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Investigation by whole-genome sequencing of two outbreaks of NDM-producing Klebsiella pneumoniae in Belgium

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Background: Extremely-drug resistant *Klebsiella pneumoniae* is recognized as a major public health problem and infection control challenge. This study aims to evaluate the usefulness of whole genome sequencing (WGS) to investigate two NDM-producing *K. pneumoniae* (NDM-Kp) outbreaks in a teaching hospital A (outbreak A) and in a general hospital B (outbreak B).

Material/methods: The outbreak A involved 9 patients colonized or infected by a NDM-Kp from August 2014 to March 2015. The outbreak B has started in November 2014 and is still ongoing in November 2016. In hospital B, 91 patients were suspected to be positive for a NDM-Kp. Molecular typing by Pulsed-Field Gel Electrophoresis (PFGE) was performed on the 9 isolates from outbreak A, the first 24 isolates from outbreak B and 42 epidemiologically unrelated NDM-Kp isolates collected in Belgium from 2014 to 2015. Genomic DNA libraries were prepared using Nextera® XT DNA library Preparation Kit (Illumina®) and sequenced using 2x200 base lengths on Illumina MiSeq®. De novo assemblies were done using SPAdes. Multi-locus Sequence Typing (MLST) and detection of acquired

resistance genes were carried out by the web-services MLST and “ResFinder” of the Center for Genomic Epidemiology (Denmark). Pan-genome MLST and single nucleotide polymorphism (SNP) analysis were done by a beta-version of Bionumerics® v7.6 (Applied Maths). The infection control measures prior and during the outbreaks as well as the medical records of the patients were retrospectively analysed in both outbreaks.

Results: Twenty-nine (88%) of the 33 NDM-Kp isolates from outbreaks A and B belonged to the same PFGE-type and ST716. Pan-genome MLST and SNP analysis confirmed close relatedness of these 29 isolates which diverged by maximum six SNPs. In contrast, the epidemiologically unrelated NDM-Kp isolates showed distinct patterns from the outbreak strain by PFGE, MLST and pan-genome MLST analysis. All but one isolate of outbreak A carried the $bla_{\text{OXA-9}}$ gene, whereas none of outbreak B harboured this resistance gene. Interestingly, the patient from hospital A, colonized by the unique $bla_{\text{OXA-9}}$ negative strain, stayed in the day-hospital of hospital B on the same day than the first NDM-Kp positive patient of hospital B. These genomic and epidemiological data suggest that this “outbreak clone” was introduced from hospital A to hospital B.

Conclusions: PFGE, MLST and WGS showed high concordance to identify a clonal NDM-Kp strain responsible of outbreaks in two hospitals. However, WGS, which has a higher resolution power, allowed us to suggest the transmission pathway of a nosocomial pathogen between a teaching and a general hospital. Further prospective studies combining the analysis of epidemiological and genetic data are needed to assess the transmission route of nosocomial pathogens in order to implement efficient and rapid strategies for infection control.