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

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To the Editor—Methicillin-resistant *Staphylococcus aureus* (MRSA) occasionally causes outbreaks in hospitals, often in departments where newborns receive treatment.^{1,2} Hospital-acquired infections by MRSA may have a lethal outcome³ and expenses for infection control measures for containing hospital outbreaks may become very high.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.^{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.⁶ Both methods have shown their value in several studies of MRSA.^{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 *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 *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 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).⁴

The genome sequences confirmed all isolates as MRSA ST22 carrying the resistance genes *blaZ* and *mecA*. One isolate was typed as a recombinant sccmec type, while all other isolates were sccmec type IV. Genes encoding Pantone–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

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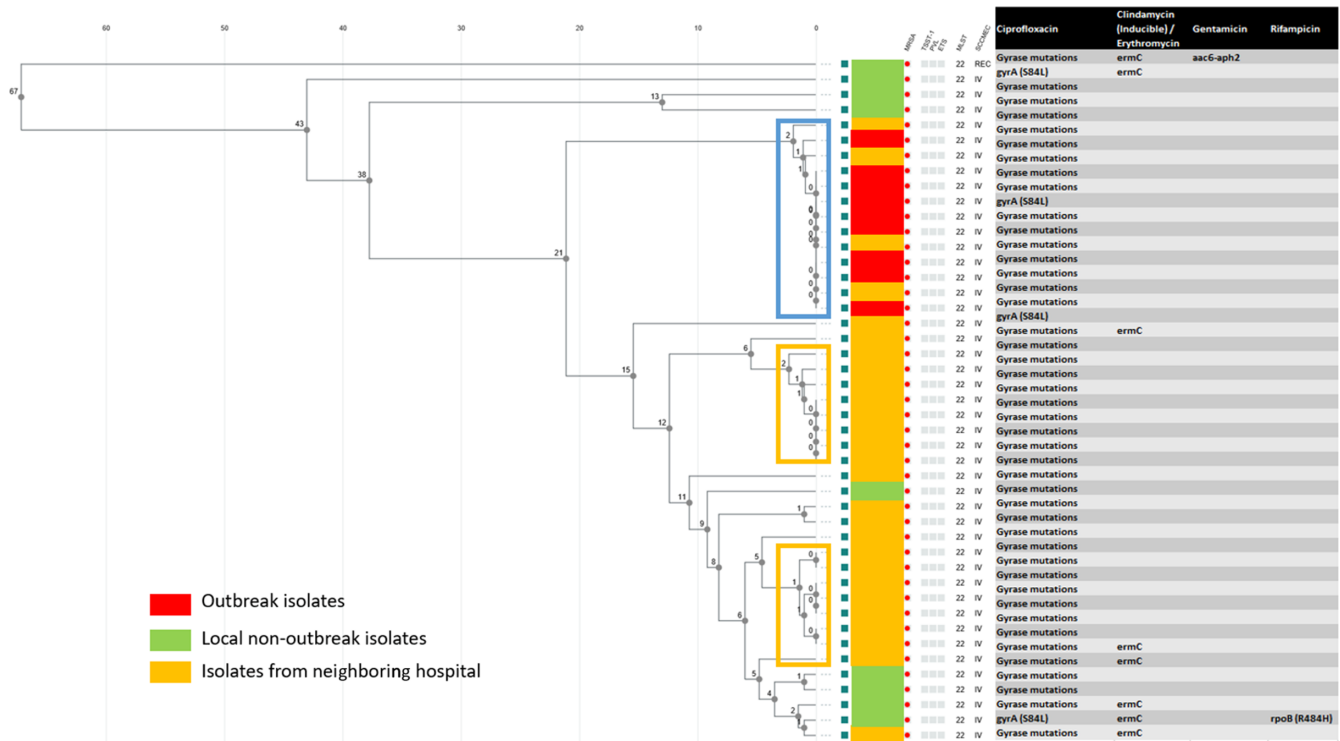


Fig. 1. Core genome based phylogenetic tree showing individual MRSA ST22 isolates. The 9 outbreak isolates (red) clearly clustered with 4 of the isolates from the neighboring area (yellow), while nonoutbreak isolates from the same area (green) and other isolates from the neighboring area were more distant. In addition to the cluster of outbreak isolates from hospital A and isolates from hospital B, marked by a blue rectangle, 2 clusters of isolates with highly similar core genomes, marked by yellow rectangles, were detected. Numbers at the nodes indicate average allelic distances between samples and clusters of samples in the tree. Genes and mutations associated with antibiotic resistance are shown for individual isolates. “Gyrase mutations” indicates that >1 mutation associated with resistance to ciprofloxacin was detected.

erythromycin/inducible clindamycin resistance gene *ermC* was detected in 8 nonoutbreak isolates. One isolate carried the high-level gentamicin resistance gene *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 *S. aureus* and *S. argenteus*.⁸⁻¹⁰

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 support suspicion of 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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Conflicts of interest. All authors report no conflicts of interest relevant to this article.

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Neosartorya hiratsukae: Environmental isolation from intensive care units in an Italian hospital

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To the Editor—Fungi are opportunistic pathogens, ubiquitously distributed. Fungal colonization acquired from the environment might evolve into an invasive infection during hospitalization due to immunosuppressive treatments to which patients are exposed. Environmental surveillance in hospital settings requires special attention to prevent fungal and non-fungal infections. Invasive aspergillosis is one of the most important infections caused by *Aspergillus*. *Neosartorya hiratsukae*, teleomorph of the *Aspergillus* section *Fumigati*, is a rare fungus isolated for the first time in Japan from indoor air and from pasteurized aloe juice.¹

Neosartorya hiratsukae is an opportunistic pathogen and only few cases of human infections have been reported worldwide.^{2–6} *N. hiratsukae* is often misidentified because it cannot be distinguished from *A. fumigatus sensu stricto* by conventional morphological macroscopic and microscopic analyses or by the extensively used matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS). However, rapid and accurate identification is important for therapeutic purposes due to the different patterns of susceptibility to antifungal drugs.

In this study, we investigated the environmental isolation of *N. hiratsukae* from 2 different intensive care units (ICUs) in a hospital in Milan, Italy. In January 2020, environmental sampling was conducted using contact plates as part of an environmental surveillance study. In total, 9 bed stations and 2 medical stations were sampled, for a total of 55 samples. After macroscopic and microscopic analyses, identification was confirmed by molecular analysis. Antifungal susceptibility testing was performed by broth microdilution assay according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) to determine the minimum inhibitory concentration (MIC).⁷ The following

antifungals were tested: itraconazole, voriconazole, posaconazole, isavuconazole and amphotericin B (Sigma-Aldrich, St Louis, MO).

Fungi grew from 18.2% of the environmental samples; molds grew from 8 samples. We identified 2 mold colonies, isolated from a cooling fan and from the handles of a patient bed, as *A. niger* and *A. fumigatus*. In total, 13 colonies of filamentous fungi isolated from 6 samples showed slow growth, with restricted white colonies and light-brown reverse. In particular, in one ICU, 12 colonies grew from the scalytic lamps (n = 7) of 2 different patient beds, from the computer keyboard of the medical station (n = 3), from the patient vital signs monitor (n = 1) and from the bed handles (n = 1). The last colony was isolated from the printer of the medical station of the other ICU. The microscopic examination of these colonies revealed *A. fumigatus*-like conidial head, a large number of cleistothecia, and hyaline, lenticular ascospores with equatorial crests. The β -tubulin sequences analysis showed a 100% homology with the reference sequence of *N. hiratsukae* (sequence AF057324).

Neosartorya hiratsukae antifungal susceptibility testing yielded the following MIC values: itraconazole, 0.12 mg/L; voriconazole, 0.03 mg/L; posaconazole, 0.06 mg/L; isavuconazole, 0.12 mg/L; and amphotericin B, <0.03 mg/L. No break points (BPs) have been specified for *N. hiratsukae*; however, the MIC values of our isolate are low and under the EUCAST BPs established for *A. fumigatus*.⁸

No cases of aspergillosis were diagnosed in the 2 ICUs in a 5-month period, 3 before the isolation of *N. hiratsukae* from the environment and 2 thereafter (Dr R. Grande, personal communication). In July 2020, we were able to perform further environmental samplings, but neither *N. hiratsukae* nor other fungi were isolated.

Like all filamentous fungi, *Neosartorya* also has an environmental origin. In the literature, *N. hiratsukae* has been reported in the indoor air¹ and on drywall, where the small white colonies are hardly visible, so the spores can easily spread in the environment causing a health risk.⁹ In the 2 ICUs examined, no renovations had

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