Letter to the Editor

Whole-genome sequence analyses by a new easy-to-use software solution support the suspicion of a neonatal ward outbreak of methicillin-resistant \textit{Staphylococcus aureus} (MRSA) and transmission between hospitals

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\textit{To the Editor –} Methicillin-resistant \textit{Staphylococcus aureus} (MRSA) occasionally causes outbreaks in hospitals, often in departments where newborns receive treatment.\textsuperscript{1,2} Hospital-acquired infections by MRSA may have a lethal outcome\textsuperscript{3} and expenses for infection control measures for containing hospital outbreaks may become very high.\textsuperscript{4} Surveillance of MRSA is essential for early detection and interruption of transmission. Whole-genome sequencing (WGS) is successfully used for comparing isolates of MRSA.\textsuperscript{1,2,5} Multilocus sequence typing (MLST) is a traditional high-resolution typing method based on allele sequences. MLST sequence types (STs) can be extracted from WGS data. An even higher resolution is obtained when the number of alleles analyzed is increased as in the WGS-based method core genome MLST.\textsuperscript{6} Both methods have shown their value in several studies of MRSA.\textsuperscript{2,4,7} 1928 Diagnostics is a WGS-based online solution that requires no bioinformatic experience from the user. The system allows comparison and characterization of several bacteria, including \textit{S. aureus} (9). Raw sequence data are uploaded to the 1928 Diagnostics server (https://www.1928diagnostics.com). A built-in quality check ensures that sequences of poor quality (low sequencing coverage) are not processed. For \textit{S. aureus}, results include individual MLST ST, antibiotic resistance mechanisms (resistance genes and mutations associated with resistance), and virulence gene profiles. A core genome sequence-based cluster tree shows the relatedness of isolates. Published experience on the use of 1928 Diagnostics for hospital surveillance is limited. We tested 1928 Diagnostics in a retrospective analysis of a neonatal ward outbreak of MRSA ST22 after transfer of a patient from another hospital.

The index patient was a newborn transferred to hospital A from the neighboring hospital B on May 3, 2014. On June 1, MRSA was cultured from blood and a skin abscess from the patient. The neighboring hospital A on May 3, 2014. On June 1, MRSA was cultured from blood and a skin abscess from the patient. The isolate was typed as ST22 at Statens Serum Institut, Copenhagen, as part of the national surveillance of MRSA. MRSA ST22 was isolated from a diagnostic sample from another patient at the ward on June 4, and patients and staff members were screened for MRSA. MRSA ST22 was isolated from additional 6 individuals, including 1 mother and 2 staff members. Infection control interventions included, among other measures, an audit in infection control at the ward focused on reinforcing standard precaution measures, replacement of worn utensils and equipment, and thorough cleaning and disinfection of parts of the ward. No MRSA ST22 were isolated from patients, relatives, or staff members after June 16. On July 12, MRSA ST22 was cultured from a patient, previously admitted to the affected ward concomitant with the index patient. No further transmission was observed.

We included isolates of MRSA ST22 (1) from 9 individuals suspected of being infected during the outbreak, (2) from 9 individuals from the same area collected over the preceding 7 years, and (3) from 27 individuals from the neighboring hospital area in the same year as the suspected outbreak. One isolate was analyzed from each individual. WGS was performed on a MiSeq (Illumina, San Diego, CA).\textsuperscript{4} The genome sequences confirmed all isolates as MRSA ST22 carrying the resistance genes \textit{blaZ} and \textit{mecA}. One isolate was typed as a recombinant SCCmeC type, while all other isolates were SCCmeC type IV. Genes encoding Pantot–Valentine leucocidin, toxic shock syndrome toxin, and exfoliative toxins were not detected. All isolates had 1 or more mutations associated with resistance to ciprofloxacin (Fig. 1). No other genetic markers of resistance to antibiotics were detected in the outbreak isolates. The erythromycin-inducible clindamycin resistance gene \textit{ermC} was detected in 8 nonoutbreak isolates. One isolate carried the high-level gentamicin resistance gene \textit{aac6-aph2}. A mutation associated with resistance to rifampicin was detected in one isolate. The study aimed at testing 1928 Diagnostics for local outbreak investigation and concordance between genetic markers of resistance and phenotypic resistance testing was not pursued. Previous studies have investigated genetic resistance determination by 1928 Diagnostics in methicillin-resistant \textit{S. aureus} and \textit{S. argenteus.}\textsuperscript{8,9}

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In the cluster analysis we arbitrarily defined a cluster as 5 or more isolates with an allelic distance of <5. All suspected outbreak isolates were within one cluster (Fig. 1), confirming the suspicion of local transmission. In addition, 4 isolates from hospital B were also in this cluster. Based on MLST typing, the outbreak was assumed to be caused by a strain transferred from hospital B by the index patient. However, all isolates from hospital B in the outbreak cluster were cultured later than the isolate from the index patient. Thus, the higher resolution obtained from cgMLST did not support transmission of the outbreak strain between the hospitals but did not confirm this taking place via transfer of the index patient from hospital B. Another 2 clusters were detected among isolates from hospital B (Fig. 1).

Rapid typing of selected bacteria is essential for effective surveillance and early detection of outbreaks in hospitals. The simple procedure for uploading data and viewing results makes 1928 Diagnostics attractive to infection control units without bioinformatic expertise. Inclusion of low-quality sequence data in the analyses may hamper the strength of conclusions, and the integrated quality control is important when the system is used by professionals without experience in bioinformatics. Our results suggest that 1928 Diagnostics may be used by local infection control units without bioinformatic expertise. However, the retrospective design is a limitation of this study, and prospective real-time studies are needed to establish the usefulness of 1928 Diagnostics and similar systems for surveillance.

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References

