of age and those with immunological impairment (children

or adults).^[4] Nevertheless, a significant proportion of adults who develop pneumococcal infection particularly IPD have no apparent preexisting risk factor.^[5] Most cases of pneumococcal disease are caused by a limited number of serotypes that vary in nasopharyngeal carriage, infectivity and virulence. Recent epidemiological study estimates about 1.6 million people, including up to 1 million children aged <5 years, die of IPD every year mainly in developing countries.^[6,7] Case fatality rates ranged from 10% to 30% in adults with IPD but are much lower (<3%) in children.^[6]

Pneumococcal vaccines effectively prevent the more severe pneumococcal disease caused by vaccine serotypes and also reduce the risk of nasopharyngeal colonization by the serotypes. Widespread use of heptavalent pneumococcal conjugate vaccine 7 (PCV7) for the pediatric population has significantly decreased the incidence of IPD in both children and nonvaccinated adults (by herd immunity).^[8-10] Unfortunately, non-PCV7 serotypes have relatively increased among asymptomatic carriers, and the incidence of IPD due to these serotypes are increasing globally.^[11,12] In 2011, a new 13-valent PCV was suggested for the prevention of IPD in persons 50 years and older in Europe, and in 2013, the suggestion was expanded to cover all ages. Recent studies on the impact of PCV13 vaccine report a lower incidence of pneumococcal disease by vaccine serotypes and the relative

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increase of pneumococcal disease by nonvaccine serotypes especially 23B and 15A.^[13-15] This suggests that the serotype replacement is occurring again. With the availability of an effective conjugate vaccine, pneumococcal disease is also the leading cause of death among vaccine-preventable infectious diseases.^[6]

PNEUMOCOCCAL COLONIZATION

Pneumococcal disease may take place when two situations coincide:

1. The host is colonized with a pneumococcal strain against which immunity has not yet been established,
2. An alteration of the natural barriers or host immune system has occurred.^[16]

The nasopharynx of humans is the ecological niche for many bacterial species including pneumococcus. At least once in our lives, it gets colonized by pneumococcus. In general, it acts simply as an asymptomatic carriage, but in some cases the spread of pneumococcus from the nasopharynx to the lower respiratory tract or other sites may cause pneumococcal disease.^[4]

The nasopharyngeal carriage rate peaks in children with the highest rates found in developing countries with reports of 80-90% of children colonized mostly during the 1st year of life in some countries in Africa.^[17]

Nasopharyngeal carriage rates in healthy children range from 20% to 50% and in healthy adult population they range from 5% to 30%.^[4,18]

Risk factors for nasopharyngeal carriage in children include: Winter season, age <6 years, having young siblings and attendance in day care centers. In adults, the risk factors include: Current smoker, asthma, and upper respiratory infection. In children, colonization may persist for a mean of 4 months but is much shorter in adults (usually 2-4 weeks).^[19] The duration of colonization can range from days to months depending on serotypes.^[20] Transmission of pneumococci from children to other children or adults through household contacts is the major cause of nasopharyngeal carriage and pneumococcal disease [Figure 1].

Not all pneumococcal serotypes are equally able to cause disease; the capsular polysaccharide is the major virulence factor, and those serotypes that produce large amounts of polysaccharide are likely to be more virulent than others. After invasion, the capsular polysaccharide also protects the pathogen by inhibiting neutrophil phagocytosis and classic complement mediated bacterial killing. Some of the important factors in the development of pneumococcal disease include the invasive properties of serotype, the ability of an organism to evade the immune system, and the absence of a type-specific pneumococcal antibody.^[21]

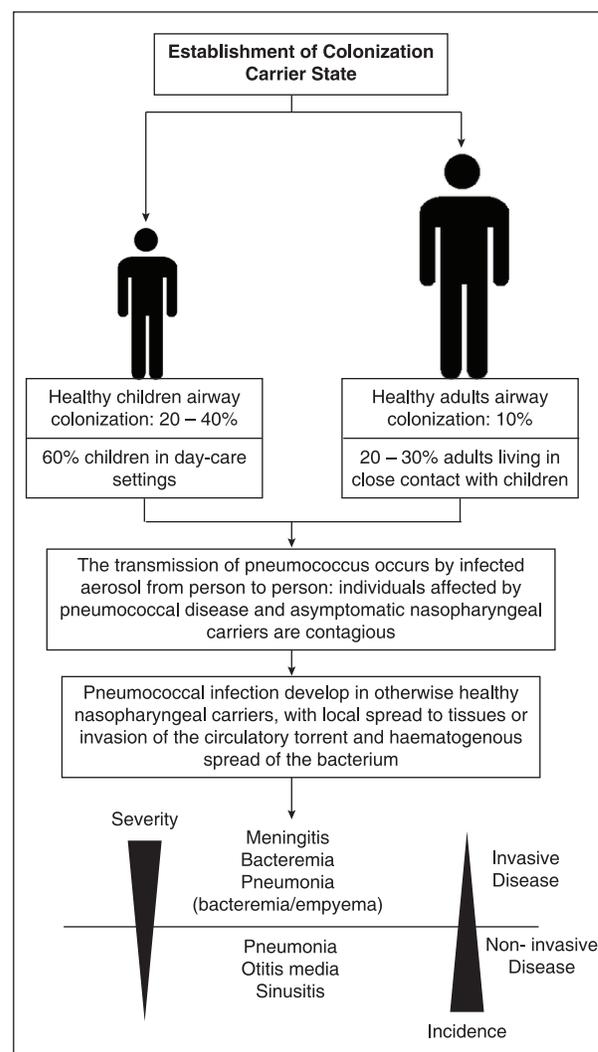


Figure 1: Pneumococcal disease

INVASIVE PNEUMOCOCCAL DISEASE AND THE PRINCIPAL RISK FACTORS

Invasive diseases caused by pneumococcus include meningitis, bacteremia, and pneumonia with bacteremia and/or empyema. The incidence of IPD in any population depends on the geographical location, season, prevalent serotype, age, and vaccination status of the population.

Extremes of age (<2 years or ≥65 years), ethnicity (African-Americans, American Indians, Native Alaskans, and Australian Aborigines), existence of comorbidities (pulmonary, neurological, hepatic, diabetes mellitus, and renal conditions), alcoholism, immunosuppression (asplenia, human immunodeficiency virus [HIV], and sickle cell), and anatomic abnormalities (cerebrospinal fluid leak, cochlear implant or congenital heart disease) are well known risk factors associated with an increased susceptibility to IPD and are further associated with higher mortality.^[19,21]

On the other hand, in healthy children the exposure to cigarette smoke and multiple children in the household are the risk factors for IPD. In the case of immunocompetent adults the incidence of IPD is increased with the following comorbidities: Congestive heart failure, chronic lung disease, asthma, diabetes mellitus, neurological disorders, alcohol abuse, cigarette smoking, recent influenza infection, institutionalization, male gender.^[22]

EPIDEMIOLOGY

Epidemiological data in United States in 2009 showed that the overall case rate of IPD was 14.3/100,000, with the highest case rates in two age groups: Children younger than 1 year and adults aged 65 years or older. In these groups, the case rates were 37.1/100,000 and 38.7/100,000, respectively. The group aged 65 years, or older has the highest rate of death from IPD (6.56/100,000 persons).^[23] Pneumococcal infection causes an estimated 40,000 deaths annually in the United States, accounting for more deaths than any other vaccine-preventable bacterial disease.^[24]

In Europe, the incidence of IPD varies considerably both by country and age group. The highest rate of IPD in Europe and in the rest of the world is reported in children of 2 years of age, declining steadily in the years thereafter. In the age group of children for whom the PCV7 is currently licensed in Europe (<2 years), the incidence ranges from 14 cases/100,000 children in Germany and The Netherlands to more than 90 cases/100,000 in Spain. These differences between European countries cannot be readily explained, but differences in surveillance systems and definitions of IPD may also contribute to this phenomenon. In European countries, reliable incidence data are not available.^[25]

Pneumococcal diseases are responsible for significant morbidity and mortality in children in the Asia-Pacific region; incidences are highest in indigenous and younger children, with rates around 100-200 cases/100,000 children aged <2 years. However, a particularly high incidence of IPD of 1500 cases/100,000 children aged <5 years has been reported in India based on hospital admissions for IPD-associated diagnoses.

In a pilot study conducted among hospital and ambulatory patients in Chile, the incidences of IPD overall and bacteremia in particular were estimated to be 33.9 and 27.0 cases, respectively, per 100,000 children aged <36 months. In the same study, fatality among hospitalized children was found to be 9.9%.^[26] An estimated 12,000-28,000 deaths due to pneumococcal disease occur in the Latin America and Caribbean children annually.^[27]

The mortality rate from pneumococcal infections is significantly higher than in developed countries; it is

estimated that mortality rate in some of the poorest regions in the world can be over 10 times higher than in developed countries.^[26]

NONINVASIVE PNEUMOCOCCAL DISEASE AND THE PRINCIPAL RISK FACTORS

Non-IPD is frequent, but less severe and includes acute otitis media, sinusitis and community acquired pneumonia (CAP).

Pneumococcal pneumonia represents the main burden of pneumococcal disease, since it has a high case fatality rate (15% of hospitalized patients) and a high incidence.

Streptococcus pneumoniae is the leading cause of CAP in adults in Europe and in the United States accounting for about 30-35% of the cases.^[28-31]

There are three factors for the progression of an infection such as pneumococcal pneumonia: Pathogen factor (virulence and presence of resistance genes), host factors (e.g., age, sex, comorbidities, and immune status) and environment (e.g., temperature, occupational exposure, and coexistence with animals). CAP incidence increase with age and the presence of comorbidity, and is higher in males than females.^[32,33]

Age and gender

Pneumococcal pneumonia results in significant morbidity, leading to high rates of hospitalizations, especially in elderly patients. Hospitalization rates due to pneumococcal pneumonia in Spain were 0.25/1,000 in patients aged 50-54 years versus 4.21/1,000 in those ≥85 years of age.^[33]

The study by Torres *et al.*^[33] reported an increased risk of CAP in men (compared with women) and in patients ≥65 years of age.

Comorbidities

Patients with certain comorbid conditions, such as previous history of pneumonia, chronic respiratory disease, chronic obstructive pulmonary disease (COPD), or HIV infection are at risk of pneumococcal CAP.^[33]

Streptococcus pneumoniae is the most frequently isolated pathogen in the respiratory tract during pneumonia in patients presenting COPD.^[34]

The study of Müllerova *et al.* reported the highest overall incidence of COPD: 22.4/1000 person/year, with rates of 23.1 and 21.4 in men and women, respectively.^[35]

Chronic cardiovascular disease increased the risk of CAP up to three-fold from 1.4 to 3.2/1000 person/year. Additional studies supported an association between chronic heart disease and the risk of CAP.

Cerebrovascular disease/stroke and dementia approximately doubled the risk of CAP.

Other neurological or psychiatric conditions were also associated with an increased risk of CAP in some studies. CAP in patients with depression or bipolar disorder ranged from 1.75 to 2.54/1000 person/year.

Patients admitted to hospital with diabetes mellitus remain at increased risk for pneumococcal infection, data from several studies suggested that the diabetes was associated with a moderate increase in the risk of CAP. Chronic liver or renal disease increased the risk of CAP approximately two-fold.

High incidence rates of pneumococcal pneumonia were also reported in immunocompromised patients. Bacterial pneumonia is the most frequent infection in HIV patients, thus recurrent bacterial pneumonia (two episodes of CAP within 1 year period) was included as a defining condition for acquired immunodeficiency syndrome.^[36,37] HIV infection is associated with 10-fold increase incidence of bacterial pneumonia.^[38] A recent study of CAP in HIV patients show pneumococcus was the most frequent pathogens in HIV patients with CD4⁺ T-cell counts $\geq 200/\text{mm}$.^[39]

Another important risk factor for pneumococcal pneumonia is a previous respiratory viral infection. A study by Yoon *et al.* suggested that previous respiratory viral infection might be one of the risk factors affecting the clinical severity of pneumococcal pneumonia.^[40] In patients with immunodeficiency or chronic lung diseases, infrequently colonizing invasive serotypes would be more likely to cause pneumococcal pneumonia after preceding respiratory viral illness.^[41]

LIFESTYLE FACTORS

Patients with specific lifestyle factors including being underweight, smoking, alcohol consumption, and regular contact with children in day care, are at risk for pneumococcal CAP.^[33]

There was consistent evidence that smoking was associated with an increased risk of CAP. Changes in the composition of the oropharyngeal microflora are associated with continuous exposure to cigarette smoke.^[42] Pathogens such as *S. pneumoniae* are frequent found in smokers and are colonizer in COPD patients.^[43] Parental smoking increases infant carriage of *S. pneumoniae* in general and the serotypes are included in the PCV7 vaccine in particular.^[44]

In a study of bacterial pneumonia in HIV patients, current smokers had more than 80% higher risk of pneumonia compared with those who never smoked.^[45,46]

A study published by Bello *et al.*^[47] showed that current smokers with pneumococcal CAP often develop severe sepsis and require hospitalization at a younger age despite fewer comorbid conditions. Almirall *et al.*,^[48] in a recent study, found that passive smoking at home is a risk factor for CAP in older adults (≥ 65 years).

Chronic alcohol abuse impairs airway defenses against microbial invasion and infections and amplifies the risk for serious pneumonias as well as their complication including sepsis and acute lung injury.^[49,50]

Samokhvalov *et al.*,^[51] in a meta-analysis, showed that subjects who consumed 24, 60, and 120 g of pure alcohol daily had 1.12 (95% confidence intervals [CI]: 1.02-1.23), 1.33 (95% CI: 1.06-1.67), and 1.76 (95% CI: 1.13-2.77) risks for CAP relative to nondrinkers, respectively. Other studies showed that bacterial pneumonias particularly caused by encapsulated microorganism, are related to alcohol consumption.^[51-53]

Being underweight was generally associated with an increased risk of CAP. Obesity is a complex condition that is characterized by excess white adipose tissue and is often accompanied by other comorbid conditions (e.g., diabetes and gastroesophageal reflux) and is known to compromise host defense against infection. The accumulation of adipose tissue may attenuate pulmonary host defense through metabolic disturbances that often accompany obesity. This leads to dysregulated immune response, impaired chemotaxis, and altered macrophage differentiation.^[54,55]

CAUSES OF PNEUMOCOCCAL DISEASES BY SEROTYPE

Pneumococcal serotypes are known to differ in their invasiveness. Traditionally, the serotypes chosen for the vaccine have been based on the rank order incidence of disease. These serotypes are often the most prevalent in carriage, but they do not necessarily exhibit the highest potential for invasiveness.^[56]

About 20 serotypes of *S. pneumoniae* are responsible for more than 80% of IPD, and the 13 most common serotypes cause at least 70-75% of IPD in children worldwide.^[6] The dominant serotypes associated with IPD worldwide include 14, 4, 1, 6A, 6B, 3, 8, 7F, 23F, 18C, 19F, and 9V. In young children, seven serotypes (1, 5, 6A, 6B, 14, 19F, and 23F) accounted for more than half of IPD in every region. Serotypes causing IPD vary greatly across geographic regions (e.g., serotypes 1 and 5 are an important cause of IPD in Africa, Asia, but are uncommon in Europe and United States^[22]), and several factors may contribute to these variations.

The introduction of PCV7 in 2000 had a profound impact on the sero-epidemiology of pneumococcal disease, with significant declines of vaccine serotypes observed in pediatric and adult patients. Initial reports indicated that the decline in vaccine serotypes was also associated with a decline in the frequency of drug resistance, due to the fact that the serotypes targeted by PCV7 were among the more common drug resistant types in the prevaccine era. However, the emergence of nonvaccine serotypes in recent years has been driven, in part, by antimicrobial drug selection pressures, and is changing the epidemiology of pneumococcal drug resistance.^[57]

The distribution of serotypes changes over time. Serotype 3 has declined in frequency over the past few decades whereas serotype 14 has become more prevalent.^[22] A large retrospective study in 1075 hospitalized adult patients with IPD from The Netherlands found that serogroups known to have high invasive disease potential in children (serogroups 1, 5, and 7) affected relatively healthy adults whereas those previously shown to have low or intermediate invasive disease potential (serogroups 3, 6, 8, 15, 19, 23, 33, and 38) were more likely to affect more fragile individuals at an older age and/or those with underlying conditions.^[58]

PNEUMOCOCCAL VACCINES

Development of an effective vaccine was extremely challenging mainly due to the low immunogenicity of polysaccharides, which are the target of opsonizing antibodies. Two vaccine formulations (pneumococcal polysaccharide vaccine and pneumococcal polysaccharide protein conjugate vaccine) are available to prevent pneumococcal infection [Figure 2].

The development of pneumococcal polysaccharide vaccines for adults and the efficacy of pneumococcal polysaccharide protein conjugate vaccines in infants and children have confirmed that active immunity to the polysaccharide can provide excellent protection against the invasive disease by pneumococci of the same serotype, and in some cases

protection against cross-reacting serotypes within the same serogroup. Vaccination of high-risk groups in addition to individual protection reduces nasopharyngeal colonization by vaccine-related serotypes.

POLYSACCHARIDE VACCINE: 23-VALENT PNEUMOCOCCAL POLYSACCHARIDE VACCINE

Licensed in 1983, this vaccine contains purified capsular polysaccharides from 23 pneumococcal serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F). Polysaccharides primarily induce a B-cell dependent immune response via release of immunoglobulin M (IgM). The vaccine covers 85-90% of serotypes responsible for invasive disease. The 0.5 ml dose of the 23 included serotypes in isotonic saline solution with 0.25% phenol as a preservative.

This vaccine was licensed for adults aged 65 years or older, as well as adults aged 19-64 years with underlying medical conditions that increase the risk for pneumococcal disease. This vaccine is not recommended for children <2 years of age, due to their immature immune system. Vaccination of adults with polysaccharide vaccines requires re-vaccination after 5 years.^[59] Nonresponders to PPV23 are frequent in older patients.^[60]

Limitation of pneumococcal polysaccharide vaccine 23

Most of the studies suggest that the PPV23 confer low protection against IPD, and data concerning the prevention of pneumococcal pneumonia and mortality in the adult population is less clear.^[61]

- Some of the serotypes included in the PPV23 are less immunogenic. The capsular polysaccharide of serotypes 6 (6A y 6B), 14, 19F, and 23F are unable to produce antibodies in children aged under 2 years and have poor immunogenicity even in adults. Moreover, these are the most frequently isolated serotypes in children with systemic infections.
- Prior analyses suggest that adult PCV could prevent more disease than PPV23 due to its potential effectiveness against both nonbacteremic pneumococcal pneumonia and IPD.
- Primary PPV23 vaccination resulted in an immune state, in which a subsequent PPV23 dose generally yielded inferior responses compared with the initial response with poor or absent immunogenicity.
- The levels of antibodies specific for the different serotypes substantially declined 5-10 years after vaccination.
- The immune response produced by the vaccine antigens is independent of T-cells, therefore, do not induce immunological memory. The vaccine mostly induced IgM production.

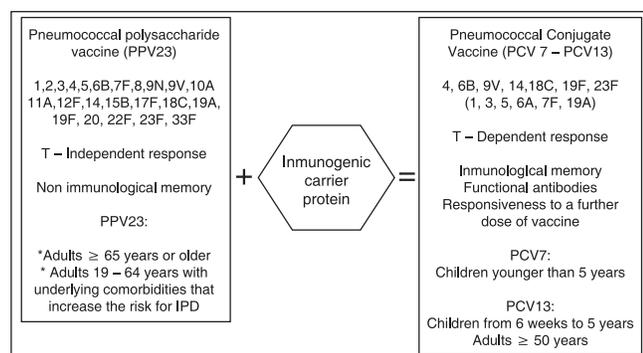


Figure 2: Pneumococcal vaccines

Polysaccharide conjugate vaccine: Pneumococcal conjugate vaccine 7/pneumococcal conjugate vaccine 13

The heptavalent conjugate vaccine (PCV7) was approved in the USA in 2000 and in Europe and much of the rest of the world in 2001 or later. PCV7 contains: Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, and are individually conjugated to a protein carrier; nontoxic diphtheria cross-reactive material CRM₁₉₇.^[62]

Employment of this pneumococcal vaccine is particularly successful in the vaccination of young children. This vaccine provides an optimal level of protection against invasive disease, with percentages of efficacy approximately 90%. The vaccine was license for all children younger than 2 years, and for children younger than 5 years with high-risk of IPD. The routine use of PCV7 has resulted not only in a tremendous reduction of invasive infection in children, but also in decreased rates of pneumococcal disease in adults. This result, likely caused by decreased nasopharyngeal carriage, demonstrates a direct or herd effect in the transmission of bacteria from children to adults.

Despite the success of PCV7, studies have also noted an increase in the incidence of IPD caused by nonvaccine serotypes, which remain as a major cause of the disease. Eradication of vaccine serotypes in asymptomatic carriers has created an ecological niche for nonvaccine serotypes (“replacement”). These strains, termed replacement strains, were 1, 3, 5, 6A, 6C, 7F, 12F, 19A, and 22F. In The Netherlands, IPD caused by nonvaccine serotypes has increased since the introduction of PCV7 and reduced the overall direct effects of PCV7 and offset the potential positive herd protection benefits in nonvaccinated individuals.^[63]

Also, there is an evidence of increased incidence in multidrug-resistant disease due to serotype 19A, as well as nasopharyngeal acquisition.^[64,65] However, other factors besides PCV7 introduction may also play a role in the increase incidence of serotype 19A since this serotype emerged in countries that have not yet introduced the vaccine.^[66]

The Food and Drug Administration (FDA) on February 2010 approved the use of a new 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13), PCV13 contains capsular polysaccharides from the serotypes 1, 3, 4, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F that are individually conjugated to CRM₁₉₇ carrier. PCV13 contains 2.2 µg of polysaccharide from each of 12 serotypes and approximately 4.4 µg of polysaccharide from serotype 6B.

Polysaccharide conjugate vaccine13 is formulated and manufactured using the same processes as PCV7 and was licensed by FDA on the basis of studies demonstrating safety and an ability comparable to that of PCV7 to elicit

antibodies protective against IPD. PCV13 is approved for use among children aged 6 weeks to 5 years and replaces PCV7, and for adults aged 50 years and older. PCV13 contains the seven serotypes included in PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) and six additional serotypes (1, 3, 5, 6A, 7F, and 19A). PCV13 also is approved for the prevention of otitis media caused by the seven serotypes also covered by PCV7. However, no efficacy data for prevention of otitis media are available for the six additional serotypes.^[67]

Recent studies show that the incidence of some nonvaccine serotypes occurring again.^[13,15,68] in Norway the nonvaccine serotypes 23B and 15A were reported^[13] after PCV13 introduction in 2011. Ben-Shimol *et al.* Reported that the rate of IPD caused by non-PCV13 serotypes in Israel increased by 54% in comparison to the PCV7 and the pre-PCV periods in children <5 years old. The increase in IPD caused by non-PCV13 IPD was similar in magnitude among children <2 and 2-4 years old. Of all non-PCV13 disease, serotypes 12F, 15B/C, and 33F were the most common, causing 28.3%, 8.0% and 6.2% of all non-PCV13 episodes in the entire study period, respectively, and 38.8%, 10.9% and 7.5% of all non-PCV13 episodes in the PCV13 period, respectively.

The more frequent reported nonvaccine PCV13 serotypes before the introduction of PCV13 vaccines were: 23A, 23B, 12F, 15A/15B/15C, 31, 33F, 7C, and 8.

As this suggests that the serotype replacement is again occurring, continued monitoring of IPD is important so that adaptations to vaccine recommendations can be issued promptly.

New vaccine formulations

Higher valency PCV that target up to 15 serotypes (PCV15, Merck) are being evaluated and have the potential to broaden protection, but with a trade-off of a higher cost and manufacturing complexity.^[69] This vaccine includes the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F that are conjugated to CRM₁₉₇. The results of preclinical evaluation of PCV15 indicate that antibody responses to PCV15 and PCV7 were comparable for the 7 common serotypes and that postvaccination responses to PCV15 were >10-fold higher than baseline for the 8 additional serotypes.

Pneumococcal hybrid conjugate and protein vaccines may be another promising alternative long-term strategy to broaden serotype coverage in both industrialized and low-resource settings.

A protein pneumococcal vaccine that includes a pneumococcal histidine triad protein D, a virulence factor and pneumococcal choline-binding protein A bacterial

surface antigen, has the potential to offer expanded protection against a broad spectrum of pneumococcal serotypes in a single formulation,^[70] and may be more accessible for resource-poor populations.

CONCLUSION

Streptococcus pneumoniae remains one of the most important causes of morbidity and mortality in adults and children throughout the world. According to the World Health Organization, pneumococcus is responsible for approximately 1.6 million deaths every year, of which nearly 1 million deaths are in children aged <5 years, mostly in developing countries.^[6] A limited number of serotypes are responsible for most cases of IPD globally.

Several studies have demonstrated the efficacy of pneumococcal vaccines in general. Pneumococcal vaccines decreased the resistant pneumococci in vaccinated and unvaccinated populations by reducing colonization of antibiotic-resistant serotypes, protecting the vaccinated population, and preventing the spread of the disease to others.

Serotype replacement and the development of antibiotic-resistant remains an important issue to consider in the future research.^[71]

It is important to continue IPD surveillance in order to identify the emergence of new relevant strains to direct the formulation of future conjugate vaccines, depending on the level of serotype replacement.

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