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Whole genome sequencing reveals a prolonged and spatially spread nosocomial outbreak of Panton–Valentine leucocidin-positive meticillin-resistant *Staphylococcus aureus* (USA300)☆

A. Kossow [a,*,1], S. Kampmeier [a,1], F. Schaumburg [b], D. Knaack [b], M. Moellers [c], A. Mellmann [a]

[a] *Institute of Hygiene, University Hospital Muenster, Muenster, Germany*
[b] *Institute for Medical Microbiology, University Hospital Muenster, Germany*
[c] *Clinic for Gynaecology and Obstetrics, University Hospital Muenster, Germany*

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SUMMARY

Background: Whole genome sequencing (WGS) helps to better investigate the transmission and characterization of meticillin-resistant *Staphylococcus aureus* (MRSA) strains.
Aim: We describe the detection and unfolding of a prolonged and spatially distributed nosocomial outbreak of Panton–Valentine leucocidin (PVL)-positive MRSA ST8 (USA300).
Methods: The outbreak was detected by the combination of whole genome sequence (WGS)-based typing, which is implemented for routine surveillance of multidrug-resistant bacteria in our institution, and in-depth epidemiological investigation. To investigate the source, processes were observed and environmental sampling performed. To contain the outbreak, regular and direct personal contact with the healthcare workers (HCWs) was maintained and staff education implemented.
Findings: The outbreak took place between October 2016 and November 2017 and included five patients who were treated in two different departments as inpatients and outpatients; three were infected, two were colonized. Additionally, three HCWs carried the outbreak strain. The strain was not found in the hospital environment. Only through non-mediated communication did the source become apparent. Decolonization of HCWs and infection control measures led to a resolution of the outbreak.
Conclusion: WGS helped to reveal an outbreak that otherwise might have stayed undetected. Nonetheless, epidemiological investigation is needed to trace the nosocomial transmission. The importance of personal communication in infection control cannot be overstated.

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* Corresponding author. Address: Institute of Hygiene, University Hospital Muenster, Robert-Koch-Straße 41, 48149 Muenster, Germany. Tel.: +49 2518352319; fax: +49 25155368.
E-mail address: kossow@uni-muenster.de (A. Kossow).

[1] Joint first authors.

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Introduction

Meticillin-resistant *Staphylococcus aureus* (MRSA) remains one of the most prevalent multidrug-resistant organisms causing nosocomial infections [1]. Therefore, specific infection control measures aim at preventing the spread of this pathogen [2]. In this context, whole genome sequencing (WGS) helps to better investigate the transmission and characterization of strains [3–5].

MRSA of multi-locus sequence type (ST) 8 carrying genes encoding for Panton–Valentine Leucocidin (PVL) are frequently also named MRSA USA300 based on the pulsed-field gel electrophoresis pattern and have spread globally during recent decades [6,7]. USA300 was first reported in the USA as a cause of skin and deep soft-tissue infections outside the hospital setting and is now among the most prevalent community-associated (CA) MRSA strains in the USA [8,9]. Isolates of USA300 have spread to other continents but prevalence in Europe remains comparatively low, even though it is recognized as an emerging pathogen of healthcare-associated infection [10,11]. In Germany isolates have been detected since 2005 [12].

In our institution, the University Hospital of Münster (UHM), isolates occur very rarely and are mainly seen in outpatients, with five to 16 cases per year in 2014–2017. Overall, ST8 accounts for 1.4% of all MRSA at the UHM.

This article reports an unusual prolonged outbreak of PVL-positive MRSA *spa* type t008 ST8 (clonal complex, CC8) that took place between October 2016 and March 2017 in a hospital setting and included five patients and three healthcare workers (HCWs). WGS, as a relatively new technology, and traditional approaches are shown to facilitate each other in infection control and prevention.

Methods

Setting

The outbreak affected the obstetrics and neonatal departments within the UHM, a 1457-bed tertiary care hospital with more than 65,000 inpatients and 460,000 outpatients in 2016. A general screening of all inpatients for MRSA is established (exception: psychiatry wards) and ~0.8% inpatients were MRSA positive at admission. The outbreak was reported to the local health agency and included five patients and three healthcare workers.

Culturing and typing

Detection of MRSA was performed by using selective agar plates (chromID, bioMérieux, Marcy l'Étoile, France at 35 ± 1°C for 24–48 h, both with and without an enrichment (Dextrose Bouillon, 24 h, 36°C).

For species identification, matrix-assisted laser desorption/ionization (MALDI-TOF) mass spectrometry (Bruker Daltonics, Bremen, Germany) was used. Antimicrobial agent susceptibility profiles were tested using the Vitek-2 system (bioMérieux, Marcy l'Étoile, France). Isolates were further screened by PBP2a (PBP2a SA Culture Colony Test, Scarborough, ME, USA) and *mecA*, *mecC*, and PVL (GenoType MRSA; Hain, Nehren, Germany) [13,14].

Environmental sampling and screening of staff

Environmental sampling was performed six times between October 2016 and May 2018 at random sites and on random items on the ward ($N = 103$). Those sites included telephones, computer keyboards, changing mats, scales, breast pumps and a bottle warmer, mobile blood pressure monitors and pulse oximeters, sideboards, an examination chair and light, refrigerator, strollers, bedside tables, drawers, stethoscopes, a chair and a pillow for breastfeeding, the area in which infusions are prepared, infusion pumps, door handles, chairs, the packaging of sterile instruments, and toilet flush buttons.

Sampling was carried out using Polywipe™ (Medical Wire & Equipment, Corsham, UK) pre-moistened sponge swabs. After incubation at 36°C for 48 h in Tryptic Soy Broth with neutralizer (Merck Life Science, Eppelheim, Germany), probes were cultured on blood agar (Oxoid, Wesel, Germany) and MRSA selective agar (chromID, bioMérieux) and incubated for another 24 h. MALDI-TOF mass spectrometry was used for species confirmation. Antimicrobial agent susceptibility profiles were tested via disc diffusion using European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints. Meticillin resistance was confirmed by the PBP2a latex agglutination test (MRSA Screen; Denka Seiken, Tokyo, Japan).

In the case that no source becomes apparent through environmental screening, we perform screening of all staff working on all wards affected by an outbreak.

Whole genome sequencing

At the UHM, infection control strategies are complemented by WGS of all multidrug-resistant strains that occur in inpatients and outpatients. The Illumina MiSeq platform (Illumina Inc., San Diego, CA, USA) was used and laboratory procedures were carried out as described previously [5]. Coding regions were compared in a gene-by-gene approach (core genome multi-locus sequence typing, cgMLST; whole genome sequence typing, wgMLST) and a single nucleotide variation analysis (SNV) using the SeqSphere + software version 5.1 (Ridom GmbH, Münster, Germany) [15]. To visualize the clonal relationship, a minimum-spanning tree was generated using the same software.

MRSA isolates differing in ≤24 cgMLST or wgMLST alleles were defined as being potentially related and underwent in-depth epidemiological investigations.

STs and *spa* types and the presence of the *arc*-gene clusters encoding for the arginine catabolic mobile element (ACME) were extracted *in silico* from WGS data.

SCC*mec* typing was performed using the SCC*mec*Finder [16].

For comparison, we used the published genome sequence of the USA300 reference genome (NC_010079.1).

Access to data

All reads are deposited at the European Nucleotide Archive under the accession number PRJEB27664.

Infection control measures

Infection control measures included the education of staff about possible transmission routes of MRSA and hand hygiene as

well as surface disinfection practices. Hand hygiene training was performed for all HCWs and presentations were given about MRSA and MRSA transmission to every HCW. The presence of infection control staff on the ward was increased to two visits per week to observe hand hygiene compliance and to re-evaluate standard operating procedures on the ward as well as to give regular feedback to all responsible persons. Disinfection was improved by the introduction of checklists for all critical sides. We introduced an informative flyer for patients and visitors. In some areas, more hand disinfection dispensers were installed. Storage policies and practices were re-evaluated and improved.

Decolonization

The decolonization protocol included: nasal ointment with mupirocin 2% three times daily, gargling with octenidine (Octenidol; Schülke & Mayr, Norderstedt, Germany) three times daily, and washing skin and hair with octenidine (Octenisan; Schülke & Mayr) once per day. This treatment was performed for five days total. Three days after the last treatment, screening was performed daily for three days to test the success of the decolonization. The screening was repeated after 10 days as well as one, three, six and 12 months to investigate the long-term success of the decolonization.

Results

The outbreak (Figure 1) started when two PVL-positive MRSA could be isolated from two patients within three days (P1 and P2) at the end of October 2016. Both isolates were confirmed as MRSA by detection of the *mecA* gene. Moreover, they all carried — as detected by specific polymerase chain reaction — the *lukS*/*lukF* genes encoding PVL and they were phenotypically resistant to fluoroquinolones and susceptible to macrolides, clindamycin, glycopeptides, trimethoprim–sulfamethoxazole, tetracycline, rifampicin, fusidic acid, fosfomycin, linezolid, daptomycin, and mupirocin.

Isolated strains were sequenced with an overall average coverage of 125. From WGS data, the isolates showed a maximum difference of four and six alleles, respectively, in cgMLST/wg MLST and SNV data analyses (Figure 2; Supplementary Figures S1–S3). Further analyses revealed that all isolates belonged to ST8, *spa* type t008, and carried the SCC*mec* type IVa(2B) as well as the ACME-I element. Direct repeats within or flanking the ACME element were identical to direct repeats of the USA300 reference strain.

Epidemiological investigation showed that P1 and P2 had been treated at clinic 1 on the same ward without direct contact (e.g. stay in the same room). After 2 h only, P1 was transferred to a different clinic (clinic 2), where a sample for MRSA was taken.

At first sight, we suspected a mix-up of swabs in the laboratory as the most plausible explanation, rather than nosocomial transmission. This was supported by the fact that the isolates had a very close clonal relationship with one allele difference in cgMLST and that no further isolates occurred in the following months. However, in March 2017 the same clone MRSA was found in two additional patients (P3 and P4). Both had been treated on the respective ward weeks or months before being tested positive for the outbreak strain. P4 had

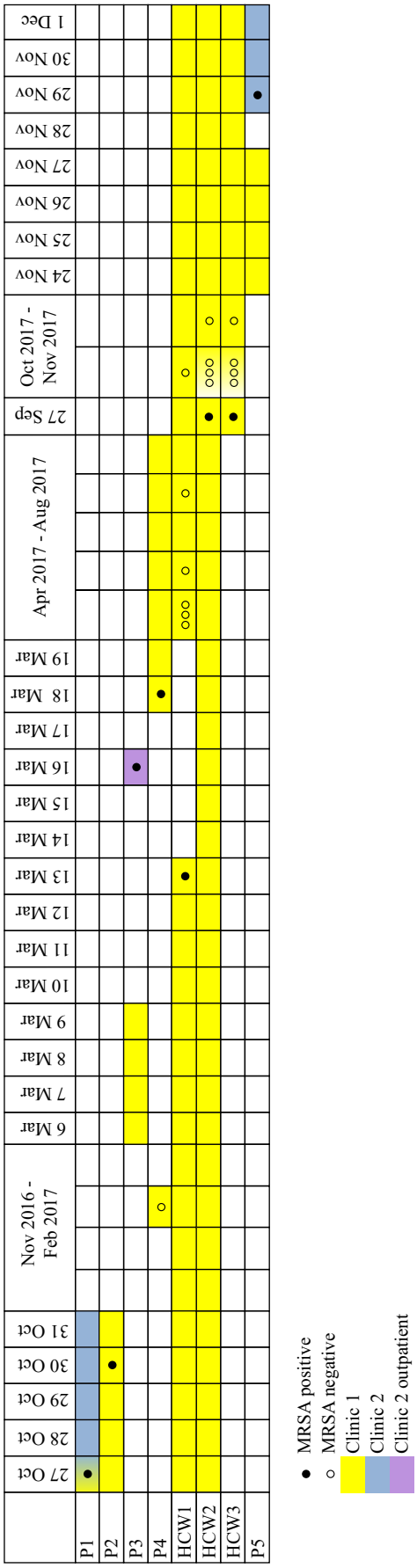

Figure 1. Timeline of the nosocomial meticillin-resistant *Staphylococcus aureus* (MRSA) outbreak. Each line represents the timeline of a single patient (P) or healthcare worker (HCW). Each coloured cell indicates contact with University Hospital of Münster either as an inpatient or outpatient. Colours represent the two different clinics. Samplings to detect MRSA are displayed as dots and coloured according to their result. After decolonization, HCWs had to present three negative swabs of nose/throat and axilla/groin before resuming work on the ward. Controls took place after one and three months and will be continued after six months and one year after decolonization.

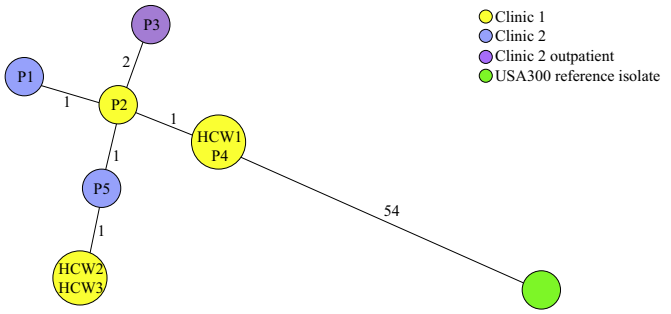

Figure 2. Minimum-spanning tree displaying the core genomic relationship of the eight meticillin-resistant *Staphylococcus aureus* (MRSA) isolates detected. Each circle represents a single genotype, i.e. an allelic profile based on up to 1861 target genes present in the isolates in a pairwise comparison. The circles are named with the isolate's ID(s) and coloured according to the ward. Connecting lines between two genotypes are labelled with the number of differing alleles in a pairwise comparison. Missing data are ignored in pairwise comparisons.

been tested negative for MRSA upon admission at his previous stay. Due to these commonalities with P1 and P2, a common source on the ward was suspected and environmental sampling was performed; however, the respective strain was not found in the environment. Processes were observed to optimize hygiene practices. During a discussion with staff members on the ward it was discovered that a staff member (HCW1) had just called in sick for MRSA decolonization after having been screened for MRSA before undergoing surgery at another hospital. With the HCW's consent and for the purpose of further analysis, the isolate was obtained, which proved to be either identical or closely related with a maximum difference of three alleles to the previous four isolates. Upon successful decolonization the source was assumed to be eliminated and no further patient cases with this MRSA clone occurred for several months. In September 2017, screening of all staff (medical and non-medical) working on both wards affected by the outbreak was performed. Two staff members (HCW2 and HCW3) were found to be carriers of the previous outbreak clone. Decolonization was successful in both cases. The presence of infection control staff on the ward was further intensified. Further environmental sampling did not reveal the outbreak isolate to be present in the environment. Infection control measures were continued, and, apart from a single patient (P5) who became positive with the outbreak clone in November 2017, no further cases occurred during the following six months.

Overall, the outbreak included five patients (four newborns/neonates and one mother) of whom three were infected and two were colonized (for clinical details of patients and HCWs see also Table I). All infections were treated successfully. P2 was treated locally with skin care products. P3 underwent drainage and was put on oral clindamycin (3 × 600 mg) for seven days. P4 was topically treated with gentamycin eye drops. Since the mothers of P1, P2, P4, and P5 had tested negative for MRSA prior to giving birth and P3 tested negative for MRSA during the pre-hospital period, it is unlikely that P1–P5 were sources of the outbreak.

Discussion

This report describes a prolonged outbreak of PVL-positive ST8 MRSA (USA300) in a German hospital. We demonstrated that high discriminatory typing efforts based on WGS may point to nosocomial transmissions that otherwise would have gone undetected due to their temporal and spatial dispersion. Our report shows – along with other studies – how WGS data help to uncover and track nosocomial transmission, and it underlines the need for in-depth epidemiological investigations in such situations where the transmission routes and infection sources are unclear, in order to prevent further spread of the pathogen [3,17].

In contrast to other MRSA outbreaks, nosocomial outbreaks of CA-MRSA are still rare in Europe. Outbreaks of CA-MRSA have been described in the healthcare setting but often included long-term care facilities [18,19]. However, hospital-associated outbreaks of CA-MRSA have been described outside of Europe [20–22]. The first outbreaks in Europe occurred in Italy and subsequently in Belgium [23,24]. A mother-to-child transmission of PVL-positive ST8 MRSA within a neonatal care unit took place as a single event in southern Germany [25]. A group of French authors recently described the emergence of ST8-USA300 in French paediatric patients [26].

With no further detection of the strain for six months, the outbreak was considered to be terminated. However, it remains unclear whether the index case was a patient (P1) or a healthcare worker (HCW1). The detection of further HCWs who were positive for USA300 suggests that colonized HCWs had a strong role in maintaining the strain on the ward. Person-to-person transmission was the suspected route of transmission since positive environmental samples were never found.

Table I
Clinical characteristics of patients (P) and healthcare workers (HCW)

	Date of first isolation	Sample type	Age (years)	Gender	Reason for admission	MRSA colonization	MRSA infection	Location of infection
P1	Oct 27th, 2016	Nasopharyngeal swab	0	M	Birth	+	–	
P2	Oct 30th, 2016	Axillary swab	0	F	Birth	+	+	Skin
P3	Mar 16th, 2017	Mammary tissue	29	F	Breast abscess	+	+	Abscess
P4	Mar 18th, 2017	Eye swab	0	M	Birth	+	+	Eye
P5	Nov 29th, 2017	Nasopharyngeal swab	0	F	Birth	+	–	
HCW1	Mar 13th, 2017	Nasopharyngeal swab	30	F		+	–	
HCW2	Sep 27th, 2017	Nasopharyngeal swab	32	F		+	–	
HCW3	Sep 27th, 2017	Nasopharyngeal swab	55	F		+	–	

MRSA, meticillin-resistant *Staphylococcus aureus*.

Unfortunately, we experienced an additional patient case (P5) after decolonization of all colonized HCWs. The source of this has not been apparent until now. However, infection control measures in regard to process optimization and improved hand-hygiene compliance appear to have had a sustainable effect. For this reason, we continue with the intensified presence of infection control staff even after termination of the outbreak.

One limitation of the study is that travel history could only be partly evaluated in order to guarantee anonymity for both patients and HCWs. For P1–3 and P5, travel history is negative for endemic countries but interviews of family members could not be performed. To elucidate, travel history of the remaining cases could have revealed an index case since USA300 is imported by intercontinental travellers [27].

In conclusion, personal communication and co-operation between clinicians and infection control staff revealed one possible source of the outbreak and sustained the successful termination. It remains a powerful tool in the prevention and even detection of nosocomial transmission despite the evolution and necessary application of the latest techniques such as WGS. By means of WGS data, this outbreak could be revealed, but in-depth epidemiological investigation is always necessary to confirm, or, in our case, make transmissions apparent. Future research should therefore include how to map WGS data with epidemiological data such as data from hospital information systems. This combination can further improve patient safety, aiding the recognition and prevention of nosocomial transmission and infection.

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Conflict of interest statement
None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2018.09.007.

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