Diverse and distinct *S. pneumoniae* cause invasive disease in Papua New Guinea

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Streptococcus pneumoniae is a common cause of pneumonia and meningitis which are key contributors to childhood morbidity and mortality in Papua New Guinea (PNG). Penicillin-resistant *S. pneumoniae* have long been reported in PNG (Douglas 2010). Approximately 21.5% of isolates from children with meningitis are penicillin-resistant (Greenhill et al., 2015). Some serotypes rarely observed in other geographic settings have been common causes of invasive pneumococcal disease (IPD) in PNG.

This study captures the baseline *S. pneumoniae* population prior to introduction of PCV-13 into the childhood immunisation programme in 2014. For the first time, whole-genome sequencing of 191 isolates has enabled characterisation of the population structure of *S. pneumoniae* causing meningitis and/or pneumonia in children <8 years of age in PNG. Relationships amongst lineages, serotypes and antimicrobial resistance traits were characterised. Serotypes of interest were contextualised using the Global Pneumococcal Sequencing (GPS) project database, consisting of ~26,000 isolates.

The analyses highlighted the diversity of the *S. pneumoniae* population in PNG, with 33 serotypes across 48 Global Pneumococcal Sequencing Clusters (GPSCs) observed. Multiple GPSCs observed in PNG have not been identified elsewhere (29 isolates), and the MLST of a further 34 isolates were unique to PNG. Concerningly, almost half of isolates (47.6%) were non-PCV13 serotypes, which had higher odds (OR 3.54 [1.27, 11.43], p=0.009) of association with meningitis than PCV-13 serotype isolates. Over a third of isolates were predicted to be resistant to at least one antimicrobial. PCV-13 serotype isolates had higher odds of being multidrug-resistant (MDR) (OR 13.6, [1.96, 589.24], p=0.001), and no isolates with GPSCs unique to PNG were MDR (n=29). However, the odds of resistance to penicillin did not differ between PCV-13 and non-PCV-13 serotype isolates, suggestive that PCV-13 would have a limited impact on reduction of penicillin resistance. Serotype 2 (GPSC 96) was the most commonly identified serotype and 82.8% of isolates were from children with meningitis. Placing PNG serotype 2 isolates in the global context identified a highly clonal cluster of serotype 2 isolates unique to PNG (ST 1504), and a distinct second cluster suggestive of intercontinental transmission (ST 1504~).

The resolution afforded by genomic data and contextualisation using the GPS collection has highlighted the distinct *S. pneumoniae* population observed in PNG, with multiple GPSCs unique to PNG. Ongoing surveillance, including WGS, is required to monitor the impact of the national PCV-13 programme upon the *S. pneumoniae* population, including serotype replacement and antimicrobial resistance.