Curr Infect Dis Rep (2014) 16:403
DOI 10.1007/s11908-014-0403-3

RESPIRATORY INFECTIONS (F ARNOLD, SECTION EDITOR)

The Relevance of Pneumococcal Serotypes

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Published online: 23 March 2014

Abstract Pneumococcal disease leads to considerable mortality, morbidity and healthcare cost worldwide, and disease rates are predicted to increase due to an aging population. There are over 90 different pneumococcal serotypes identified to date, each with unique capsular characteristics capable of eliciting serotype-specific immunity in its host. Several recent studies have demonstrated important differences in invasiveness, disease severity, complications from disease and antibiotic resistance patterns that are specific to individual serotypes. This knowledge is particularly pertinent given the ongoing seroepidemiological changes worldwide, partly due to the introduction of pneumococcal conjugate vaccination to childhood immunization schedules. Further characterization of pneumococcal serotype-specific clinical features, and continued surveillance of serotypes in nasopharyngeal carriage and disease, will help guide treatment and prevention strategies in pneumococcal disease.

Keywords *Streptococcus pneumoniae* · Pneumococcal · Serotype · Invasive · Disease severity · Mortality · Vaccine

Introduction

Streptococcus pneumoniae is estimated to cause around 14 million episodes of serious illness and over 800,000 deaths amongst children under the age of 5 years annually across the world [1•]. In the adult population, it is the most frequent pathogen responsible for community-acquired pneumonia (CAP) (about 40 %), which leads to the hospitalization of 2 – 3 per 1,000 adults each year in Europe, with an associated mortality of 10 – 25 % [2–5]. Annual estimates in the US of adults aged ≥50 years show over half a million episodes of pneumococcal disease with attributed healthcare costs of $5.5 billion [6]. Given the current demographic transition due to an aging population, rates due to pneumococcal pneumonia are predicted to double by 2040 [7].

Dissemination of this human-restricted, gram-positive, extracellular bacterial pathogen occurs via droplet infection [8]. Following establishment of nasopharyngeal colonization, either immune-mediated clearance or asymptomatic colonization occurs in the majority of individuals. However, a minority may go on to develop disease [8–10]. Local spread or microaspiration of organisms can lead to sinusitis, otitis media or nonbacteraemic pneumonia (noninvasive pneumococcal disease), whereas direct invasion of the bloodstream results in bacteraemia and/or meningitis (invasive pneumococcal disease, IPD) [10]. The reservoir for pneumococcal infection in the community is young children; nasopharyngeal colonization rates in the developed world peak during early childhood (43 – 52 %) and decline to <10 % in adults [11, 12]. Carriage rates can be considerably higher amongst all age groups in developing countries [13, 14]. Acquisition of homologous pneumococcal serotypes from children has been demonstrated in adults living in the same household in nasopharyngeal carriage studies, and close contact with children is an independent risk factor for IPD and pneumonia in adults [11, 15, 16].

Among its armoury of virulence factors, the polysaccharide capsule surrounding the pneumococcus is by far the most important. It is covalently attached to the underlying bacterial cell wall and highly charged, enabling the pathogen to evade mucus-mediated clearance, complement-mediated phagocytosis, neutrophil extracellular traps and direct exposure to antibiotics [17, 18, 19•, 20]. Defined by the differences in the immunochemistry of the polysaccharide capsule, over 90

This article is part of the Topical Collection on *Respiratory Infections*

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different pneumococcal serotypes have been identified to date [21].

Several recent studies have emphasized the importance of better understanding the disease characteristics of specific pneumococcal serotypes with regard to invasive disease potential, severity of disease, mortality, complications of disease and treatment failure. There is considerable geographic variation in the distribution of pneumococcal serotypes (Table 1) [22•]. Worldwide pneumococcal serotype distribution has undergone significant changes in the recent past, in part due to the introduction of limited valency pneumococcal conjugate vaccination (PCV), which has affected implicated serotypes in nasopharyngeal carriage and disease, in both vaccinated and unvaccinated groups through herd protection [23–31]. The aims of this article were to (a) provide an overview of important differences in pneumococcal serotype-specific clinical features, and (b) highlight recent changes in worldwide pneumococcal seroepidemiology.

Invasive Disease Potential and Disease Severity

The polysaccharide capsule is a major virulence determinant of a pneumococcus; isolates lacking a functional capsule rarely cause invasive disease and have diminished virulence in animal models, and all invasive clinical isolates are encapsulated [32–34]. Of the 94 pneumococcal serotypes identified to date, 11 serotypes account for ≥70 % of IPD globally in children <5 years of age, with serotypes 1, 5, 6A, 6B, 14, 19F and 23F being the most common (Table 1) [22•]. By comparing serotypes causing invasive disease with those predominantly found in nasopharyngeal carriage, 'invasive odds ratios' can be determined for individual serotypes. Serotypes 1, 4, 14, 7F and 8 have high invasive odds ratios, whereas serotypes 3, 6B, 19A, 19F and 23F are less invasive [35, 36]. Multiple clones of the same serotype also appear to differ with regard to invasive disease potential suggesting that both pneumococcal serotype and genotype are important determinants of virulence [36, 37].

The invasive odds ratio calculation assumes a constant duration of nasopharyngeal carriage of pneumococcal serotypes. Using 'serotype-specific attack rates' (defined as the ratio of the incidence of IPD to the incidence of acquisition) to compare the invasiveness of specific serotypes yields broadly similar results, suggesting that the variation in duration of nasopharyngeal carriage between capsular serotypes is small in comparison to their variation in the incidence of invasive disease [38]. Furthermore, an inverse relationship between duration of nasopharyngeal carriage and serotype-specific attack rates has been reported. Future pneumococcal vaccine formulations may need to take account of the differing invasiveness of individual pneumococcal serotypes, in addition to serotype distribution.

Baseline characteristics of the host such as extremes of age, presence of comorbid illnesses and immunosuppression are established risk factors for the development of greater severity pneumococcal pneumonia and associated complications [39, 40]. However, several pneumococcal serotypes also appear to be independently associated with poorer outcomes (Table 2). A Spanish study of IPD found serotypes 3, 19A and 19F to be independently associated with a 2- to 3.5-fold greater risk of respiratory failure [39]. Serotype 3 was also found to be an independent risk factor for the development of septic shock in two adult studies of IPD [41, 42]. In a US cohort study of pediatric IPD, serotype 3 was associated with a greater odds of necrotizing pneumococcal pneumonia [43].

In a study of adult IPD investigating baseline characteristics, disease severity and mortality in affected individuals according to serotype invasiveness, pneumococcal serotypes 3, 6A, 6B, 8, 19F and 23F affected older adults and individuals with greater levels of comorbid illness, resulted in more severe disease and led to higher mortality, in comparison to serotypes 1 and 7F [44]. The latter group of serotypes was described as 'primary pathogens' as disease occurred mainly in healthy individuals, but disease severity and mortality was lower in this group. In contrast, the former group of 'opportunistic pathogens' affected older, frailer adults and was associated with higher mortality. In a systematic review and meta-analysis of nine studies to specifically characterize serotype-associated risk of death in individuals with IPD, serotypes 1, 7F and 8 were associated with a decreased risk of death in comparison to serotype 14, while serotypes 3, 6A, 6B, 9N and

Table 1 Regional distribution of the seven most prevalent pneumococcal serotypes in invasive pneumococcal disease amongst children under 5 years of age prior to the introduction of pneumococcal conjugate vaccination (data adapted from Johnson et al. [22•])

Country	Serotype										
	1	4	5	6A	6B	9V	14	18C	19A	19F	23F
Africa	X		X	X	X		X			X	X
Asia	X		X	X	X		X			X	X
Australia		X			X	X	X	X		X	X
Europe	X				X		X	X	X	X	X
North America		X			X	X	X	X		X	X
South America	X		X	X	X		X	X			X

Table 2 Summary of disease characteristics associated with specific pneumococcal serotype(s)

Disease characteristic studied	Reference	Population studied	Country/ region	No. of subjects	Study period	Associated serotypes
Antibiotic resistance	[81•]	Children with IPD	US	4,478	1994 – 2008	Serotype 19A was the commonest serotype in the post-PCV7 era and 34 % were multidrug-resistant
Complicated PPE	[71]	Hospitalized adults with complicated PPE	UK	920	2008 – 2010	Serotypes 1, 3, 7F and 19A were independently associated with PPE
Complicated PPE	[70]	Hospitalized children with PPE	Spain	219	2005 – 2009	Serotypes 1, 7F, 3 and 19A were most prevalent
Complicated PPE	[68]	Hospitalized children with complicated PPE	UK	635	2006 – 2011	Serotypes 1, 3, 7 and 19A were most prevalent
Complicated PPE	[69]	Hospitalized children with pneumococcal pneumonia	USA	49	2007 – 2009	Serotypes 1, 3, 7F/A and 19A were most prevalent
Meningitis	[77]	Population-based surveillance of pneumococcal meningitis	US	1,379	1998 – 2005	Serotypes 19A, 22F and 35B increased significantly in 2004 – 5 versus 1998 – 99
Meningitis	[78]	Systematic review of population data on meningitis in African 'meningitis belt'	Africa	–	1970 – 2010	Serotype 1 caused majority of disease in children over 5 years of age
Mortality	[45•]	Systematic review of IPD due to pneumonia or meningitis	Worldwide	–	1928 – 2010	Serotypes 1, 7F and 8 were associated with a lower risk of death and serotypes 3, 6A, 6B, 9N and 19F were associated with a higher risk of death, in comparison to serotype 14
Necrotising pneumonia	[43]	Hospitalized children with pneumococcal pneumonia	US	124	1997 – 2006	Serotype 3 was most often associated with necrotizing pneumonia
Respiratory failure	[39]	Hospitalized adults with invasive pneumococcal pneumonia	Spain	1,258	1996 – 2013	Serotypes 3, 19A and 19F were independently associated with respiratory failure
Septic shock	[41]	Hospitalized adults with pneumococcal pneumonia	Spain	1,041	1995 – 2008	Serotype 3 was independently associated with septic shock
Septic shock	[42]	Hospitalized adults with invasive pneumococcal pneumonia	Spain	653	1996 – 2001; 2005 – 2009	Serotype 3 was independently associated with septic shock

PPE parapneumonic effusion, *IPD* invasive pneumococcal disease

19F were associated with a higher risk of death [45•]. The risk ratio for death correlated with carriage prevalence and capsular thickness, but was inversely correlated with invasive disease potential. One hypothesis is that heavily encapsulated serotypes are less likely to interact with the host efficiently and cross the epithelial barrier to cause invasive disease; these serotypes are therefore more likely to persist as carriage isolates. However, when invasion does occur, these same serotypes result in more severe outcomes. This hypothesis is supported by experimental data from in vitro assays and murine models of infection [46]. Estimated risk ratios for death in the meta-analysis showed good correlation when compared with cohorts with no comorbid illnesses, low levels of antimicrobial resistance, and across different geographic locations, suggesting that the risk of death is a stable serotype-associated property.

Changes in Pneumococcal Seroepidemiology as a Consequence of the Introduction of Pneumococcal Vaccination

A 23-valent pneumococcal plain polysaccharide vaccine (PPV23) was first licensed for use in 1983 (Table 3), and has been shown to be effective in reducing the risk of IPD in adults [47, 48]. However, as it induces T-cell-independent immunity, it has little impact on the nasopharyngeal carriage of *S. pneumoniae,* and is poorly immunogenic in young children and immunocompromised adults [49, 50]. A 7-valent protein-polysaccharide pneumococcal conjugate vaccine (PCV) capable of inducing T-cell-dependent immunity was first introduced to the child immunization schedule in the US in 2000 and the UK in 2006 (Table 3). PCV7 does not offer coverage for some common serotypes such as serotype 1, 5 and 6A which were commonly seen in Africa, Asia and Latin America in the pre-vaccine era (Table 1) [22•]. As a consequence of this and widespread serotype replacement, PCV7 has been broadly replaced by higher valency pneumococcal conjugate vaccines across the world (PCV10 and PCV13) based on World Health Organization (WHO) recommendations [51].

Nasopharyngeal carriage studies in the era following the introduction of PCV showed significant reductions in vaccine-type serotypes in vaccinated children, with similar changes observed in unvaccinated age groups, most likely due to herd protection [30, 31, 52]. Reductions were also seen in IPD in individuals of all age groups during this period. National data from the US Active Bacterial Core Surveillance comparing the prevaccination period to 2007 (7 years following the introduction of PCV7) showed a 45 % reduction in overall IPD incidence from 24.4 to 13.5 cases per 100,000 population, and a 94 % reduction from 15.5 to 1.0 cases per 100,000 population in IPD due to PCV7 serotypes, and UK national IPD data from Public Health England comparing the prevaccination era to 2009 – 2010 (3 to 4 years following the introduction of PCV7) showed a 34 % reduction in overall IPD from 16.1 per 100,000 population to 10.6 per 100,000 population [23, 24, 53]. The benefits of PCV also appear to extend to noninvasive disease, which forms the largest burden of pneumococcal disease in adults. Analysis of the US Nationwide Inpatient Sample database demonstrated an age adjusted annual reduction of 54.8 per 100,000 admissions for pneumonia in the 2007 – 2009 period (7 to 9 years after the introduction of PCV) in comparison to the prevaccine era (1997 – 99), which translates to 168,000 fewer hospitalizations annually [54].

Whilst reductions in pneumococcal disease due to serotypes included in the vaccines (vaccine-type serotypes) have been encouraging, the insidious rise in nonvaccine-type serotypes has raised concerns. Whereas Australia, Brazil, Israel, The Netherlands, Norway, UK and the US have reported overall declines in IPD rates despite increases in nonvaccine-type serotypes [23–27, 29, 55], Belgium and Spain have reported an increase in overall IPD rates in the post-vaccination period owing to the expansion of nonvaccine-serotype IPD [28, 56]. The non-PCV7 serotypes that have increased in IPD during the post-PCV7 era include 1, 7F, 12F, 19A, 22F and 24 [23, 24, 28, 56]. Studies of nasopharyngeal carriage in the US and Europe have also shown an increase in non-PCV7 serotypes, especially serotype 19A, in the post-PCV7 era [30, 57–59]. Apart from the introduction of PCV7, other factors that may be contributing

Table 3 Serotypes covered in specific pneumococcal vaccines

Vaccine	Serotype coverage
23-valent pneumococcal polysaccharide vaccine (PPV23)	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F
7-valent pneumococcal conjugate vaccine (PCV7)	4, 6B, 9V, 14, 18C, 19F, and 23F
10-valent pneumococcal conjugate vaccine (PCV10)	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F
13-valent pneumococcal conjugate vaccine (PCV13)	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19, 23F
15-valent pneumococcal conjugate vaccine (PCV15)	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F

PPV pneumococcal polysaccharide vaccine, *PCV* pneumococcal conjugate vaccine

to the increase in non-PCV7 serotypes include underlying secular trends in serotypes, clonal expansion of specific pneumococcal genotypes, changes in patterns of antibiotic use and consequently antibiotic resistance, and changes in the baseline characteristics of populations studied [28]. Whatever the reasons, these increases in non-PCV7-serotypes underline the rationale for higher valency vaccines as recommended by the WHO in 2012, and the need for continued monitoring of pneumococcal serotypes in carriage and disease globally [51, 60].

Disease-Specific Serotype Associations

Pneumonia and Parapneumonic Effusion

In the adult population, noninvasive pneumococcal pneumonia accounts for the largest burden of pneumococcal disease in patients requiring hospitalization, with IPD accounting for less than 25 % [61]. Although there is overlap in the pneumococcal serotype distribution between adults with IPD and noninvasive CAP, several recent cohort studies of pneumococcal pneumonia that have used urine antigen detection techniques to identify pneumococcal serotypes have demonstrated important differences in comparison to contemporary IPD data. A UK study of adult pneumococcal CAP for the period 2008 – 2010 (2 to 4 years following the introduction of PCV7) found serotypes 14, 1, 8, 3 and 19A to be the most prevalent. In contrast, contemporary UK national IPD cohort data show serotypes 19A, 3 and 22F as the most prevalent in those older than 65 years, with serotype 14 being relatively underrepresented [23, 62]. IPD data from elsewhere in Europe for this period also show relatively low numbers of serotype 14 [63]. Similarly, a US study in adults aged ≥50 years admitted to hospital with pneumococcal CAP during the period 2010 – 2011 (10 to 11 years following the introduction of PCV7) found serotypes 19A, 7F/A, 3 and 5 to be the most prevalent, although serotype 5 has been rarely observed in contemporary US IPD cohorts [64].

Parapneumonic effusions (PPE) occur in 20 – 57 % of all individuals hospitalized with CAP, with empyema (complicated PPE) occurring in 5 – 10 % of that proportion [65]. PPE leads to excess mortality, longer length of hospital stay and the need for surgical intervention in some individuals [63, 66]. *Streptococcus* species account for complicated PPE in over half of all those affected [67, 68]. Pneumococcal serotypes 1, 3, 7F and 19A were independently associated with the development of complicated PPEs in cohorts of pediatric patients with empyema in the US and Europe [68–70]. A similar association was reported in an adult study of pneumococcal CAP in the UK [71]. An increase in the incidence of pediatric empyema rates was reported in some countries following the introduction of PCV7 to the child immunization schedule [72, 73]. Serotype replacement by non-PCV7 serotypes such as 1, 3, 7F and 19A in the post-PCV7 era may partly explain the observed increase in empyema incidence in these countries, although in the UK, childhood empyema rates decreased following the introduction of PCV7 [74].

The exact pathogenic mechanisms leading to complicated pneumonia with some pneumococcal serotypes are unclear. The ability of the more heavily encapsulated serotypes such as 3 and 19F to resist neutrophil-mediated killing may lead to the rapid accumulation of capsular polysaccharide; the resulting antigen load then generates a vigorous inflammatory response with tissue necrosis [43, 45•]. In contrast, serotype 1 has a thin polysaccharide capsule, and its high prevalence in pneumococcal empyema may be due to the presence of zwitterionic capsule polysaccharides, which, unlike the majority of pneumococcal serotype capsules, can directly activate T-helper cells [75]. In support of this hypothesis, the presence of zwitterionic polysaccharide capsules has been shown to aid the formation of intraabdominal abscesses in murine models [76].

Meningitis

Streptococcus pneumoniae is the leading cause of bacterial meningitis in children across the world; over 100,000 cases of pneumococcal meningitis leading to about 60,000 deaths per annum are estimated to occur globally [1•]. In a US population-based surveillance of isolates from individuals of all age groups with pneumococcal meningitis between 1998 and 2005, declines of 30 % and 73 % in the incidence of overall and PCV7-serotype meningitis, respectively, were observed following the introduction of PCV7 to the child immunization schedule [77]. Concurrently, the incidence of meningitis due to non-PCV7 serotypes increased by 60 % in the post-vaccination period, specifically due to serotypes 19A, 22F and 35B. A major concern was the increase in the proportion of isolates not susceptible to penicillin in this study.

The incidence and mortality associated with pneumococcal meningitis is significantly greater in Africa than in the rest of the world [1•]. Nasopharyngeal carriage rates are significantly higher across all age groups in Africa [14]. In contrast to data from the US, 60 – 80 % of cases in the African meningitis belt were attributed to serotype 1 in a recent systematic review [78]. The incidence of meningitis due to serotype 1 was highest amongst children aged over 5 years, which differs from the bimodal age distribution observed in the developed world [14, 78]. These differences highlight the importance of vaccine policy that is targeted to the specific needs of a population.

Antimicrobial Resistance

Serotype 19A is by the far the most widely reported serotype associated with antimicrobial resistance. The prevalence of serotype 19A, a non-PCV7 serotype, has increased in studies of both nasopharyngeal carriage and IPD since the introduction of PCV7 across the world [23–25, 28, 30, 56, 79, 80]. For example, IPD data from Spain for the period 2007–9 (1 to 3 years following the introduction of PCV7) found serotype 19A to be the most frequent serotype in children under 5 years of age [80]. Similarly, prospective surveillance of IPD in children from eight centers in the US found that 46 % of non-PCV7 serotypes during the period 2007 – 2008 (7 to 8 years following the introduction of PCV7) were serotype 19A. Of the serotype 19A isolates in the US study, 34 % were reported to have intermediate sensitivity or resistance to penicillin, and were more likely to be resistant to clindamycin, erythromycin, cotrimoxazole, and three or more classes of antibiotics in comparison to non-serotype 19A isolates [81•].

Although the increase in IPD due to serotype 19A in the post-CV7 era has stabilized, a continued increase in the proportion of antimicrobial resistance amongst serotype 19A isolates has been observed. Expansion of specific drug resistance clonal complexes comprising serotype 19A may account for this. Genotyping of serotype 19A isolates causing IPD, identified through Centers for Disease Control Active Bacterial Core surveillance in the US during the period 2004 – 2008, found an increase in the resistant clonal complex 320/271 from 20.9 % to 32.9 % during the period 2005 – 2007, which paralleled the increase in penicillin resistance among serotype 19A isolates during this period [82]. A study of pediatric IPD isolates collected from 1993 to 2011 in the US found that clonal complex 320 predominated among serotype 19A isolates [83].

Injudicious antibiotic use may favor the selective expansion of antibiotic-resistant pneumococcal strains. In a study of pediatric pneumococcal isolates in South Korea, the proportion of serotype 19A increased from 0 % to 26 % in the 12-year period prior to the introduction of PCV, and remained stable following the introduction of PCV [84]. The expansion of sequence type 320, belonging to the clonal complex 320/271, was largely responsible for the observed increase in serotype 19A in this study. Surveillance of pneumococcal isolates collected from 11 Asian countries by the Asian Network for Surveillance of Resistant Pathogens (ANSORP) during the period 2008 – 2009 showed that serotype 19A was the most prevalent non-PCV7 serotype; 86 % and 80 % of serotype 19A isolates showed erythromycin resistance and multidrug resistance, respectively [79]. Very few countries included in the study had introduced PCV7 to the national immunization program, and overall vaccine coverage remained low, suggesting that factors other than serotype replacement due to PCV7 are likely to explain the high prevalence of serotype 19A. Increases in serotypes 6C and 6D with associated drug resistance have also been reported [85, 86].

Conclusion

Despite widespread availability of effective antimicrobial therapy and vaccine-led preventative strategies, pneumococcal disease remains a challenge to healthcare systems around the world due to its substantial morbidity, mortality and cost burden. Recent studies, largely based on IPD data, have increased our understanding of the pathogenesis, complications and outcomes of pneumococcal disease with regard to specific pneumococcal serotypes. Worldwide pneumococcal seroepidemiology is currently undergoing significant changes, in part due to the introduction of PCVs to national immunization schedules. Continued surveillance of pneumococcal serotypes in nasopharyngeal carriage noninvasive disease and invasive disease is required. This is especially pertinent given the increasingly described associations between specific serotypes and different clinical phenotypes of disease, including disease severity.

Compliance with Ethics Guidelines

Conflict of Interest Wei Shen Lim is an advisory board member for Wellcome Trust, received research funding from the NIH and Pfizer Ltd., and is an editor of the *Handbook of Acute Respiratory Infections* published by Oxford University Press. Chamira Rodrigo received a grant from Pfizer and NIHR.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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