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Differences in serious clinical outcomes of infection caused by specific pneumococcal serotypes among adults

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ABSTRACT

Background: Infections due to *Streptococcus pneumoniae* serotypes differ in clinical manifestations among adults, varying in propensity for severity, invasiveness, and lethality. To characterize differences in serious outcomes between pneumococcal serotypes, we systematically reviewed the literature.
Methods: After distilling 676 hits to 28 relevant articles, statistically significant differences in individual serotypes associated with serious clinical outcomes were assessed. Serotypes associated with elevated risk of serious clinical outcomes were evaluated in terms of serotypes included in licensed adult pneumococcal vaccines (i.e., 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13)). Repeated findings were considered a measure of robustness.
Results: Among adult studies evaluating serious clinical outcomes, the following serotypes were associated with elevated risk: Empyema (serotypes 1, 3, 5, 7F, 8, 19A), necrotizing pneumonia (serotype 3), septic shock (serotypes 3, 19A), meningitis (repeatedly serotypes 10A, 15B, 19F, 23F), reduced quality-adjusted life years (QALYs, serotypes 15B, 3, 10A, 9N, 19F, 11A, 31), and increased case-fatality rates (repeatedly serotypes 3, 6B, 9N, 11A, 16F, 19F, 19A).
Conclusion: Both vaccine formulations include multiple pneumococcal serotypes associated with increased risk for serious clinical outcomes. Three studies found elevated risk from serotype 6A (unique to PCV13). Fourteen studies found elevated risk from nine serotypes unique to PPSV23 (repeatedly: case-fatality—11A & 9N, meningitis—10A & 15B). Seven studies found elevated risk from serotypes not represented in either vaccine formulation (notably 16F). The pneumococcal serotypes repeatedly associated with elevated risk of serious outcomes in adults are an important consideration for vaccine policy making.

Streptococcus pneumoniae remains the most commonly identified pathogen associated with hospitalization and death among adults. Despite improvements in the diagnosis and effective antibiotic therapy of suspected pneumococcal pneumonia cases, mortality rates remain high, ranging from 5% to 35% [1].

Pneumococcal serotypes differ based on their antigenically distinct capsules. The serotypes also differ markedly in their pathogenicity. Individual serotype prevalence can change over time or geography [2–5], or between age groups or anatomic niches [2,6–12]. Serotypes vary in their propensity to colonize or infect younger versus older or healthy versus comorbid adults [13–15]. Among pneumococcal serotypes, some are associated with an increased degree of disease severity [13–15], an increased risk of invasiveness (e.g., meningitis, bacteremia) [11,14,16], or an increased case-fatality rate [17,18]. Some serotypes are more likely to exhibit antibiotic resistance [3,19–21], which may provide a selective advantage over other serotypes. These associations should be considered in deciding which pneumococcal vaccine to recommend and use in specific populations. Reviews of pneumococcal serotype propensities of this type focusing on children have been published [11,22–24], but little information is available for adults, which this review aims to address.

1. Methods

To identify published articles describing differences in serious clinical outcomes related to individual pneumococcal serotypes among adults, we searched the entire PubMed database through February 2014, regardless of language. The search terms were

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[(Streptococcus pneumoniae OR pneumococcal infections) AND (epidemiology OR pathogenicity OR mortality OR immunology OR risk factors) AND (serotyping OR bacterial typing techniques) AND adult)]. We also considered relevant articles identified from references cited in these articles. Eligible studies included at least 100 cases of pneumococcal disease. Studies were accepted if age-stratified results excluded patients younger than 5 years of age. Because studies of general populations were sought, studies of specific patient groups (e.g., those with leukemia, HIV infection, chronic obstructive pulmonary disease) were excluded.

The PubMed query yielded 676 papers. All 676 abstracts were reviewed for applicability to this project, but many were excluded, because they were in vitro studies, review articles, evaluations of single serotypes or pediatric populations, because they considered only demographic risk factors or pneumonia alone, or for other forms of irrelevance. Forty-seven articles were reviewed in entirety based on their abstracts. Of these, 23 either provided no statistical tests ($n = 11$), did not exclude children (9), dealt with antibiotic resistance only (2) or carriage only (1), was a case report (1), or lacked serotype specificity (1). Thus, that step yielded 24 relevant articles. We also considered an additional 14 articles identified from references cited in the 47 articles, and included 4 of them. Thus, the final bibliography encompassed 28 articles.

The final set of studies chose various reference serotypes upon which to assess increased risk; the most common selections were all other serotypes together (typically via logistic regression) or serotype 14 (typically because it was the most common serotype identified). Some studies assessed elevation of risk within serotype, contrasting patients with invasive pneumococcal disease (IPD) with or without the serious outcome. These reference frames were considered as the core of the analysis, with studies using other reference frames considered supplementally. In cases where authors grouped several serotypes together for analysis, the individual serotypes are designated in the tables as "bundled."

Relative to these reference serotypes, the other serotypes were categorized as either comparable to (not statistically different from) the reference serotypes, or significantly increased or decreased relative to the reference serotypes. Findings were categorized as increased or decreased if the risk involved a significant statistical value (e.g., odds ratios or relative risks with confidence intervals excluding 1 or $p < 0.05$). Other findings solely of a trend or designated by authors as noteworthy were disregarded. Where authors presented both unadjusted and adjusted odds ratios or relative risks, only the adjusted values were used for this review (see Supplemental Table 1 for description of study-specific treatment of covariates for adjustment). Because small studies could lack statistical power to find a meaningful elevation in risk [25], only significant elevations in risk were considered in respect to vaccine formulations; thus risks and rates comparable to reference serotypes were noted, but disregarded from further analysis.

An additional step was applied to studies that found more than 10 serotypes to have statistically elevated risk [14,16,17], which included very large samples and/or those that used only one or a few serotypes for the reference group. In such cases, to focus on serotypes with substantial elevation in risk, only those serotypes with a point estimate for the adjusted odds ratio greater than 3 were considered in the subsequent assessment of vaccine content.

Repeated associations with elevated risk of serious clinical outcome, defined as elevations found in three or more independent studies, were considered a measure of robustness of elevated risk. These were evaluated for relevance to serotypes included in adult vaccine formulations (i.e., 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13)).

2. Results

The literature review yielded studies of important clinical outcomes involving empyema (or parapneumonic effusion), necrotizing pneumonia, septic shock, meningitis (each summarized in Table 1), and lethality (as measured by case-fatality rates), summarized in Table 2. One study assessed effect on quality-adjusted life years (QALYs), as a means of aggregating clinical consequences into a single quantitative parameter (Table 1) [16].

3. Specific clinical outcomes

Among four adult studies evaluating empyema or parapneumonic effusion [7,26–28], the serotypes associated with elevated risk were 1, 3, 5, 7F, 8, and 19A (Table 1). Across the four studies, serotype 1 was the serotype associated with increased risk for empyema. In one adult study evaluating necrotizing pneumonia [29], serotype 3 was associated with elevated risk. Among three adult studies evaluating sepsis or septic shock [8,30,31], one study found no elevations, whereas the other two studies associated serotypes 3 and/or 19A with increased risk for septic shock in patients with pneumococcal pneumonia.

Among seven adult studies evaluating meningitis [6,8,14,16,32–34], the following serotypes were associated with elevated risk: 3, 6A, 6B, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 18C, 19F, 19A, 20, 22F, 22A, 23F, 23A, and 35F (Table 1). Serotypes 10A, 15B, 19F, and 23F were found to be associated with increased risk of meningitis in three or more studies. The large datasets finding odds ratios > 3 involved serotypes 3, 6A, 6B, 6C, 8, 9N, 10A, 12F, 15A, 15B, 16F, 16B, 18C, 19F, 20, 22F, 22A, 23F, 23A, and 35F [14,16]. van Hoek and colleagues stratified their analysis into two adult age groups [16], finding the serotypes associated with greatest risk among adults 65 years of age or older also represented those associated with greatest risk among individuals 5–64 years old, for whom the list of elevated serotypes included more serotypes than those identified for the older population.

In the study that assessed loss of quality-adjusted life years (QALYs) due to pneumococcal disease [16], the upper quartile of serotypes included serotypes 15B, 3, 10A, 9N, 19F, 11A, 31, and others (Table 1). These investigators found greater difference in elevated serotypes between age cohorts than seen with meningitis.

Among 18 adult studies evaluating case-fatality rate [7,8,10,13,14,16,17,30,35–43], plus one meta-analysis [18], the following serotypes were repeatedly found in three or more studies to be associated with elevated risk: 3, 6B, 9N, 11A, 16F, 19F, and 19A. The elevations with odds ratios > 3 involved serotypes 3, 6A, 6B, 8, 10A, 11A, 14, 15B, 16F, 17F, 19F, 19A, 23F, 31, and 35F.

Thirty of 36 study analyses used one of the primary reference frames (e.g., all other serotypes, within serotype, serotype 14). Omitting studies using other reference frames [7,13–15,17,28,40] did not meaningfully change the findings presented above for empyema, necrotizing pneumonia, sepsis, or case-fatality rate. This restriction would change the number of studies finding increased risk for meningitis due to serotypes 10A from three to two.

Twenty-seven of 36 study analyses adjusted their findings for various combinations of potential confounding variables (Supplemental Table S1). Omitting studies finding elevated risks that did not control for at least two of three key categories of covariates (i.e., age, acute presentation, comorbidities) [6,7,13,18,27,32–34,37–40] did not meaningfully change the findings presented above.

4. Risk in relation to vaccine formulations

Most pneumococcal serotypes associated with a statistically significant elevation in risk for serious clinical outcomes are included