

Infection and colonization with methicillin resistant *Staphylococcus aureus* ST398 versus other MRSA in an area with a high density of pig farms

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Abstract The purpose of this study was to evaluate the impact of the emergence of animal related methicillin resistant *Staphylococcus aureus* ST398 in an area with a high density of pig farms. A retrospective analysis was performed of all MRSA isolates in the laboratory database from 2002 till 2008 including typing results and clinical data from infection control archives and patient charts. The implementation of the screening of people in contact with pigs and veal calves for MRSA led to an increase in the

average number of newly identified carriers from 16 per year between July 2002 and July 2006 to 148 between July 2006 and December 2008. This is a 925% increase of which 82% (108/132) was due to ST398. The majority (74%) came from targeted screening but 7% was due to unexpected findings. A wide range of infections with ST398 occurred in patients with and without contact with livestock varying from post-operative wound infections to sepsis and post-trauma osteomyelitis with an overrepresentation of spa type t567 among the clinical isolates. ST398 isolates were more often multi-resistant than isolates of other spa-types. The emergence of MRSA ST398 led to an increase in both MRSA carriers and MRSA infections.

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Introduction

The PAMM Laboratory for Medical Microbiology has an adherence area of 800,000 people in the south-east of the Netherlands, which is also an area with a high density of pig farms. The laboratory serves four hospitals and all nursing homes and general practitioners in the area. In the region, MRSA screening is performed according to the national Dutch guidelines as issued by the Working Group on Infection Prevention (WIP; www.wip.nl). Since the carriage of MRSA in the general population is low [1, 2], this policy consists mainly of screening people from foreign hospitals and/or contacts of known MRSA positive patients. In July 2006 these guidelines were changed when it became clear that contact with pigs and/or veal calves was a risk factor for MRSA carriage [3–6]. Consequently, persons in contact with these types of livestock were included in the risk groups. As of January 2007, the changed guidelines were fully implemented in the entire region. Livestock related MRSA at that point could be

distinguished from other MRSA strains since they were “non-typable” by the method used by the National Reference Laboratory (PFGE using SmaI restriction endonuclease) [7], and by the fact that it consists of a number of closely related spa types which all correspond to MLST ST398 [6]. The main spa-types in the Netherlands are t108, t011, t567 and t034 [8] (<https://mrsa.rivm.nl/>).

To analyze the impact of both the change in guidelines and the clinical impact of livestock related MRSA in this region, a retrospective analysis of all MRSA positive individuals was performed with regard to infections and colonization of patients and health care workers.

Materials and methods

An overview of all MRSA positive cultures was made from the laboratory system between July 2002 and December 2008. Data consisted of gender, age, whether it was a targeted screening culture or a routine culture isolate, patient or health care worker, typing data from the National Reference Laboratory and presence of PVL.

For screening cultures, only first isolates per person were included, unless a person was negative for more than one year in at least three sets of screening cultures and was later found to be positive with another type of MRSA. Data were collected from infection control archives, the medical microbiology consultation system and culture request forms. Established reasons for screening were transfer from either a foreign hospital or from a Dutch health care institution with an ongoing MRSA outbreak, contact with a MRSA positive patient/healthcare worker (referred to as “outbreak screening”), contact with an MRSA positive family member and, from July 2006, contact with livestock (e.g. pigs and veal calves).

If MRSA came from a routine culture of a patient not belonging to any designated risk group, the term “unexpected

MRSA” was used. For the analysis of the infection burden of other MRSA versus MRSA ST398, a further analysis was made of all routine cultures that yielded MRSA between January 1st 2007 and December 31st 2008, divided into urine cultures, blood cultures, sputum cultures and for swabs in skin and soft tissue infections, swabs of pre-existing wounds (trauma, diabetic foot ulcers, etc.) and cultures of post-operative wounds. If cultures of more than one body site were positive, the most clinically relevant sample was taken into account, e.g. if blood and wound swabs were positive, the blood culture was counted. Spa-type, potential risk group, presence of PVL and antimicrobial susceptibility testing including clindamycin, erythromycin, fusidic acid, gentamycin, mupirocin, rifampin, tetracycline, vancomycin, ciprofloxacin, linezolid and trimetoprim-sulfamethoxazol were collected for these isolates.

Results

MRSA positive individuals 2002–2008

A total of 640 isolates from 637 persons were identified of which 25 were excluded because of missing MRSA-typing data. The main characteristics of the 612 remaining MRSA positive individuals are shown in Table 1. There were two patients with two different types of MRSA and one health care worker (HCW) with three different types of MRSA.

In order to assess the impact of ST398 on the number of MRSA positive individuals in our population without hospital transmission, an analysis was made excluding isolates from outbreak screenings. As shown in this figure, the average number of newly identified MRSA positive individuals increased from 16 per year between July 2002 and July 2006 to 148 per year between July 2006 and December 2008, a 925% increase of which 82% (108/132) was due to ST398. From the newly identified MRSA

Table 1 Main characteristics of MRSA positive individuals including reason for screening

Characteristic	MRSA (N = 323)	MRSA ST398 (N = 292)
Male	135 (42%)	196 (67%)
Age (median)	52 (range 0–102)	43 (range 1–95)
Patients	235 (72%)	276 (94%)
Health care workers	88 (27%)	16 (6%)
Risk group		
Foreign hospital	41	6
Livestock contact	9	224
MRSA in family	15	8 ^a
Other Dutch HCI	6	1
Outbreak screening	166	21 ^b
Reason unknown	8	3
Unexpected	78	28

MRSA methicillin resistant *Staphylococcus aureus*, HCI health care institution

^a Although the indication for screening was an MRSA positive family member, four people of one family possibly had direct contact with livestock

^b Nine patients had another PFGE/spa-type as the index strain of the outbreak which should be considered co-incident findings

Table 2 Clinical samples of MRSA ST398 versus other MRSA patients

Characteristic	Other MRSA (N = 50)		MRSA ST398 (N = 30)	
Male	30 (60%)		21 (70%)	
Age (median)	50 (range 0–98)		56.5 (range 1–91)	
Age average	57.2		58.5	
No known risk group	42		18	
Livestock contact	0		11	
MRSA in family	2		0	
Other Dutch HCI	1		0	
Outbreak contact	2		1	
Community associated infections	27		16	
Health care associated infections	23		14	
PVL	13		0	
Spa-types				
Type of culture material	No risk group (n)	From known risk group (n)	No risk group (n)	From known risk group (n)
Blood	4	1	0	1
Diabetic foot	0	0	4 (p<0.05)	2
Operative wound	5	2	4	2
Otitis	1	0	0	2
Skin & soft tissue	12 (p<0.05)	1	0	0
Sputum	6	0	3	0
Urine	7	3	2	0
Wound	7	1	5	5
Total	42	8	18	12

MRSA methicillin resistant *Staphylococcus aureus*, HCI health care institution

One patient was positive in an outbreak setting and developed an osteomyelitis

positive patients, the majority came from targeted screening, but the “unexpected cases”, e.g. patients with an MRSA from a routine culture, mostly representing MRSA infections, also increased from an average of nine per year between July 2002 and July 2006 to 28 per year between July 2006 and Dec 2008. Of the 37 unexpected MRSA before July 2006, six (16%) were caused by ST398 and of the 69 after July 2006, 22 (32%) were caused by ST398.

MRSA infections 2007 and 2008

Between January 1st 2007 and December 31st 2008 a total of 416 new MRSA positive persons were identified of which 259 (62%) had MRSA ST398. Eighty persons had routine culture samples positive, which is indicative of an infection. In 73 cases the patient presented with the infection, in seven cases, infection developed in a known carrier. Four patients had two periods of infection: one had a sepsis following a diabetic foot infection, one was a patient with an acute myeloid leukaemia with two episodes of pneumonia with positive sputum cultures, one patient had an urinary tract infection (UTI) after a wound infection, and one patient had two episodes of UTI. Of these patients,

only the first infection was included. Table 2 shows an overview of all infections. Of the 30 patients with an MRSA ST398 infection, only 11 patients had documented contact with livestock. The three most frequent spa types involved in infections with ST398 were t567 (n=11), t011 (n=9) and t108 (n=5). While only 8% (18/229) of all MRSA ST398 carriers were colonized with spa-type t567, nearly 40% of the infections (11/30) were due this spa-type.

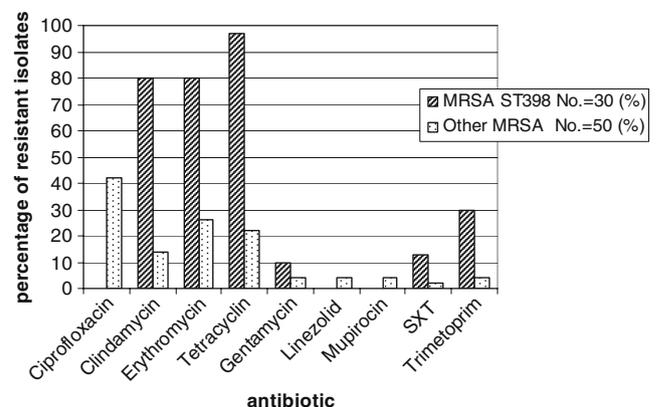


Fig. 1 Number of clinical isolates not susceptible

No PVL positive MRSA ST398 was found. Among the 156 other MRSA isolates, a total of 21 PVL positive isolates were found of which 13 were associated with infections: ten skin/soft tissue infections, two urinary tract infections and one wound infection. All these were community associated infections (CAI) without risk factors, except in one patient which was a family member of another MRSA positive patient. The associated spa types were t008 ($n=3$), t044 ($n=9$) and t202 ($n=1$). The PVL positive isolates that were not involved in infections were t008 ($n=3$), t044 ($n=3$), t852 ($n=1$) and t3361 ($n=1$).

Susceptibility data for the clinical isolates are shown in Fig. 1. Of the MRSA ST398, 21 (70%) isolates were resistant to three or more antibiotics, whereas 5 (17%) were resistant to four or more antibiotics. Among the other MRSA isolates this was the case in 6 (12%) and 3 (6%), respectively. Exclusively looking at the isolates that caused CAI, 13 (81%) of the MRSA ST398 isolates were resistant to three antibiotics versus 3 (11%) of all non-ST398 MRSA isolates.

Discussion

Over the past 5 years there has been a vast increase of MRSA positive patients in our region. The vast majority of that increase can be explained by the change of the screening protocol, with the inclusion of patients in contact with livestock. Over 80% of all newly identified MRSA positive patients belong to this latter group. Presently, the majority of patients with ST398 MRSA are just carriers and only a single outbreak has been documented. Still, the recent emergence of ST398 MRSA is cause for concern. Of all patients with a routine culture with MRSA, indicative of an infection with this micro-organism, one third has MRSA ST398. The spectrum of ST398 infections is not radically different from that of other MRSA with the exception of skin and soft tissue infections, which are primarily caused by CA-acquired, PVL positive MRSA. Although ST398 does not appear to be as virulent as CA-MRSA, it does cause infections in hosts with risk factors for *S. aureus* infections such as diabetic ulcers and other wounds and is frequently multi-resistant, making empirical antibiotic therapy in the out-patient setting difficult. Why spa type t567 is overrepresented in the MRSA ST398 infections might in part be explained by the fact that three infections occurred in the context of a hospital outbreak [9], but even if these are excluded with 27% this is still an overrepresentation of this spa type in infections. Spa type t567 is specifically higher in the south-east region of the Netherlands. In 2007, 42 isolates of this spa-type were sent to the National Reference Laboratory, of which 20 were from our region. It constitutes 5.3% of all ST398 in the Netherlands [10] but 14.1% in our region. MRSA spa-type t567 was found to be

limited to farms belonging to one supply chain [11], which might play a role in this overrepresentation.

While we tried to classify MRSA infections as health care associated and community associated infections respectively, the question remains whether this classification is still applicable in the present Dutch situation. It is implied that a health care associated infection (HAI) with MRSA represents acquisition of this microorganism in the health care institution. With the low prevalence of MRSA in Dutch hospitals, and the emergence of ST398 MRSA in the community, chances are that a majority of the patients acquire MRSA previous to admission to the hospital. In our hospitals, an unexpected MRSA infection is always followed by screening of health care workers and fellow patients in contact with the index. The current experience with HAI caused by MRSA ST398 shows that in 14 cases only one resulted in transmission to fellow patients and HCWs [9]. Furthermore, the total number of HCW colonized with ST398 seems to be low [12], thus while the infection may start in the hospital, the acquisition of ST398 is most likely due to direct contact with livestock. Although the prevalence of MRSA ST398 in the general population appears to be low [13], acquisition through contact with contaminated environment, air or through direct contact with carriers cannot be excluded. Environmental contamination, e.g. outside “open” stables, has been described [14], but the question remains whether this could be the case in the Netherlands where most stables are “closed”. While rare case reports such as MRSA ST398 endocarditis in a woman living next to a pig farm [15] and ST398 post-operative osteomyelitis after having an accident on a rural country road (within the cohort of the present study) have been described, more research is needed to establish the risk of acquisition of MRSA ST398 in persons with only environmental contact.

MRSA ST398 has led to a significant increase in MRSA positive patients thereby putting a considerable strain on infection control practices in hospitals. At present the main health risk of MRSA ST398 lays with those persons in contact with livestock.

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