

Pneumococcal capsular serotypes and lung infection

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Streptococcus pneumoniae is second only to *Mycobacterium tuberculosis* as a bacterial cause of worldwide mortality. Unlike *M tuberculosis*, *S pneumoniae* remains a major cause of death in the developed world, with a standardised mortality rate of 25 per 100 000 in the UK. *S pneumoniae* is the commonest pathogen causing community acquired pneumonia (CAP),¹ and the majority of serious *S pneumoniae* infections are cases of CAP in infants and older people. *S pneumoniae* is also an important cause of septicaemia, meningitis and infective exacerbations of chronic obstructive pulmonary disease and bronchiectasis. *S pneumoniae* is surrounded by an extracellular layer of polysaccharide called the capsule which promotes immune evasion and is an essential virulence factor.² The structure of the capsule differs between *S pneumoniae* strains, with 93 variants identifiable by serotyping. Serotype prevalence is unequal, with the majority of disease caused by around 20 common serotypes. Which serotypes are predominant varies with age, geography and site of infection (eg, the nasopharynx, pleural space or the blood). In the paper by Bewick *et al*, technical advances in microbiology have been used to identify which *S pneumoniae* capsular serotypes are the commonest causes of CAP in a UK centre.³ Why do these rather technical data matter to a clinician, and how could they affect future developments in the management of *S pneumoniae* lung infection?

First, the ability to identify which serotypes are causing CAP is in itself a major advance. Previously, capsular serotyping required cultured bacteria and was therefore biased towards serotypes that cause septicaemia as respiratory cultures have such low sensitivity in CAP. For example, in Bewick *et al*'s paper only 58 of 366 cases of *S pneumoniae* CAP had positive cultures, mainly from blood.³ By using urine samples for a highly sensitive multiplex immunoassay based on xMAP bead technology, Bewick *et al* were able to identify *S pneumoniae* capsular serotype in

culture negative cases of CAP, providing for the first time a largely unbiased assessment of which serotypes cause CAP. At present the multiplex serotype immunoassay is restricted to only 14 serotypes, the pneumococcal conjugate vaccine (PCV13) serotypes and serotype 8, and this limitation is probably why no serotype was identified for one-third of their patients with *S pneumoniae* CAP. Future technical developments are likely to increase the numbers of serotypes that can be detected and partially overcome this problem. Interestingly, the multiplex immunoassay increased the sensitivity of microbiological confirmation of *S pneumoniae* CAP, identifying 144 cases in which the established urinary antigen test (Binax NOW, Portland, Maine, USA) was negative.³ This provides a potential justification for using this technology independent of the possible advantages in identifying serotype.

Second, capsular serotype could identify patients at risk of specific complications of CAP. Serotype affects *S pneumoniae* resistance to complement, phagocytosis, adhesion to epithelial cells and virulence in mouse models.^{4–6} Probably related to these biological effects of serotype, in human disease duration of *S pneumoniae* colonisation, the number of episodes of invasive disease per colonisation event, mortality and ability to cause empyema are all linked to serotype.^{7–9} For example, before the introduction of infant vaccination the top five capsular serotypes causing *S pneumoniae* septicaemia and meningitis were 14, 19F, 6B, 23F and 18C, yet 80–90% of cases of *S pneumoniae* empyema are caused by serotypes 1, 3, 7F and 19A.⁹ Until now it was not clear whether the serotypes commonly causing empyema simply reflected their dominance as serotypes causing CAP or a specific affinity for invading the pleural space. Bewick *et al* found that only one of the three commonest CAP serotypes frequently causes empyema, and overall only 40% of cases of CAP were caused by serotypes associated with empyema. Similarly a recent Spanish study which used a multiplex PCR to identify *S pneumoniae* serotypes in culture-positive patients with CAP showed serotypes 4, 5

and 8 are more likely and serotypes 19F and 6B less likely to cause an associated septicaemia.¹⁰ In addition, infection with serotype 3 is clearly associated with increased mortality.⁸ These data demonstrate specific *S pneumoniae* serotypes are associated with important complications of CAP such as empyema, septicaemia and death. Identifying infecting serotype could therefore help risk stratify patients with *S pneumoniae* CAP, and identify those who might benefit from earlier intervention such as drainage of pleural effusions. Furthermore, comparing the biology of serotypes associated with specific disease phenotypes will help characterise the bacterial and host factors involved in the pathogenesis of infection at different sites.

Third, Bewick *et al* have provided additional data suggesting that *S pneumoniae* infection in younger patients is largely restricted to a limited number of highly invasive serotypes. As discussed above, serotype affects the ability of *S pneumoniae* to cause invasive disease with attack rates (number of cases of meningitis or septicaemia per colonisation episode) ranging from 0 to 75 for different serotypes.⁷ Bewick *et al* found a direct correlation between increasing age and comorbidities and infection with less invasive serotypes, supporting the hypothesis that advancing age allows less aggressive *S pneumoniae* serotypes to cause disease.³ The increasing incidence of less invasive serotypes with age and comorbidity (both markers for increased mortality) may also explain the seemingly paradoxical observation that infection with more invasive serotypes has a lower mortality than infection with less invasive serotypes. One caveat to these data is that the exclusion of serotype 14 and 19A strains from the invasive serotype group by Bewick *et al* could be challenged as both serotypes have high attack rates⁷; including these serotypes in the invasive group could have altered the statistically significant association of less invasive serotypes with increasing age and comorbidities.

The final reasons why data on *S pneumoniae* serotypes causing adult lung infection are important are the implications for prevention by vaccination. Although most of the serious *S pneumoniae* infections occurring in adults are CAP, the adult *S pneumoniae* vaccine (PPV, based on pneumococcal capsular polysaccharide from the commonest 23 serotypes) only prevents *S pneumoniae* septicaemia and meningitis and has little efficacy against lung infection.¹¹ The childhood PCV vaccine also uses capsular antigen but

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linked to a protein carrier so it is much more immunogenic in children than PPV. PCV has been highly successful in children, preventing invasive *S pneumoniae* infections and colonisation with vaccine serotypes, and reducing the incidence of pneumonia.¹² Due to herd immunity, PCV vaccination of children has also been associated with reduced incidence of *S pneumoniae* CAP with vaccine serotypes in adults.¹² PCV coverage was originally limited to seven serotypes, but has recently increased to 13. The increased immunogenicity of PCV over PPV (at least in children) and the evidence that it induces mucosal immunity suggests that vaccination of adults with PCV might prevent *S pneumoniae* CAP. However, there are no data to support the use of PCV in adults as yet; large-scale trials are in progress. PPV and PCV only give serotype-specific protection, so identifying which serotypes cause CAP is clearly critical for assessing what the impact of PCV13 could be on adult CAP, and perhaps for choosing serotypes to be included in a future version of PCV for adults. Bewick *et al* show that if PCV is effective at preventing adult CAP, then using the PCV13 could prevent up to 57% of cases of disease.³ This proportion is probably an underestimate as in their study one-third of cases could not be serotyped and the multiplex assay is unlikely to be 100% sensitive. Hence even if the PCV13 vaccine only prevents a proportion of adult CAP caused by vaccine serotypes this still could have considerable effects on respiratory morbidity and mortality. As a consequence, the results of the current trials of PCV in adults are of great importance. A theoretical bonus of PCV vaccination in adults could be prevention of infective exacerbations of COPD. However, PCV13 serotypes cause only 43% of infective exacerbations of COPD associated with *S pneumoniae*,¹⁰ and whether PCV can improve mucosal immunity within a damaged bronchus adequately to prevent infective exacerbations needs to be established.

S pneumoniae is a nasopharyngeal commensal, and infants are thought to be the major reservoir for infection due to their high levels of colonisation. Routine childhood vaccination in the UK since

2006 with PCV has resulted in dramatic falls in the prevalence of vaccine serotypes as commensals, including serotype 14.¹³ Hence the discovery by Bewick *et al* that serotype 14 was still the commonest cause of adult CAP is surprising,³ and perhaps suggests that the relatively low level of *S pneumoniae* colonisation of adults maybe an alternative reservoir for infection. Colonisation of adults with vaccine serotypes could therefore lead to re-emergence of these serotypes in children if they are no longer included in a future PCV vaccine. Another important consideration is the incredibly rapid expansion of non-vaccine serotypes since the introduction of PCV, which has limited the impact of PCV on the overall incidence of *S pneumoniae* infection.¹³ PCV13 includes many of the serotypes that have increased in incidence since introduction of the PCV7, so may help counter these changes in *S pneumoniae* ecology. However, a lower proportion of adult CAP is caused by PCV13 serotypes than paediatric or invasive disease. This larger reservoir of non-vaccine serotypes makes serotype-replacement disease in response to adult vaccination with PCV more likely to be a major problem than it has been in children. Any introduction of PCV into adult populations will need to be supported by a post-vaccination surveillance program.

The data presented by Bewick *et al* on capsular serotypes causing adult CAP is a significant breakthrough. The sensitivity of the multiplex immunoassay makes this technology a potentially useful diagnostic test for *S pneumoniae* CAP, and knowing the infecting serotype could help clinicians identify patients at higher risk of important complications. If trials demonstrate a beneficial effect against lung infection of PCV in adults, identifying serotypes causing CAP will be an essential tool for choosing which serotypes should be included in future PCV preparations and for monitoring changes in *S pneumoniae* ecology in response to vaccination.

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