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Whole-genome sequencing reveals the secrets of the Salmonella Dublin invasome

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Background: *Salmonella enterica* serovar Dublin (*S.* Dublin) is a zoonotic infection that can be transmitted from cattle to humans through consumption of contaminated milk and milk products. Outbreaks of human infections by *S.* Dublin have been reported in several countries including high-income countries. A high proportion of *S.* Dublin cases in humans are associated with systemic illness. The genetic basis of invasiveness of *S.* Dublin is not well characterized. The aim of this study is to characterize the invasome of *S.* Dublin that enable the bacteria to invade blood causing systemic illness in humans.

Material/methods: A set of *S.* Dublin submitted to Centre National de Référence des Salmonella, Institut Pasteur were selected for whole genome sequencing (WGS). The set of isolates included 22 human invasive isolates from blood, urine and pus. For comparison, we included 6 clinical non-invasive isolates from stool and 7 veterinary isolates. Furthermore, the reference *S.* Dublin isolate isolated from cattle in France in 1982 was also included in addition to the original human *S.* Dublin isolate isolated in Dublin in 1929 giving the name of Dublin serovar. Genomic DNA was prepared for Illumina pair-end (PE) sequencing using the Illumina NexteraXT® and the libraries were sequenced using an Illumina platform and MiSeq Control Software 2.3.0.3. All isolates were pair-end sequenced using 100bp PE libraries. Reads were assembled using Velvet. Single nucleotide polymorphisms (SNPs) were identified using samtools mpileup. The best-fit model for nucleotides substitution was determined by jModelTest then a maximum likelihood (ML) phylogeny based on SNPs was constructed by MEGA6 software using 1000 bootstrap replicates.

Results: WGS revealed several mobile genetic elements (MGEs) that potentially enable the bacteria to cause invasive disease in humans including Gifsy-2 prophage, virulence plasmid and *Salmonella* pathogenicity islands; SPI-7 harbouring the Vi antigen, SPI-6 and SPI-19 harbouring T6SSs and the novel pathogenicity island ST313-GI. Interestingly, the virulence plasmid, the pathogenicity island ST313-GI and the Vi antigen were absent from some invasive clinical isolates indicating that they are not the main virulence determinants in *S.* Dublin. The phylogenetic SNP analysis of *S.* Dublin isolates showed that invasive and gastroenteritis isolates were intermixed as SNPs were randomly distributed around the chromosome of *S.* Dublin. Interestingly, two invasive human isolates were resistant to multiple antibiotics indicating the emergence to multi-drug resistance in *S.* Dublin.

Conclusions: WGS revealed several virulence factors that form the bacterial invasome and enable the bacteria to cause systemic illness in humans however no genomic markers were detected that differentiate among invasive and non-invasive isolates suggesting that host factors and immune response play a significant role in the disease outcome.