

## **Vaccine escape: emergence of a multidrug resistant and virulent *Streptococcus pneumoniae* lineage GPSC10/CC230 post PCV-13 poses a global threat**

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### **Background**

Pneumococcal Conjugate Vaccine (PCV) which targets 13 serotypes of *Streptococcus pneumoniae* is very effective at reducing disease in young children, however, increases in replacement with non-PCV serotypes remains a concern. Serotype 24F is one of the major invasive serotypes contributing to serotype replacement in France, Spain and multiple other countries. We aimed to investigate the global genetic diversity of serotype 24F, identify and characterize the major pneumococcal lineage that drive the increase of serotype 24F in France and Spain, and elucidate its spatiotemporal transmission dynamics at the national and international level.

### **Methods**

We whole-genome sequenced two collections of serotype 24F *S. pneumoniae*: 1) 419 isolates from asymptomatic colonization (n=229) and invasive disease cases (n=190) among individuals <18 years old in France, 2003-2018; 2) 68 invasive disease isolates from children <5 years old from Catalonia, 2009-2018. We extracted relevant genomes and metadata from the Global Pneumococcal Sequencing project database (n=~26,000) to provide a global context of serotype 24F and strain of interest. All genomes *in silico* typed as serogroup 24 (n=671) were clustered

into Global Pneumococcal Sequence Clusters (GPSCs). Phylogenetic, evolutionary, and spatiotemporal analysis were conducted. We measured the invasive disease potential using odds ratio that compares prevalence in invasive disease to carriage.

### **Findings**

Serotype 24F was identified in numerous countries, in part, due to clonal spread of three pneumococcal lineages (GPSC10/CC230, 16/CC156 and 206/CC7701) rather than to recent capsular switching. Of these lineages, GPSC10 is the only multidrug resistant lineage, which drives the increase in 24F in France and Catalonia. Compared to other genetic backgrounds, GPSC10 has a relatively high disease potential and propensity to cause meningitis. To place GPSC10-24F in global context, a dataset of GPSC10 (n=888) from 33 countries was extracted from the database and revealed that this lineage expresses 16 other serotypes, with only 6 included in PCV13. All serotype 24F isolates belong to GPSC10 were clustered in a clade. Spatiotemporal analysis of GPSC10-24F clade indicates that this sub-lineage took ~5 years to spread across French provinces and there is evidence of long-range transmissions from Europe to North Africa and Asia.

### **Interpretation**

GPSC10 is the major pneumococcal strain that drives the increase in serotype 24F in France and Spain. The combination of high disease potential, multidrug resistance and expression of multiple serotypes suggests continued surveillance is needed to monitor this globally spreading lineage and include serotype 24F for optimization of the next generation of vaccine formulations.