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Development of a *Corynebacterium diphtheriae* Core Genome Multilocus Sequence Typing (cgMLST) Scheme

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**Introduction**

- Infections caused by *C. diphtheriae* are increasing, with more cases reported globally in 2018 than any year since 1996.
- Genomic investigations of diphtheria outbreaks have relied on core genome multilocus sequence typing (cgMLST) to identify potential epidemiological links between cases; however, these schemes have not been published for public use.
- Previously, we found that the choice of cgMLST scheme can lead to different allele distances between *C. diphtheriae* isolates.
- We investigated a novel scheme for uniform typing and outbreak investigation.

**Methods**

- We downloaded all publicly available, complete and chromosome-level *C. diphtheriae* assemblies from Refseq (n=24).
- An additional assembly, GCA_900312965.1, representing the type strain of the recently proposed *C. diphtheriae* subsp. *lausannense* subsp. *nov*, was also included.
- Plasmid sequences were removed.
- A cgMLST scheme was generated and alleles called with chewBBACA, an open-source tool designed for scheme development and application.
- Loci present in 100% of isolates were retained and paralogous loci removed.

**Results - Development**

- We identified a core set of 1474 loci present in all complete *C. diphtheriae* genomes.
- The conservation of core loci was evaluated in all contig- and scaffold-level *C. diphtheriae* assemblies from Refseq (n=198).
- Ninety-five percent or more of core loci were found in 99.0% (n=196) of all assemblies (Figure 1).
- The two assemblies missing more than 5% core loci were in the bottom 5% of all assemblies when ranked by completeness (Figure 2).

**Results - Validation**

- We applied our novel scheme to 2 pairs (n=4) of *C. diphtheriae* cases reported in the literature with a probable direct transmission between patients.
- There was a 1 and 4 allele difference between the isolates with direct transmission, compared with 1338 to 1342 allele difference between isolates across the two studies (Figure 3).

**Conclusions**

- We developed and evaluated a novel cgMLST scheme for *C. diphtheriae* molecular epidemiological investigations.
- Further analyses of epidemiologically linked cases are needed to validate the scheme more extensively.

**References**