Paediatric Respiratory Reviews 13 (2012) 258–264

Contents lists available at SciVerse ScienceDirect

Paediatric Respiratory Reviews

Review

Streptococcus pneumoniae – a review of carriage, infection, serotype replacement and vaccination

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ARTICLE INFO

Keywords:
Pneumococcus
carriage
invasive infection
vaccination

SUMMARY

Invasive pneumococcal infection remains a leading global cause of morbidity and mortality in young children. In developed nations, a substantial decrease in the incidence of IPD has been achieved with inclusion of the 7 valent protein conjugated pneumococcal vaccines (7vPCV) into paediatric vaccine schedules. In contrast, the incidence of IPD has changed little in developing nations. This is likely due to poor access to medical care and pneumococcal vaccination, the accompanying HIV and malnutrition burden, and the fact that 7vPCV does not contain the most common serotypes (1,5, 6A) responsible for IPD in many developing nations. The battle against IPD in developed nations is not over, with the rise of non-7vPCV serotypes since routine 7vPCV vaccination. This has necessitated the development and distribution of pneumococcal vaccines containing 3 or 6 additional serotypes. This article provides an overview on pneumococcal carriage and risk factors for IPD, the rise of non-7vCPV serotypes in the era of 7vPCV vaccination, and the current and newly available broader valent pneumococcal vaccines.

INTRODUCTION

Streptococcus pneumoniae (pneumococcus) remains one of the leading global causes of childhood pneumonia and meningitis.[1] Almost all isolates that cause infection are encapsulated, and to date 91 separate capsular serotypes have been identified. Ten years ago pneumococcal pneumonia caused an estimated 1.8 million deaths worldwide in children < 5 years of age.[1] The single most important advance in the fight against pneumococcus has been the development of the penta-valent pneumococcal protein conjugated vaccine (7vPCV; Prevenar 7, Wyeth Pharmaceuticals). 7vPCV is now registered in > 70 countries. The pneumococcal disease spectrum encompasses invasive pneumococcal disease (IPD), defined as the isolation of pneumococcus from normally sterile body fluids (e.g. meningitis, sepsis and bacteraemic pneumonia), as well as non-IPD such as non-bacteraemic pneumonia and otitis media. Surveillance systems of pneumococcal disease vary by country and reduction in IPD incidence is often used as a measure of vaccine success. Since its inclusion into many paediatric vaccination schedules, the incidence of and mortality from IPD in children has fallen[2–8] (Figure 1). A concomitant decrease in adult IPD cases has been attributed in part to herd immunity.[6] The efficacy of 7vPCV (i.e. disease reduction) is typically greater for IPD (>80%), compared to radiological or hospital admitted pneumonia (usually < 20%) and otitis media (typically < 10%) (reviewed in[4]). This is not unexpected, since many other potential pathogens can cause pneumonia and otitis media, and definitions for these two diseases are more problematic. Pressures exerted by antibiotic overuse in inducing multi-resistant strains,[9] limited access to vaccination and medical care with accompanying HIV burden in developing nations and the rise of IPD by non-7vPCV serotypes[10,11] has meant pneumococcus remains a significant cause of paediatric infection morbidity, mortality and health care cost.[12,13] This review will discuss carriage and risk factors for IPD, the rise of non-7vPCV serotypes causing infection, and the current and more recent pneumococcal vaccines.

CARRIAGE

Pneumococcus is carried in the nasopharynx, and often with other encapsulated bacteria, such as *Haemophilus influenza* and *Moraxella catarrhalis*.[14–16] It is spread by respiratory droplet and children are the main source of transmission to adults. Universally, carriage rates are highest in young children (40–60%), compared with older children (12%), adolescents (6–10%) and adults (3–4%).[17,18] Pneumococcal colonisation is a dynamic process. One serotype is usually carried at a time, with the first strain often being carried the longest.[19] Reacquisition of the same serotype is relatively common.[19]

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doi:10.1016/j.prrv.2011.12.001

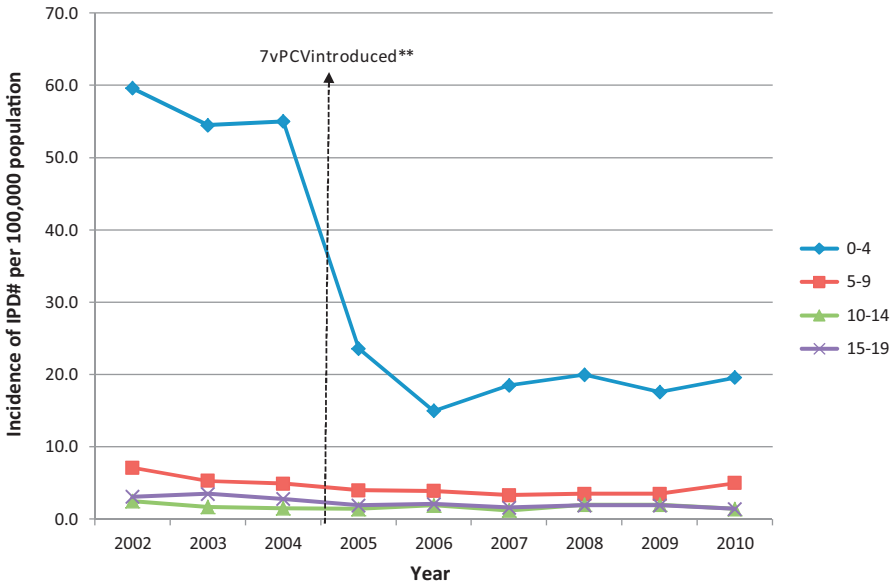

Figure 1. Incidence of invasive pneumococcal disease in Australian children from 2002–2010*.
* Data from the Communicable Diseases Surveillance (Australian Government, Department of Health and Ageing).[79]
** 7vPCV was made available to all children in Australia in January 2005 (having been part of the immunisation programme for Indigenous children since mid-2001).
# IPD = pneumococcal invasive disease

Colonisation rates are higher (i.e. > 50%) in situations of overcrowding such as in day-care centres, orphanages, slums and in indigenous populations.[14–16,20] Winter,[19,21,22] recent viral respiratory infection,[15–17] maternal pneumococcal carriage,[23] and passive smoke[17,19] have been reported by some, but not by others,[14,15,19] to be associated with higher rates of colonisation. Prior antibiotic use does not appear to alter the rate of carriage[19,24] but does promote carriage with antibiotic resistant strains, particularly to β-lactam antibiotics.[14,19,21]

Nasopharyngeal colonisation is advantageous to both the pathogen and the host. For the pathogen, it allows for the exchange of genetic material and potential acquisition of virulence and antibiotic resistance properties. For the host, natural B-cell mediated immunity against the polysaccharide capsule, the major virulence determinant, is promoted. Serotypes of low immunogenicity, such as 6,14,19 and 23[25] are more likely to be carried in the nasopharynx for longer periods, and more likely to be re-acquired,[19] promoting transmission and survival in the human host. These low immunogenic pneumococci are also more likely to harbour antibiotic resistance than their more immunogenic counterparts.[26] Low immunogenicity does not equate to low virulence, particularly in immune-naive hosts such as young children. In Australia, prior to routine 7vPCV use, serotypes 6, 14, 19 and 23 were responsible for 73% of IPD cases in Western Australian children < 5 years of age, compared with 46% of cases in adolescents/adults.[10]

INFECTION

Host and pathogen factors that increase the risk of IPD are summarised (Table 1). Carriage is a pre-requisite for infection and infection usually occurs within a month of acquiring of a new serotype.[19] IPD is more likely in individuals that have the highest carriage rates, such as in young children and in indigenous populations.[10,27] Increased predisposition to IPD in infants may be due to a combination of poor natural humoral immunity to the polysaccharide capsule[25] and increased predisposition to viral respiratory infections.

Influenza A infection has been associated with increased IPD risk (reviewed in[28]). Co-infection with both pathogens has been noted to result in severe, life threatening pneumonia in humans.[28] In the 1918 influenza pandemic, most deaths were attributable to secondary bacterial pneumonia, with pneumococcus being the most common co-infecting pathogen.[29] During the recent H1N1 pandemic, pneumococcus was the most common co-infecting agent isolated from patients with fatal H1N1 infection.[30]

The Centre for Disease Control and Prevention (CDC) currently recommends influenza vaccination for all children > 6 months of age.[31] Could routine influenza vaccination further reduce IPD incidence? To date, there have been no randomised controlled trials (RCT) in children evaluating the benefit that dual influenza/pneumococcal vaccination may confer to additional IPD risk reduction. Co-vaccination in one adult study was not found to offer any additional protection from pneumococcal pneumonia, but did reduce the risk of pneumococcal bacteraemia compared to pneumococcal vaccination alone.[32] Dual vaccination in one paediatric RCT was shown to reduce influenza infection and otitis media, but influenza vaccination alone produced a similar risk reduction, and the study did not evaluate IPD as an outcome measure.[33] Although studies on dual vaccination are required, the benefit of co-vaccination on additional IPD risk reduction may be limited given other respiratory viruses have been associated with IPD risk.[34]

Table 1
Factors associated with invasive pneumococcal disease in children.

Host factors	Age (< 2 years)
	Ethnicity (indigenous population)
	Respiratory viral co-infection (e.g. influenza A)
	No prior pneumococcal vaccination
	Primary/secondary immunodeficiency
	Co-morbid disease (e.g. CSF leaks, cardiac disease, renal disease, diabetes)
Environmental factors	Winter months
	Parental smoking
	Crowding
Pathogen factors	Nasopharyngeal acquisition of a new serotype

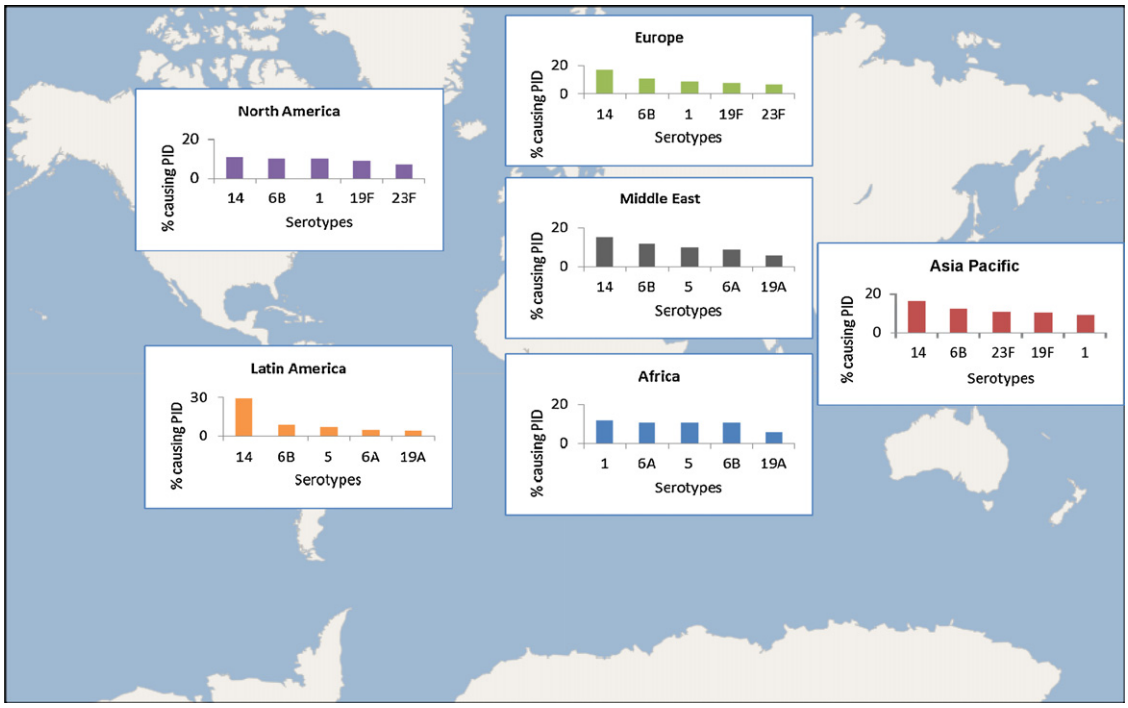

Figure 2. Five most common serotypes causing invasive pneumococcal infection by continent (modified from Reinert et al[37]).

SEROTYPE REPLACEMENT

The pattern of predominant IPD associated serotypes varies with age, country, and over time.[35] In young children and immune-compromised hosts, typically less immunogenic serotypes (e.g. 6, 14, 19 and 23) predominate. More invasive serotypes (e.g. 1, 5, and 7) tend to infect individuals without co-morbidities.[36] Globally, seven serotypes account for the bulk of IPD disease (1, 5, 6A, 6B, 14, 19F and 23F).[37,38] Serotypes 1, 5, 6A/6B, and 14 are the predominant strains causing IPD in most countries[37,38] (Figure 2), particularly in developing nations.[37,38] Serotypes 1, 5 and 6A are not contained within 7vPCV.

Natural fluctuations in serotypes responsible for IPD occurs over time.[39,40] Concerns were raised almost 10 years ago regarding the potential for 7vPCV vaccination to exert selective pressure and promote serotype replacement with non-7vPCV strains.[41] Since routine 7vPCV use, there has been a steady increase in the incidence of paediatric non-7vPCV IPD in a number of countries.[10,11,27,35,42–44] The risk of non-7vPCV IPD in children has been associated with the number of prior 7vPCV vaccinations received.[45] This increase in non-7vPCV IPD has meant that the overall rate of IPD in young children has recently plateaued in some countries[11,27] (Figure 1). In one cohort, the incidence of IPD among native Alaskan children actually increased following 7vPCV use, with the rise in non-7vPCV IPD being greater than the concomitant decline in 7vPCV IPD.[46]

Most of the rise in non-7vPCV IPD is attributable to serotype 19A[10,11,27] (Figure 3). Using CDC data from eight states in the USA, the incidence of 19A IPD in children < 5 years of age rose from 2.6 cases per 100,000 population (pre-7vPCV era; 1998-1999) to 9.3 cases per 100,000 population over 6 years (post-7vPCV era; 2005). Since 7vPCV vaccination, at least a 2 fold increase in the incidence of 19A IPD has been reported in Asia-Pacific[10,43,44] and Europe.[42] 19A is now one of the most common causes of IPD in young children from developed countries, accounting for up to half of all IPD cases.[10,11,27,45] Of concern, is the propensity for 19A serotypes to be multi-resistant[2,45] and along with serotype 3 has been associated with higher rates of IPD mortality in older children and adults.[47]

The factors that determine serotype replacement are complex. Even prior to routine 7vPCV availability, natural fluctuations in serotypes responsible for IPD were noted to occur.[39] 19A IPD incidence rose in Denmark before 7vPCV use from 0.28 per 100,000 in 2003 to 0.64 cases per 100,000 in 2007.[39] What is not known is whether the incidence has further increased since 7vPCV inclusion into the Danish paediatric schedule in late 2007. Not all studies have reported a rise in non-7vPCV IPD with 7vPCV use.[48,49] However, the post-surveillance periods in these studies have been shorter compared with those that have documented a rise in non-7vPCV IPD.[10,11,27]

PNEUMOCOCCAL VACCINES

23vPCV vaccination

The polysaccharide 23vPCV vaccine contains more serotypes than any other available pneumococcal vaccines, and potentially could cover $> 85\%$ of serotypes causing IPD in many countries.[43] However its use in children $<$ 18 months of age is not recommended, the group most risk of IPD, since such children exhibit poor antibody responses to polysaccharide antigens.[25] Balloch et al[50] demonstrated 23vPCV is potentially more immunogenic than previously thought, examining responses in infants 12 months of age. However only 21% of infants produced an adequate response to serotypes 14 and 6B (two of the most common causes of IPD worldwide[38]), and responses to other serotypes were short lived in the majority of children.[50] Furthermore administration of 23vPCV prior to 7vPCV has the potential to attenuate responses to subsequent doses of 7vPCV.[51] The 23vPCV vaccine is currently recommended in children $>$ 18 months of age who are at greater risk of IPD once primary series with protein conjugated pneumococcal vaccines have been completed (e.g. children with immune deficiency, chronic medical illness such as bronchiectasis or cystic fibrosis, cochlear implants, indigenous background, intracranial shunts, etc.).[4]

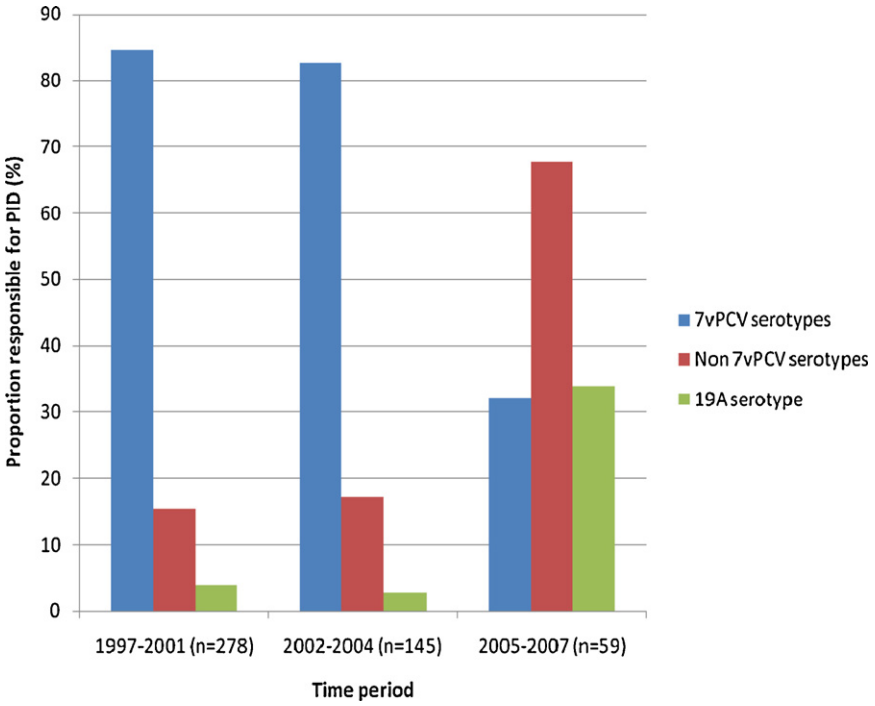

Figure 3. Increasing proportion of IPD caused by non-7vPCV serotypes in Australian children < 5 years of age (modified from Lehmann et al[10])*.
* Data from Indigenous and non-Indigenous children combined.

10vPCV and 13vPCV vaccines

The introduction of protein conjugated pneumococcal vaccines covering a broader range of serotypes has been prompted not only by the rise in non-7vPCV IPD, but also because a considerable proportion of IPD worldwide is currently caused by serotypes not covered by the 7vPCV vaccine. Broader coverage is offered by the 10-valent (10vPCV; Synflorix, GlaxoSmithKline) and 13vPCV conjugated vaccines. In addition to serotypes in 7vPCV, 10vPCV contains serotypes 1, 5, 7F, and 13vPCV contains serotypes 1, 3, 5, 6A, 7F and 19A (Table 2). 10vPCV also contains protein D from non-typeable *Haemophilus influenzae*. The inclusion of protein D is expected to reduce the burden of middle ear disease due to non-typeable *Haemophilus influenzae*.[52]

Serotypes 1 and 5 have been selected since they account for ~10% of IPD cases in many countries, and almost a third of cases from Africa (Figure 2). Targeting these serotypes is imperative if there is to be substantial worldwide reduction in paediatric IPD mortality. The 10vPCV and the 13vPCV vaccine are ideally placed to combat IPD in developing nations, since both contain serotypes 1 and 5 and 13vPCV also covers 6A.[38] Initiatives made by the Global Alliance for Vaccines and Immunisations (GAVI) and Pneumococcal vaccines Accelerated Development and Introduction plan (PneumoADIP) has meant that these new pneumococcal vaccines can be made available to a number of impoverished nations within a year of their development and at a fraction of the price payed by developed countries.[55] In 2011, Kenya introduced the 10vPCV vaccine and

Table 2
Serotypes covered pneumococcal vaccines.

	7vPCV	10vPCV	13vPCV	23vPCV
Name	Prevenar 7	Synflorix	Prevenar 13	Pneumovax
Protein conjugated	+	+	+	-
Proteins used in conjugation	CRM197*	Protein D/ diphtheria toxoid/ Tetanus toxoid**	CRM197	-
1		+	+	+
3			+	+
4	+	+	+	+
5		+	+	+
6A			+	
6B	+	+	+	+
7F		+	+	+
9V	+	+	+	+
14	+	+	+	+
18C	+	+	+	+
19A			+	+
19F	+	+	+	+
23F	+	+	+	+
Other serotypes				(2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F)

* CRM197 is a mutated diphtheria toxin.
** 19F is conjugated to diphtheria toxoid protein; 18C to tetanus toxoid and all other serotypes to protein D from non-typable *Haemophilus influenza*.

Sierra Leone the 13vPCV vaccine into their national immunisation schedules.

The selection of 3, 6A, 7F and 19A is primarily based upon the steady rise of these serotypes in a number of countries. Targeting 6A is complex. In 2007, it was recognised that a proportion of 6A disease was caused by a separate and distinct serotype, 6C.[56] Some have re-examined 6A serotypes and have shown the rise in 6A disease is in part due to the rise in 6C.[57]

The immunogenicity of the pneumococcal vaccine, that is the ability of the host to produce functional IgG against serotype specific polysaccharide capsules, is used as a surrogate marker of protection against IPD. Based on data from randomised controlled studies of 7vPCV and 9vPCV, a protective immunological response against a pneumococcal serotype is defined by the World Health Organization (WHO) as a 4 week post-vaccination titre of anti-capsular polysaccharide IgG $\geq$ 0.35 μg/mL and an opsonophagocytic activity antibody titre $\geq$ 1:8 (i.e. functional ability of these antibodies to induce neutrophil pneumococcal phagoctyosis).[58]

Immunological cross-reactivity, and thus cross-protection, against closely related serotypes can occur. Serotypes 6A and 19A were not included in 7vPCV, since it was anticipated and demonstrated sufficient cross-reactivity would occur with 6B and 19F respectively;[59,60] both of which are contained in 7vPCV. Even if in vitro cross-reactivity is demonstrated, this may not translate into clinical protection, as demonstrated by the rise in 19A IPD despite routine vaccination with the 19F containing 7vPCV. Immunological cross-reactivity has been demonstrated between 6A (contained within 13vPCV) and 6C.[59] Whether this will translate into a clinical effect will only become evident with time.

No randomised controlled studies have been performed evaluating the ability of 10vPCV and 13vPCV to reduce IPD against a control group. Such a study would be considered unethical given the availability of 7vPCV, and although the control group could comprise children vaccinated with 7vPCV, large populations would need to be studied to determine the difference in IPD reduction between the two groups.[37] Manufacturers of 10vPCV and 13vPCV have been able to introduce these vaccines into the market by demonstrating non-inferiority; that is a comparable immunogenic and safety profile as the 7vPCV vaccine. Based on the WHO definitions of immunogenicity, both the 10vPCV and 13vPCV have been shown to be as/nearly as immunogenic as the 7vPCV vaccine, and induce sufficient protection against the additional non-7vPCV serotypes in the vaccines.[37,53,54,61–64] The immunogenicity and safety profile of both these vaccines has been comprehensively reviewed by Croxtall et al[53] (10vPCV) and Duggan[54] (13vPCV).

In the UK, USA and Australia, the current 7vPCV vaccine used in national immunisation schedules has or will soon be replaced by the 13vPCV vaccine. Countries are using a 3 dose primary course in infancy or a 2+1 schedule, with the third dose given in the second year of life, as has been used with 7vPCV.[65] Published guidelines are available assisting with the transition, particularly in children who may have already received prior doses of 7vPCV or require catch up doses.[66,67]

Future directions for vaccination

Will the introduction of 13vPCV simply result in an increase non-13vPCV IPD over time? Pneumococcal vaccination is fraught with difficulties. There are at 91 serotypes, 20 of which a responsible for bulk of IPD,[2] and each with differing levels of immunogenicity.[25] The antigens need to be protein conjugated, thus limiting the number of serotypes that can be included in the vaccine due to issues of technical complexity and cost.[41,68] Pneumococcus has the ability to switch capsular types, thus producing clones that can evade vaccine conferred immunity.[69]

Driven serotype replacement may therefore continue to be a long term problem, necessitating vaccine revision in the future. The alternative is for there to be a paradigm shift in vaccine strategy by targeting immunogenic, stable, cell surface virulence protein(s) that are shared by many pneumococcal serotypes. Pneumococcal surface protein A (PsPA) and pneumolysin are two potential targets under evaluation.[41] Both play a role in pneumococcal virulence.[70] Infants with higher antibody levels to pneumolysin and PsPA have been reported to have delayed onset[23] or reduced[71] rate of pneumococcal nasopharyngeal carriage. However, in experimental animal models, immunisation with pneumolysin[72] or PsPA[73] only conferred partial protection against fatal pneumococcal challenge. More recently, vaccination of mice with PsPA conjugated to a bacterial flagella protein, was found to be more immunogenic and provided better protection against fatal pneumococcal infection.[74] Human vaccine trials with pneumolysin and PsPA are in pre-clinical stages of development.[75] Many other pneumococcal protein targets have been studied in animal models,[76–78] with the most promising being BVH-3 and BVH-11 pneumococcal protein fragments.[68,75] The role of these cell surface proteins is still to be elucidated but they are highly conserved among a number of pneumococcal strains, immunogenic, and vaccination in mice protected against lethal pneumococcal sepsis and pneumonia.[68] Humans have been found to naturally produce antibodies to BVH-3/11.[68] Phase I trials with BVH-3/11 in humans are now underway.[75]

SUMMARY

IPD in children has significantly decreased in countries that have included 7vPCV into paediatric vaccination schedules. However, unless developing nations are offered prompt, affordable access to pneumococcal vaccines, IPD will remain a major global cause of death in young children. Initiatives such as GAVI and PneumoADIP are currently addressing this imbalance. Pneumococcal vaccination, however, may be a two-edge sword. The initial benefits in disease reduction may be followed by a steady increase in IPD incidence caused by non-included strains. If future surveillance demonstrates serotype replacement, targeting a common, stable immunogenic protein will be required to minimise pneumococcal disease burden.

STATEMENT OF APPROVAL

This is the work of Dr Sam Mehr and Dr Nick Wood.

CONFLICTS OF INTEREST

None to declare

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