STREPTOCOCCUS PNEUMONIAE SEROTYPE DISTRIBUTION AFTER THE INTRODUCTION OF PNEUMOCOCCAL CONJUGATE VACCINES – REVIEW

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ABSTRACT

Streptococcus pneumoniae serotypes are changing due to the widely introduced pneumococcal conjugate vaccines. Surveillance studies have proven valuable in monitoring these vaccine effects. *S. pneumoniae* is highly adaptable to its human reservoir and colonises mucosal surfaces of upper airways mainly in children. Carriage decreases during the first 2 years of life because of the development of naturally acquired adaptive immune memory. Most of the serotypes do not cause serious illnesses but few of them are responsible for severe pneumococcal infections. Ten of the most common serotypes are estimated to cause over 60% of invasive diseases worldwide. The virulence factor of *S. pneumoniae* is the polysaccharide capsule as non-encapsulated strains are absent among the strains causing invasive pneumococcal disease. Prevalence of serotypes differs depending on the age group and geographic area of patients. Differences in PCV implementation lead to changes in serotype distribution and to significant reduction of disease caused by vaccine types.

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ABBREVIATIONS

AOM – Acute otitis media
CSF – Cerebrospinal fluid
Hib – *Haemophilus influenzae* type b
IgG – Immunoglobulin G
IPD – Invasive pneumococcal disease
NVT – Non-vaccine serotype
NP – Nasopharynx
PCV – Pneumococcal conjugate vaccine
PCV7 – 7-valent pneumococcal conjugate vaccine
PCV10 – 10-valent pneumococcal conjugate vaccine
PCV13 – 13-valent pneumococcal conjugate vaccine
Ply – Pneumolysin
RCT – Randomised controlled trial
U5 – Under five (years of age)
UNICEF – United Nations International Children's Emergency Fund
URT – Upper respiratory tract
VT – Vaccine serotype
WHO – World Health Organisation

INTRODUCTION

Streptococcus pneumoniae is a Gram-positive diplococcus and opportunistic pathogen colonising the human nasopharynx. Pneumococcal polysaccharide capsule and its chemical structure define the antigenicity and virulence of the strains. The host produces specific antibodies depending on the capsule type (1). This antibody-related immunity defines 98 different serotypes of *S. pneumoniae* by 2018 (2). Pneumococci are naturally competent and colonisation provides an opportunity for genetic recombination between serotypes or with other closely related species. This remarkable capacity of *S. pneumoniae* to remodel its genome may lead to antibiotic resistance or capsular switching (2, 3).

From 27% to 65% of children and more than 10% of adults are pneumococcal carriers. Normally the host`s innate and adaptive immune responses protect from invasion and retain the bacterium in a commensal state (3, 4). After colonisation pneumococci could be shed in the environment at levels allowing them to transmit

and colonise other hosts, where they may cause invasive pneumococcal disease (IPD) (3). The World Health Organisation (WHO) included *S. pneumoniae* as one of the 12 priority pathogens because of the remaining high burden of disease and the rising rates of antimicrobial resistance in pneumococci. The most common form of serious disease is pneumonia with highest mortality rates among children under the age of 5 (U5) worldwide (3, 4).

Development of pneumococcal vaccines started in the early 20th century but the first PCV was licenced in the year 2000 (1). This was PCV7 and it included purified capsular polysaccharides of 7 serotypes of *S. Pneumoniae* (4, 9V, 14, 19F, 23F, 18C, and 6B) conjugated to a non-toxic variant of diphtheria toxin (4). To date 10- and 13-valent formulations of PCV are used worldwide; the capsular polysaccharides are conjugated to a carrier protein, either protein D of *Haemophilus influenzae* type b (HiB), tetanus toxoid or diphtheria toxoid. In PCV10 protein D is used as the carrier protein for 8 serotypes (1, 4, 5, 6B, 7F, 9V, 14 and 23F), whereas 19F is conjugated to diphtheria toxoid and serotype 18C – to tetanus toxoid. PCV13 provides coverage also of serotypes 3, 6A and 19A. Additional products are expected to be licensed in the coming years (1, 4). PCVs effectively prevent the most serious forms of pneumococcal disease caused by the serotypes included in the vaccine and also reduce the risk of nasopharyngeal (NP) carriage of those serotypes (5). In Bulgaria PCV10 was introduced in the National Immunisation Calendar in 2010 with over 90% coverage in the period 2011-2017 according to data provided by WHO and UNICEF estimates of national immunisation (6).

Transmission, colonisation and carriage of *S. pneumoniae*

Until recently, all that was known about pneumococcal transmission was that it required close contact with one or more carriers, most probably young children. Colonisation in children was found to be frequent in fall and winter months, when viral infections of URL are common and nose secretions are abundant. (3). Animal models were examined and described – the ferret model and the infant murine model, both co-infected with influenza A virus (IAV) which increased transmission. “Shedding” from the host or leaving the human body, the survival of bacteria in the environment and the realisation of transfer between hosts, has been studied in detail with the infant mouse model. These studies have proven the need for large numbers of shed pneumococci so that at least one to be successful in reaching a new host (7). Another study with the same model, points out the necessity of the pneumolysin (Ply), the single toxin produced from *S. pneumonie*, as the key inflammatory and shedding agent in the colonized NP. This contributes to the transmission and the disease state by promoting the survival of bacteria in the environment and in the host at the same time (8). Studies of the *cps* promoter on the other hand showed that encapsulation may contribute to transmission of certain serotypes as capsules were more effective in facilitating shedding (7).

Transmission through secretions of carriers could involve direct person-to-person contact or spread involving bacteria on contaminated surfaces. *S. pneumoniae* is shown to survive on surfaces touched frequently by children carriers. The period of survival outside the human in saliva can reach a couple of days and bacterial expression of Ply increases survival in airway surface fluid (3). Ply-induced toxin-dependent inflammation and consequently, increased nutrients in secretions help bacteria survive outside the host (8). When the strain has a capsule it was shown it survives longer, since the capsule serves for nutrition through the carbohydrate reserve in it (7). Furthermore, pneumococci could survive drying up for many days, and biofilm bacteria retain viability *in vitro* better than planktonic bacteria (3).

According to data shown in murine models and experimental human carriage, colonisation increased antibody levels which had immunising effects and protected against subsequent disease (7). Colonisation increased nasal, lung and serum antibody levels and protected against reacquisition of the same strain up to 1 year. These protective events were found to be specific to the serotype and strain of *S. pneumoniae* that the volunteer was carrying and if different serotype was introduced there was no increased protection (9).

Correlation between NP carriage of pneumococci and disease was found mainly in studies with children U5 and as disease consequence – AOM manifestation being the most common. Although long periods of carriage were common with this

age group the acquisition of a new serotype was related to disease development (5). Several bacterial factors were required for colonisation and persistence in order for *S. pneumoniae* to effectively transfer to another host. Adherence was found to be compromised by the mucus, antimicrobial peptides, immunoglobulins of the NP and after overcoming these obstacles pneumococci might access and attach to the surface of epithelial cells (3). *S. pneumoniae* serotypes interact with the NP flora and this relationship is likely extensive and complex. Pneumococcal carriage was also related to the colonisation with other microbial species, usually in children during the first 2 years of life when the microbiome changes intensively (10). Dynamics in the relationships between the different serotypes colonising the same host were studied, and competitive pneumocins were found to be type–specific for pneumococci (3). Serotype distributions varied by syndrome, disease severity and carriage prevalence. There were factors found contributing certain serotype's colonisation – as the age of the host; also interactions with many children carriers daily, as in the family or in kindergartens (11).

Pneumococcal disease burden

Pneumococci could spread from the NP by contiguous extension in the respiratory tract to cause infection in the middle ear (otitis media), sinusitis or non-bacteremic pneumonia. *S.pneumoniae* could also invade the bloodstream and spread to other sites in the host causing secondary, more distal infection (Table 1.) (1, 4). IPD is defined as "isolation of pneumococcus from a normally sterile body site" (such as blood, CSF or pleural fluid) and can range clinically from bacteremia with fever but no focus of infection (the so-called occult bacteremia) to life-threatening infection. According to these definitions, Table 1 shows the different diseases caused by pneumococci classified as invasive or non-invasive (1). There are serotype-specific differences in the frequency and site of disease following NP colonisation. Some serotypes are more commonly found causing bacteremic pneumonia and others are more commonly found causing meningitis, for example (11). Recent studies show a link between pneumococcal bacterial load and invasiveness of a specific serotype compared to other carried serotypes. The higher NP concentration of a certain serotype compared to the others colonising the host suggests higher probability for the numerous serotypes causing IPD. This quantitative assay may potentially predict invasiveness and distribution of some of the S. pneumoniae serotypes according to their numbers in the nasopharynx (12).

Table 1. Invasive and non-invasive pneumococcal diseases.

Invasive pneumococcal diseases	Non-invasive pneumococcal diseases
• Bacteremia without a clinical focus of infection • Bacteremic pneumonia • Cellulitis with bacteremia • Endocarditis • Pericarditis • Septic arthritis • Osteomyelitis • Peritonitis • Epiglottitis	• Acute otitis media • Non-bacteremic pneumonia • Bronchitis • Sinusitis • Conjunctivitis • Mastoiditis • Periorbital cellulitis

Pneumococcal mortality is a significant contributor to the U5 mortality rate worldwide. *Streptococcus pneumoniae* is the most common cause of bacterial pneumonia in children and accounted for 16% of all deaths of children U5 according to WHO 2015 report. Invasive disease accrues in younger children more commonly in developing countries – through the first year of their life, compared to developed countries were there were less common and at later age (1, 4). The leading IPD was meningitis, which leaded to severe consequences like neurological sequelae, hearing loss and mental retardation. Case fatality rates from IPD in children can be high, ranging up to 50% according to the disease type and the country of occurrence (11).

Effects of PCVs on invasive disease and carriage

Despite the high coverage of PCV's in Europe and the United States and the global vaccine funding for low income countries, *S. pneumoniae* remains the leading cause of childhood mortality worldwide (1, 11). Before the introduction of PCV's, studies have shown that around ten serotypes caused the majority of IPD in children. PCV7 included serotypes that were responsible for meningitis and were nonsusceptible to penicillin. In the United States, following PCV7,

only 5% of the clinical isolates were of serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F). Prevalence of NVT had then increased with 19A becoming a leading cause of IPD with a high percentage of MDR strains. The PCV13 with added coverage of 19A and other serotypes (1, 3, 5, 6A and 7F) was approved and by 2012-2013 and had the desired effect, with serotype 19A strains falling to 10%. The new PCV13 covered 19A serotype but not long after that the niche was replaced with 35B also not susceptible to penicillin (13).

Globally serotype 14 was known to cause IPD most frequently and 6B was the next common IPD serotype. In Africa there were differences in distribution – there was serotype 1 as most prevalent, together with serotype 5 on second place (11).

In Bulgaria a study during a period after the introduction of PCV10 demonstrates distribution of NVT 3 and 19A causing meningitis in vaccinated people. Other serotypes/serogroups in the study causing IPD are 8, 9N/L, 10A/D, 10B, 11A/D, 15B/C, 15A/F, 24 A/B/F that are not included in the PCV10 nor PCV13 (14). According to another study from Bulgaria, in Plovdiv region, serotypes 3 and 19A causing meningitis in the period 2013-2017 were confirmed as most abundant (15).

The major difference between the two PCVs used was the additional inclusion of serotypes 3, 6A and 19A. There were not any cross-reactive serotypes in PCV10 against serotype 3, but serotype 6A was assessed to have cross-reactive immunogenicity with serotype 6B and no effect with 6C. Serotype 19A was estimated to have cross-reactivity with 19F and was supposed to be covered by both the ten and thirteen – valent conjugate vaccines (11).

Most notably PCV7 had effects on AOM in vaccinated children. However, these effects were limited to primary infections of the middle ear, not the chronically accruing otitis media high risk group children (4). The vaccination with PCV protects against acquisition of VT in children but does not contribute to clearance of carriage. (1, 6). Random control trials report about 50% decrease in VT carriage and increase of NVT colonization and serotype replacement is observed in all countries implementing the vaccines (1, 11).

In conclusion, many factors are being responsible for the effects of PCVs on disease burden and related pneumococcal serotype carriage. Serotypes causing IPD changed throughout the years after PCV implementation and NVT are now responsible for invasive disease. However, the revue data showed severe reduction of VT carriage and VT pneumococcal diseases worldwide and definitely confirmed the positive outcomes of the IPD implementation (11, 14, 15).

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