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**Title: Emergence of multidrug resistant serotype 16F lineages in infants in South Africa.**

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**Background**

Given the emergence of non-vaccine serotypes in colonised/vaccinated individuals, *Streptococcus pneumoniae* (*S. pneumoniae*) remains a major global health challenge despite advances in vaccine development. Serotype 16F is among the predominant non-vaccine serotypes identified among vaccinated infants in South Africa (SA). To understand the genomic epidemiology of this serotype, we used whole genome sequencing to characterise lineages and antimicrobial resistance in 16F isolates obtained from SA and compared them to 16F isolates from a global database.

**Methods**

A longitudinal analysis of *S. pneumoniae* serotype 16F isolates obtained from nasopharyngeal swabs of infants recruited into a SA birth cohort study between 2012-2014 (n=944), and a cross-sectional analysis of serotype 16F isolates from the Global Pneumococcal Sequencing (GPS) database (n=563). Whole genome sequencing was performed on Illumina HiSeq.

**Results**

Serotype 16F is predominant in GPSC33 and GPSC46 lineages. Compared to other 16F lineages, GPSC33 was associated with carriage (72%) and GPSC46 with invasive pneumococcus disease (IPD) (83%), ($p<0.0001$, Fischer's exact test). 85% of infants were colonised with one lineage indicating within-host lineage dominance. Isolates delineated to GPSC46 and GPSC33 had mutations associated with resistance to co-trimoxazole (18%-GPSC46; 15%-GPSC33) and penicillin (18%-GPSC46; 11%-GPSC33) and erythromycin (0.1%-GPSC46; 1.6%-GPSC33). 1% of GPSC33 isolates, obtained from SA, had mutations associated with resistance to both co-trimoxazole and penicillin.

**Conclusions**

Emergence of multidrug resistance (MDR) serotype 16F lineages pose a challenge to effective prevention and treatment of IPD. Monitoring for resistance, judicious antibiotic use and vaccine strategies that protect against a wide range of serotypes/lineages remain essential.