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Clustered cases of infections due to an uncommon methicillin-resistant *Staphylococcus aureus* originating in a maternity ward

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Disclosure of interests

The authors declare no conflict of interest.

Ethical approval

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Highlights

- Description of an uncommon methicillin-resistant *Staphylococcus aureus* (African clone) community outbreak in Metropolitan France originating in a maternity ward.
- This clone produced Panton-Valentine leukocidin and belonged to the sequence type 88 (ST 88).
- Skin and soft tissue infections and one necrotizing pneumonia case were described.
- This outbreak highlights the underestimated risk of healthcare-associated infections in maternity wards.

Abstract

Objective. We aimed to report a community outbreak of an uncommon methicillin-resistant *Staphylococcus aureus* (MRSA) originating in a maternity ward.

Patients and methods. Cases were defined by epidemiological, clinical, and microbiological investigations. Microbiological investigations included phenotypic analysis, molecular typing, and whole genome sequencing. To control the outbreak, we applied both national recommendations to prevent in-hospital transmission and the French High Council for Public Health guidelines on the management of community-acquired MRSA infections.

Results. Between March and July 2016, seven patients with MRSA infections were identified: six skin and soft tissue infections and one pulmonary infection, including six microbiologically confirmed infections. Infections occurred in community settings, but a link with the same maternity ward was found for all patients. All MRSA strains had a t690 spa type, were tetracycline-resistant, and produced Panton-Valentine leukocidin. All isolates belonged to the sequence type 88 (ST88).

Conclusion. This outbreak highlights the largely underestimated risk of healthcare-associated infections in maternity wards. Healthcare workers should be aware of the importance of standard hygiene precautions and use of alcohol-based hand sanitizers for neonates and mothers.

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is responsible for both healthcare- and community-acquired infections [1]. Healthcare-acquired MRSA and community-acquired MRSA were first differentiated by specific genetic traits and epidemiological features [2, 3]. Healthcare-acquired MRSA was first identified in the 1960s and spread all over the world, although remaining confined to hospital settings [4]. The first epidemic of community-acquired MRSA infections was described in 1993 in patients with no exposure to the healthcare system and who were infected by MRSA with a genetic background not previously described [5]. Similar events have since multiplied, and community-acquired MRSA is now responsible for outbreaks on all continents [6]. Community-acquired MRSA seems to be more virulent than

healthcare-acquired MRSA because of the near-exclusive presence of genes encoding Panton-Valentine leukocidin (PVL), a bi-component synergohymenotropic toxin responsible for necrotizing and recurrent infections [7].

However, the epidemiological differences between healthcare- and community-acquired MRSA faded over time with the spread of community-acquired MRSA in healthcare institutions [8]. This is notably true for the USA300 clone which is now responsible for most hospital-acquired MRSA infections in the United States [9] and for other community-acquired MRSA [10, 11]. In addition, hospital-acquired outbreaks due to MRSA strains previously considered as community-acquired MRSA have been described in several countries such as the United States, Israel, or Italy; many of them occurring in maternity and neonatal wards [12-19].

In France, most PVL-positive MRSA infections are sporadic, community-acquired, and due to a CC80 clone originating from North Africa. Few outbreaks were reported, some of them involving the USA300 clone [20, 21]. We aimed to describe an outbreak originating in a maternity ward and involving an uncommon PVL-producing ST88 clone, which is thus far considered to be a community-acquired MRSA clone [22].

2. Methods

2.1 Outbreak case definitions

A confirmed case was defined as a person, exposed to the maternity ward of a Rennes University Teaching hospital between March and July 2016 and who had clinical manifestations consistent with staphylococcal disease (abscess or other infection) involving ST88 MRSA.

A probable case was defined as a person with a clinical presentation consistent with staphylococcal disease as described above and exposed to the maternity ward but without microbiological documentation.

Contact persons were defined as:

- any woman who gave birth between March and April 2016 in the same unit of the maternity ward;
- any medical and paramedical staff who took care of the cases (88 caregivers);
- the close family of cases living in the same house and any person with close and repeated physical contact with the cases.

2.2. Clinical investigations

Medical records of patients were consulted to collect data on medical history, delivery conditions, infection characteristics, antibiotic therapy, and surgical management. All caregivers of the maternity ward but one, who managed cases were screened by nasal swab for MRSA detection. Women who gave birth between March and April 2016 were identified. An information letter on the outbreak was sent to them and their family physician. A telephone on-call service was then set up by the hospital to identify any potential new cases in the community. All personal data were collected and processed according to the European General Data Protection Regulation and the French Data Protection Authority (French acronym CNIL) recommendations.

2.3. Microbiological investigation

All suspected MRSA isolates were identified and characterized in the microbiology laboratory of Rennes teaching hospital according to microbiology laboratory methods. Identification was performed by Matrix-Assisted Laser Desorption/ionization-Time-of-Flight Mass Spectrometry (MALDI-TOF MS). Antibiotic susceptibility was obtained using the disk-diffusion method as recommended by EUCAST 2016 guidelines. Genomic DNA was extracted using InstaGene Matrix[®] kit. Detection of the genes encoding PVL was performed by polymerase chain reaction.

Spa typing was also performed on all suspect MRSA isolates and compared to the online database (Ridom Spaserver[®]) as previously described [10]. For further characterization, all MRSA isolates identified were sent to the National Reference Laboratory for staphylococci (Lyon, France). They were characterized by DNA microarrays with the *S. aureus* genotyping kit 2.0[®] (Alere, Germany) according to previously described procedures [23]. Whole Genome Sequencing (WGS) was also performed with Illumina Miseq (Illumina, San Diego, CA, United States) to generate 300-bp paired end reads and a minimum coverage of x30. They were also compared with other ST88-related strains added to the NCBI database.

MRSA screening samples were collected by swabbing the anterior nares of caregivers and cultured on CHROMID[®] MRSA medium (bioMérieux, France). In case of isolation of suspect colony, identification and characterization were performed as described above.

One of the first control measures implemented was to strengthen biocleaning and as a result no environmental control was performed.

As the milk bank specifically tests milk samples for *S. aureus* contamination, we retrospectively analyzed MRSA strains recovered from the breast milk bank from 2016, to detect an hypothetical spread of ST88 MRSA strains among breastfeeding mothers. Stored isolated strains were compared to the epidemic strain to determine if this strain was already circulating.

2.4. Control of the outbreak

Control of the outbreak was achieved by implementing the 2014 recommendations of the French High Council for Public Health (French acronym HCSP) [24].

The following measures were implemented for all patients and their close family:

- daily skin decolonization by 4% chlorhexidine shower, nasal decolonization with 2% mupirocin for both adults and children;

- pharyngeal decolonization only for adults with gargle and 0.2% chlorhexidine mouthwash, for five days;
- daily cleaning of homes with a quaternary ammonium disinfectant and laundry treatment for items such as clothes, linen, and towels.

Healthcare workers of the maternity ward were informed of the outbreak, the bacteria and the risk of cross transmission through an information sheet provided by the infection control team (ICT). The ICT implemented control measures such as contact precautions, reinforcement of environmental cleaning and awareness of the use of alcohol-based hand sanitizer.

3. Results

3.1 Clinical presentation of the cases series

Seven patients with MRSA infections were identified: six patients with skin and soft tissue infections (SSTIs) and one patient with a pulmonary infection. There were six confirmed cases (four mothers, two babies) and one probable case (one father). All cases had stayed in the same unit of the maternity ward or had had close contact with a confirmed case during this period. Cases 2, 3, and 5 were indeed hospitalized during the same period. Cases 4 and 7 were born in the maternity ward and were twins. Cases 5 and 6 were living together. Onset of all cases occurred at home after discharge from the maternity ward, with a mean time to infection onset of 34 days for mothers and babies (range 12-116 days). Cases from different families did not know each other and no epidemiological link between them except for frequenting the same maternity ward was identified. Clinical presentations of confirmed and probable cases are presented in Table I.

The chronology of events is summarized in the synoptic timeline (Figure 1). Two MRSA breast abscesses set off the alert at the end of April 2016, in women who had given birth in March in

the same unit of the maternity ward (cases 1 and 2). During prospective investigation, a third case was discovered (case 3). Through retrospective analysis, one baby born on March 6, 2016 in the ward was identified as the first reported case (case 4). He had been re-hospitalized on March 22 in the neonatal intensive care unit for necrotizing pleuropneumonia with initial life-threatening prognosis.

Letters sent to women who had given birth and the phone-based assistance made it possible to identify two other cases (cases 5 and 6). Case 6 was the husband of case 5. He was considered a probable case as no microbiological sampling was performed during surgical drainage and as he was not hospitalized; but the timing, his living with an infected person, and clinical features (SSTI) strongly suggested a possible infection related to the same strain. The last case (case 7) was recorded in July and was the twin of case 4. MRSA was isolated from a labial lesion. Both infants developed infections 17 weeks apart. The mother of cases 4 and 7 had no clinical infection.

3.2 Microbiological characteristics

The six available isolates were susceptible to antibiotics except to methicillin and tetracycline. Sequencing of the protein A repeat region showed that the isolates possessed the same *spa* type (Ridom type t690). By DNA microarray, the six isolates were positive for *sep*, and *lukF-lukS-PV* genes, but not for *tsst-1*. All isolates had the following resistance genes: *blaZ*, *mecA*, and *tetK*. Neither the *mupA* gene involved in mupirocin resistance nor the *qac* genes involved in antiseptic resistance were detected. The arginine catabolic mobile element (ACME) was not present. The accessory gene regulator (*agr*) system was a type III allelic profile, and the *SSCmec* was type IV. Based on MLST analyses, they were classified into the ST88 lineage. The six isolates were grouped into the CC88 MRSA-IV clone. Retrospectively, WGS confirmed the clone with a maximum of four SNPs between the six sequenced isolates (Figure 2). The three

closest strains also came from the French CNR and had been isolated in Mayotte, a French overseas administrative district. These isolates are closely related to our isolates (73 SNPs) but distant enough to suggest a phylogenetic link between our cluster and the MRSA isolates from Mayotte (Figure 3). By comparison with other ST88 strains available in the NCBI database, the pairwise SNP distance did not suggest any link (Figure 3).

See supplementary materials (e-component 1) for details of complete microbiological characteristics.

3.3 Infection control measures and outcomes

We strictly applied French recommendations related to community-acquired MRSA outbreaks to control this outbreak. Particular attention was paid to compliance with hand hygiene.

All screened caregivers were negative for ST88 MRSA; screening was not performed in one caregiver because they no longer worked at the hospital and could not be contacted. No notion of SSTI history among caregivers was reported. We did not find the epidemic strain among isolates from the breast milk bank. The outbreak transmission route was not identified due to obvious missing links in the synoptic timeline but risk factors for cross-transmission were observed, particularly lack of compliance with hand hygiene. Indeed, there was a disincentive to hand hygiene with alcohol-based hand sanitizer, especially in contact with newborns. Various reasons were given by caregivers such as "newborns are always clean", and the fear of potential risk of skin lesion or unpleasant smell due to the alcohol-based hand sanitizer.

Initial treatment of infected mothers in the gynecological emergency department was not optimal (no sampling, inadequate antibiotics for MRSA strains). The risk of community-acquired MRSA infection was unknown by medical staff. We handed out an information sheet to caregivers to explain the physiopathology of these infections, risk factors for acquisition, cross-contamination risk, and symptoms suggestive of community-acquired MRSA infections

to improve recognition and management of SSTIs. Maternity staff was also assisted by ICT members in complying with appropriate prevention measures.

A gynecologist and an ICT member received all infected mothers to explain the decolonization procedure and home environment cleaning. All cases and their close family benefited from nasal and skin decontamination (and pharynx for adults). No check for success of decolonization was carried out. However, case 7 was positive after complete decolonization of all family members. Neither resistance to mupirocin nor scabies infection or active exfoliating skin conditions that could compromise decolonization were detected. A new decontamination procedure was thus used. No new clinical cases linked to community-acquired MRSA has since been reported, and this particular strain has never been isolated again.

4. Discussion

This is the first outbreak due to an ST88 PVL-positive MRSA strain described in metropolitan France. This clone, considered as an African clone, is mainly encountered in Senegal, Madagascar, Ghana, Cameroon, and Nigeria, but is unfrequently reported in Europe [22]. In sub-Saharan Africa, the prevalence of ST88 MRSA ranges from 24% to 83% of MRSA infections [25]. These infections both occur in hospital and community settings.

MRSA involved in community-acquired infections are considered more virulent than those responsible for hospital-acquired infections [26]. The presence of virulence factors such as PVL or phenol-soluble modulins would explain infection severity. During this outbreak, most breast abscesses required surgical drainage. Two cases of infections could be considered severe: a mother presented with sepsis due to large abscesses on both breasts and further reconstructive surgery was necessary (case 2); and a baby presented with pleuropneumonia and was transferred from home to the neonatal intensive care unit (case 4).

Five of the seven cases were directly attributed to the maternity ward. The two remaining cases occurred in close contacts of confirmed cases. Most infections occurred less than one month after discharge from the maternity. Nevertheless, case 7 developed an infection at 4 months of life after decontamination of all family members, suggesting decolonization failure. Two hypotheses were discussed: non-compliance with the proposed protocol or resistance to mupirocin. Cases of mupirocin resistance have indeed been described [27] and prolonged carriage of community-acquired MRSA has already been reported, with mupirocin resistance acquisition [20], but all isolates were susceptible to mupirocin including the strain of case 7. A new decolonization protocol was proposed to the family after treatment of the skin infection. No infection has been reported since then.

Healthcare-associated infections due to community-acquired MRSA are increasingly reported [8, 28], including cases of community-acquired MRSA outbreaks in maternity and neonatal units. The main reasons for these infections would be the asymptomatic colonization of family members or healthcare staff [4], but we could not identify any asymptomatic carrier. The index case identified was one of the twins (case 4). Our investigation did not reveal any ST88 carriers among hospital staff. As screening was performed only once, we could not exclude that at least one caregiver was an intermittent MRSA carrier and did not carry the strain at the time of screening [29]. However, as the last case was observed on July 7 and no new case has been reported after that, it seems unlikely that caregivers remained carriers. Individuals living in the same household as cases were decolonized without sampling, to reduce the risk of dissemination in the community. Similar isolates were not retrospectively identified among samples from the breast milk bank. Environmental controls were not carried out or did not allow for the origin of the contamination to be traced [13] because of the gap between the start of the outbreak and the implementation of corrective measures [12]. Environmental cleaning has already been done [15], thus explaining our approach not to perform environmental controls.

Nonetheless, risk factors for cross-contamination exist in maternity wards. Some healthcare professionals working there did not consider maternity wards as conventional medical units and pregnant women as patients, especially for uncomplicated pregnancies. Consequently, hygiene measures such as standard and additional precautions may be less frequently applied than in a conventional medical unit, thus facilitating the risk of cross transmission. Hands of caregivers are the vehicles for healthcare-associated infections and failure to comply with hand hygiene can lead to high transmission of *S. aureus* [18].

This outbreak clone is predominant in Africa or in countries with an important African community [22, 19]. For instance, ST88 strains harboring a t690 spa type, with a related background were identified in Tanzania [30, 31]. None of the cases had an African origin and no notion of travel was identified, but we did not verify whether cases had any links with people of African origin or the origin of nursing staff. However, the hospital is located in a district in Rennes with many inhabitants originating from Africa or the Middle East. Moreover, the maternity, gynecology and pediatric wards mostly manage women and children from this district. It is therefore likely that the suspected index case was not the source of the ST88 MRSA outbreak, but that the strain was introduced in the maternity ward by another women or family. These observations suggest cross-contaminations within the maternity ward as infected mothers did not know each other. Furthermore, community-acquired MRSA outbreaks usually appear in populations with high level of close contact [28]. We therefore assumed that the ST88 strain was introduced during the medical management of a parturient, with secondary dissemination of the epidemic strain within the ward and in the community by cross-transmission.

5. Conclusion

We reported an episode of clustered infections due to a PVL-producing MRSA ST88 strain in metropolitan France with evidence of first spreading in a maternity ward. Although reports of

nosocomial infections with community-acquired MRSA infections are increasing, they are still rarely described in our regions. It is therefore necessary to recognize and identify the epidemiological and clinical features of these infections, including in maternity or gynecology wards. This outbreak highlights the largely underestimated risk of healthcare-related infections in maternity wards. The ward, where women stayed for a short time, should here be considered as the place of nosocomial transmission of MRSA. Healthcare workers have to be aware of the importance of standard hygiene precautions and use of alcohol-based hand sanitizer for neonates and mothers. Further spreading in the community resulted in several family clusters of infection. In case of such outbreaks a follow-up should be implemented in the community to prevent the spread of these strains. Communication between health authorities, expert centers and local networks including clinicians and laboratories, is essential.

Authors equally contributed to the work.

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Figure 1. Synoptic timeline of clustered cases by month.

Red lines indicate hospitalization in the maternity ward. Black, green and red arrows respectively represent the date of symptom onset, biological confirmation of ST88 MRSA infection, and surgical drainage.

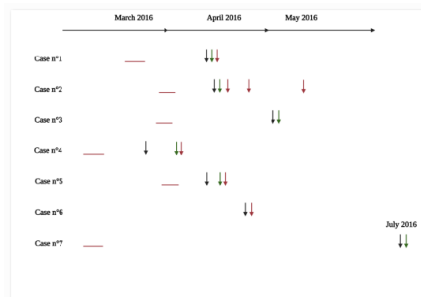


Figure 2. Number of single nucleotide polymorphism (SNP) relative to the most ancient strain (case 4) of the ST88 MRSA-IV strains isolated from newborns and mothers at Rennes CHU.

Strains isolated from mothers are labeled in green and strains isolated from newborns (twins) are labeled in purple. The delivery or date of birth and isolation dates are respectively indicated in red and black under the cases.

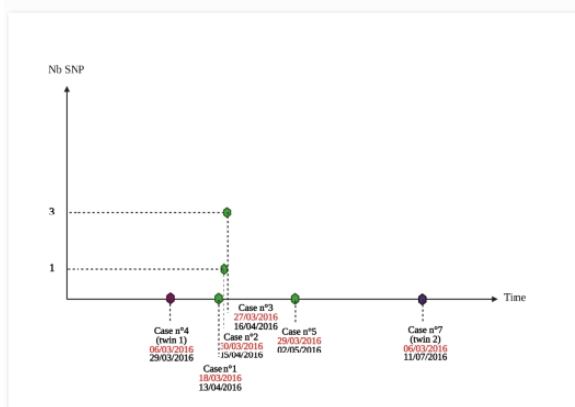
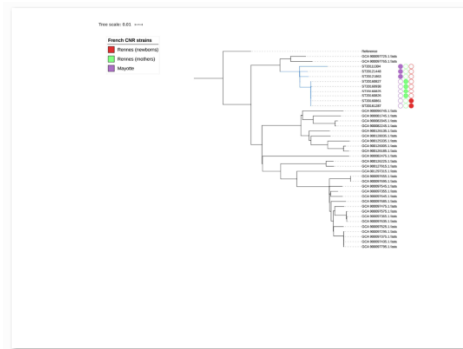


Figure 3. ST88 MRSA-IV SNP-based phylogeny.

Maximum likelihood phylogeny based on 2,530 core genome SNP from French CNR ST88 MRSA strains (n=9) and publicly available ST88 genomes (n=30). The clade formed by the French CNR strains is highlighted in blue.



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Table 1. Clinical features of cases

Cases	Sex	Age (years)	Delivery condition	Infection onset*	Month of clinical sign onset	Breastfeeding	Type of SSTI	Microbiological documentation	Surgical drainage	Therapy	Corrective surgery
No. 1	F	38	Caesarean section	20	April	Yes	Breast abscess	Yes	Yes	amoxicillin-clavulanic acid + local treatment	No
No. 2	F	40	Vaginal delivery	29	April	Yes	Breast abscess (left and right) with bacteremia	Yes	Yes	vancomycin + clindamycin	Yes
No. 3	F	43	Vaginal delivery	12	April	Yes	Breast abscess	Yes	No	amoxicillin followed by pristinamycin	No
No. 4	M	0	-	13	March	-	Pleuropneumonia	Yes	Yes	vancomycin + linezolid	No
No. 5	F	38	Vaginal delivery	12	May	Yes	Breast abscess	Yes	Yes	pristinamycin	No
No. 6	M	-	-	-	May	-	Paronychia	No	Yes	-	No
No. 7	M	0	-	116	July	-	Oral lesion	Yes	No	Local treatment	No

*number of days from hospital discharge

SSTI: skin and soft tissue infection; F: female; M: male