*Thorax Editorial October 2024 for '*Pneumococcal pneumonia trends in adults hospitalised with community-acquired pneumonia over 10 years (2013-2023), and the role of serotype 3 *' Lansbury et al.'*

word count

Streptococcus pneumoniae **pneumonia; the clinical relevance of capsular serotype**

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Lower respiratory tract Infections (LRTIs) remain a common cause of respiratory mortality, responsible annually for approximately 40,000 deaths in the United Kingdom and 2.7 million globally (**1**). The most severe common LRTI in the UK is community acquired pneumonia (CAP), which for hospitalised patients has a mortality of 8% (**2**) and the incidence of which is increasing as the population ages (**3**). Despite being the only common bacterial cause of LRTIs for which we have an effective vaccine, *Streptococcus pneumoniae* still remains the dominant bacterial cause of LRTIs, responsible for 16% of fatal cases globally (**4**) and 40% of hospitalised CAP in the UK (**2**). The manuscript published in this edition of Thorax by Lansbury et al. (**5**) provides additional data that further underlines the challenges in trying to reduce the persisting high morbidity and mortality caused by *S. pneumoniae*.

Lansbury et al. (**5**) present data from 5186 patients with CAP admitted to two Nottingham hospitals between 2013 to 2023, of which 2193 (42%) were caused by *S. pneumoniae*. The study has several advantages, including (i) its size and duration allowing the assessment of changes over time, (ii) being based at research sites with a long pedigree of CAP research, and (iii) using the Bioplex-24 urinary antigen test to diagnose *S. pneumoniae* CAP and identify the causative capsular serotype. *S. pneumoniae* is surrounded by a capsule that consists of repeating chains of usually three or four monosaccharide units, with the different chemical compositions resulting in over a 100 different capsular serotypes. All existing *S. pneumoniae* vaccines are based on capsular antigens and only protect against the serotypes contained in the vaccine; hence which serotypes are the predominant cause of CAP is crucial for vaccine efficacy. The Bioplex-24 test identifies the presence of capsular antigen from 24 common disease-causing *S. pneumoniae* serotypes in urine, and a positive result suggests infection with that specific *S. pneumoniae* serotype. Concordance of Bioplex-24 results with blood culture data on infecting serotype is 80%, with the remaining 20% split between identification of discordant serotypes, infection with serotypes not identified by Bioplex-24, or a negative Bioplex-24 result (**2**). How often *S. pneumoniae* nasopharyngeal colonisation without pneumonia causes a positive Bioplex-24 test is not known, but the lower bacterial load during

colonisation and the high concordance with blood culture results strongly suggests that a positive Bioplex-24 in a patient with CAP reflects the causative pathogen. Even though it does not identify infection with *S. pneumoniae* serotypes not included in the test, the Bioplex-24 test doubled the proportion of CAP cases attributed to *S. pneumoniae* (**5)** and hence could considerably improve the existing lamentable rate of identification of the causative pathogen in patients with CAP.

Lansbury's et al. show that the proportion of CAP caused by *S. pneumoniae* increased from 36% in 2013 to 67% in 2023 (**5**), a surprisingly large increase that is hard to fully explain. A closer inspection of the data indicates that before the COVID pandemic the proportion of CAP caused by *S. pneumoniae* increased steadily from a low of 32% in 2015-16 to 44% in 2018-19, but a major additional increase occurred during the COVID pandemic (**5**). The reasons underpinning this shift are not at all clear. Some of the increase in the proportion of CAP attributed to *S. pneumoniae* probably reflects the higher proportion of CAP caused by *S. pneumoniae* with increasing age. However, the proportional increase in CAP caused by *S. pneumoniae* seems to be mainly driven by an unexpected fall in non-pneumococcal CAP over time. Suppression of respiratory virus prevalence during lockdowns may have reduced non-pneumococcal CAP, but the increased proportion of pneumococcal CAP continued into the post-pandemic period when the incidence of respiratory viral infections had rebounded. The threshold for admission for patients with CAP may have shifted over time to exclude less severe CAP cases, and as *S. pneumoniae* CAP has higher CURB65 scores and rates of intensive care admissions (**5**) this may reduce the relative prevalence of non-*S. pneumoniae* CAP. Furthermore, if non-*S. pneumoniae* CAP tends to develop slower than *S. pneumoniae* CAP the increase in remote consultations and antibiotic prescribing (**6**) could disproportionately reduce admissions of the former. Whatever the underlying reason(s) for the increase in proportion of CAP admissions attributed to *S. pneumoniae*, this change further emphasises the need for a more effective *S. pneumoniae* vaccination policy for adults.

Lansbury et al. also identified a striking increase in the proportion of CAP cases attributed to serotype 3 from 13% in 2013 to 49% in 2023, and also increases in the proportion of cases in which Bioplex-24 was positive two or more capsular serotypes which reached 37% by 2023 (most often serotypes 3 combined with 8) (**5**). The lack of chemical similarity between serotypes 3 and 8 indicate this is not likely to be a false positive association due to cross-reactivity for these serotypes with the Bioplex-24 test. In contrast, blood culture results were dominated by serotype 8, but this is a particularly invasive serotype that is probably more likely to cause septicaemia than serotype 3. Serotype 3 was also the dominant cause of *S. pneumoniae* CAP in recent studies from Germany, Sweden, Greece, Spain, and at other UK sites (but not Bristol) (**2,7,8**), showing this is a widespread phenomenon. The main reservoir for adult *S. pneumoniae* infection is thought to be strains colonising the nasopharynx of their infant contacts (one downside of having grandchildren); hence, any increase in serotype 3 CAP should be reflected by increases in serotype 3 colonisation in infants. Since 2010 the routine vaccination of infants with Pneumococcal Conjugated Vaccine 13 (PCV13) has markedly reduced the prevalence of vaccine serotype strains as colonisers and causes of invasive infection in children; however, the exception are serotype 3 strains, against which PCVs seem to have poor efficacy (**9,10**). Despite this, the proportion of *S. pneumoniae* strains colonising infants that are serotype 3 is considerably less than 50%, making this serotype's dominance as a cause of adult CAP hard to explain. Potential reasons include a shift in colonising serotype 3 strains to those that are more able to cause CAP than other colonising serotypes, or the existence of additional reservoirs for disease transmission (for example, other adults) with higher levels of serotype 3 colonisation than infants. These possibilities need exploring by future studies.

As serotype 3 CAP does not cause more severe CAP than other serotypes (**5**), the high prevalence of serotype 3 does not have major implications for clinical management. But it does have very important potential implications for vaccine policy. Adults are vaccinated with the Pneumococcal Polysaccharide Vaccine which protects against 23 serotypes (including

serotype 3), but has a relatively poor efficacy at preventing pneumonia especially in people aged over 75 years (**11**). The poor efficacy of PPV has stimulated recent interest in vaccinating adults with newer PCVs that protect against an expanded range of serotypes (PCV15, 20, and 21), which theoretically could protect against 80+% of CAP serotypes (**5**). However, the poor efficacy of *S. pneumoniae* vaccines against serotype 3 (**9,10**) means that a prevalence of serotype 3 strains as the cause of *S. pneumoniae* CAP close to 50% will undermine the overall cost effectiveness of vaccination, even if the policy changes to include the new higher valency PCVs.

To conclude, Lansbury et al. demonstrate a continued and increasingly high burden of *S. pneumoniae* CAP in adults that further emphasises the need for an effective vaccination policy, yet their finding that serotype 3 strains are the dominant cause will complicate the design of more effective vaccination policies (potentially using new higher valency PCVs) due to their relative resistance to prevention by vaccination.

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