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The Global Population Structure of *Neisseria meningitidis*

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### Background

Meningococcal disease caused by the bacterium *Neisseria meningitidis* is controlled primarily through vaccination campaigns targeting subsets of the population. However, the evolutionary consequences of this intervention in the global population are not well-understood. Research has focused on understanding clonal complexes (CC) associated with disease, and therefore *N. meningitidis*' global population structure remains uncertain.

### Aim/Methods

Here we assembled a dataset of publicly available whole-genome sequenced *N. meningitidis* isolates with 2046 newly sequenced isolates from 58 countries and spanning a 93-year period; a combined dataset of 22,222 isolates. We determined the global population structure of *N. meningitidis* by applying whole-genome clustering to these data. To corroborate and further study the identified lineages, we inferred the pan-genome

of all isolates, allowing reference-free comparative analysis between lineages, and examination of population structure within the accessory genome.

## Results

We find that the global *N. meningitidis* population is dominated by relatively few lineages; with 25 major lineages accounting for >92% of the dataset. All 25 major lineages contained isolates collected from at least two different continents, and 10 of them contained isolates from 5 or 6 continents. Whole-genome clustering was generally concordant with CC, though we detected CC changes within a lineage, likely due to recombination. Nineteen major lineages showed evidence of capsule switching. The accessory genome provided supporting evidence of the lineage structure inferred from whole-genome clustering.

## Conclusions

These results confirm that the global population of *N. meningitidis* is composed of stably-evolving globally-distributed lineages. Lineage distribution is variable globally, with predominant lineages in some regions found at low frequency elsewhere, suggesting frequent global migration. Gene sharing within the accessory genome, as well as nucleotide diversity within and between lineages' core genomes indicated uneven relatedness and rates of gene flow between major lineages, highlighting the need for a deeper understanding of inter-lineage interaction and the mechanisms spawning novel major lineages. These results suggest that the elimination of lineages globally is unlikely, and regional reintroduction from elsewhere likely. Capsule switching, while rare, occurs in most major lineages and has implications regarding the consequences of vaccination on meningococcal evolution.