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Transmissibility of livestock-associated methicillin-resistant *Staphylococcus aureus* (ST398) in Dutch hospitals

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Abstract

We quantified nosocomial transmission rates of sequence type (ST) 398 methicillin-resistant *Staphylococcus aureus* (MRSA) (an emerging livestock-associated MRSA clone) and non-ST398 MRSA isolates in patients hospitalized without infection control measures in 51 Dutch hospitals. Identification of 174 index patients initiated 139 post-exposure screenings of 9925 persons. There were 65 genotype-confirmed secondary cases (three and 62 for ST398 and non-ST398 MRSA, respectively), yielding a relative transmission risk for ST398 MRSA of 0.28 (95% CI 0.09–0.90), which was not sensitive to adjustment for duration of hospitalization at time of detection. Nosocomial transmission of ST398 MRSA is 72% less likely than that of non-ST398 MRSA strains.

Keywords: Livestock-associated MRSA, methicillin-resistant *Staphylococcus aureus*, nosocomial transmission, ST398
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Introduction

The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) among invasive nosocomial *S. aureus* infections has remained below 1% in countries using a nationwide search and destroy policy, such as The Netherlands (http://www.rivm.nl/earss/database/) [1]. Here, MRSA epidemiology changed dramatically in 2005 when a new community-acquired MRSA clone of animal origin emerged [2–4]. The animal-related MRSA isolates appeared to represent a distinct clone, characterized as sequence type (ST) 398 by multilocus sequence typing [4]. ST398 MRSA is now also emerging in other countries, including the USA [5].

Since July 2006, in The Netherlands, all individuals who have had professional contact with pigs or veal calves are considered to be at risk of MRSA carriage [6]. Accordingly, such persons are pre-emptively isolated when admitted, while the microbiological results of MRSA screening are awaited. When MRSA is detected in a non-isolated patient (i.e. index patient), the patient is isolated, and the room-mates and healthcare workers (HCWs) involved in direct care for the index patient are screened for MRSA carriage. Before July 2006, most individuals at risk of MRSA carriage were patients who had been admitted to hospitals abroad, but from July 2006 onwards, the risk group also included pig and veal calve farmers, their family members and veterinarians. However, the transmissibility of ST398 MRSA in hospitals has never been investigated. We therefore determined nosocomial transmission rates of livestock-associated MRSA (ST398 MRSA) and other (healthcare-associated) MRSA isolates (non-ST398 MRSA) by calculating the numbers of secondary cases following the detection of MRSA index patients who were hospitalized without MRSA-specific infection control measures. Importantly, human-derived community-acquired MRSA isolates (such as USA300 and USA400) were only sporadically encountered, and were therefore not included as a separate group in our study.

Materials and Methods

Collection of data

All Dutch infection control practitioners and medical microbiologists were contacted and asked to collect data on all patients and HCWs who had been screened for MRSA after exposure to MRSA index patients from July 2006 to October 2006 (3 months retrospectively) and from October 2006 to January 2007 (3 months prospectively). Information was obtained from the index case (type of MRSA: ST398 or non-ST398), location of index case (outpatient clinic or hospital ward), number of hospital days without isolation measures, total length of hospital stay, number of screened HCWs and contact patients, number of secondarily colonized HCWs and contact patients, and type of MRSA. Detection of MRSA genotypes in screened HCWs or patients that differed from the genotype of index cases was considered to be an accidental finding. Secondary cases were defined as persons colonized with the same MRSA genotype as the index case on the basis of pulsed-field gel electrophoresis (PFGE) patterns. We assumed that all index cases were already colonized at the time of hospital admission. All calculations are based on the assumption that all secondary cases were directly infected by the index case.

MRSA screening

The strict Dutch search and destroy strategy includes, among other things, screening of patients at high risk of MRSA carriage when admitted to the hospital or visiting the outpatient clinic. Swabs from the anterior nares, throat, perineum and, if present, wounds and catheter insertion sites, and sputum and urine samples (in cases of an indwelling urinary catheter), are obtained according to our guideline (MRSA guideline, Dutch Working Party on Infection Control: http://www.wip.nl/free_content/richtlijnen/mrsa%20ziekenhuis080310.pdf). HCWs are screened for MRSA carriage after contact with an unsuspected MRSA carrier, which means without taking protective measures. For HCWs, swabs from the anterior nares, throat and, if present, skin lesions are taken. Conventional microbiological cultures, including a broth enrichment step for all swabs combined with selective and non-selective agar plates, are performed according to the guidelines of the Dutch Society of Medical Microbiology [7]. All first MRSA isolates of newly identified carriers are sent to the Dutch MRSA reference laboratory of the National Institute of Public Health and the Environment (RIVM) for typing. In 2006, according to the protocol at that time, isolates were initially genotyped by PFGE with the enzyme *Sma*1. Additional typing methods (e.g. multilocus sequence typing and *Spa*-typing) were used for livestock-associated strains, as these isolates can not be typed using PFGE with *Sma*1 [8].

Statistical analysis

Differences in transmission of ST398 and non-ST398 MRSA isolates were assessed by calculating relative rates and relative risk ratios. Continuous variables were compared with the Mann–Whitney *U*-test; categorical variables were compared with the chi-square test and Fisher's exact test. All analyses were performed using SPSS 15.00 for windows (SPSS Inc., Chicago, IL, USA), with significance defined as $p < 0.05$.

Results

Fifty-one hospitals (52% of all general and academic hospitals in The Netherlands) participated, yielding data on 306 months of MRSA policy. There were 174 MRSA-positive index patients, and post-exposure screenings were performed in 139 cases in 38 hospitals (with 9925 individuals being screened for MRSA). MRSA carriage was documented in 24 of 139 (17%) contact screenings, in most cases (75%) in a single person only. Data on the length of hospital stay and duration of isolation measures were missing for 17 index patients, and the corresponding post-exposure screenings were therefore excluded from the analysis. Eighty post-exposure screenings (with 7892 persons screened) were performed because of non-isolated hospitalized patients, and included in our study. The remaining 42 post-exposure screenings were performed in the outpatient clinic (with 507 individuals being screened) and were therefore not included. When categorized according to the MRSA type (ST398 or non-ST398), the characteristics of index patients were comparable, except for the duration of hospitalization without isolation measures, which was longer for non-ST398 MRSA carriers (Table 1).

Secondary cases were documented in three of 964 (0.3%) HCWs and none of 183 patients screened (0.3% of all individuals screened) for ST398 MRSA, and in 29 of 4794 (0.6%) HCWs and 33 of 1951 (1.7%) patients screened (0.9% of all individuals screened) for non-ST398 MRSA (Fig. 1). The relative risk of transmission of ST398 MRSA, as compared with non-ST398 MRSA, was 0.28 (95% CI 0.09–0.90). The number of days in hospital without infection control measures were 94 (median: 1.5) and 489 (median: 4.0) for index patients carrying ST398 and non-ST398 MRSA, respectively. The numbers of secondary cases per 30 days of hospitalization of a colonized patient without isolation measures were 1.0 and 3.8 for ST398 and non-ST398 MRSA, respectively (p 0.01;

Characteristics of index patients	ST398 MRSA	Non-ST398 MRSA	p
Length of hospital stay (days)	7	8	0.36
Number of contacts, screenings/day exposure	16	12	0.75
Post-exposure screenings in ICUs (%)	13	18	0.34
Time of exposure before isolation measures (days)	1.5	4.0	0.04
Time of exposure in cases with transmission, (days)	3.0	13.0	0.06

ICU, intensive-care unit; ST, sequence type.

TABLE 1. Characteristics of 80 index patients found to be colonized with methicillin-resistant *Staphylococcus aureus* (MRSA) (values are expressed as median unless otherwise stated)

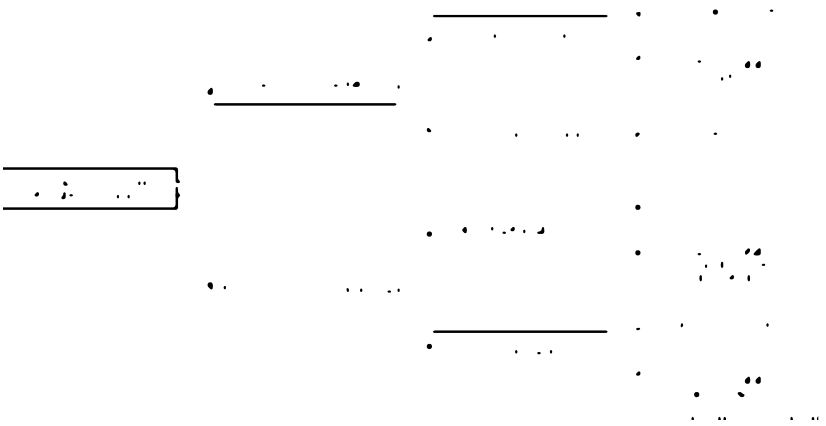

FIG. 1. Numbers of genotype-confirmed secondary cases and persons carrying other methicillin-resistant *Staphylococcus aureus* (MRSA) genotypes than the index patient in 80 post-exposure screenings. HCWs, healthcare workers; ST, sequence type.

Fisher's exact test), yielding a relative transmission rate of 0.27 (95% CI 0.09–0.86) for ST398 as compared with non-ST398. The three HCWs secondarily colonized with ST398 had no other risk factor for carriage of ST398; they had had no contact with livestock and did not live on a farm.

The proportions of individuals carrying MRSA genotypes other than those of index patients were 0.04% for ST398 MRSA (0.06% HCWs; 0% patients) and 0.2% for non-ST398 MRSA (0.14% HCWs; 0.47% patients) (p 0.35; Fisher's exact test) (Fig. 1).

Discussion

Livestock-associated ST398 MRSA is 72% less transmissible than other MRSA genotypes in Dutch hospitals. The lower transmission capacity may be caused by pathogen-related or patient-related characteristics. These findings suggest that ST398 MRSA isolates that are now emerging worldwide represent a lower risk of nosocomial spread than so-called healthcare-associated MRSA isolates, and that less stringent infection control measures might be sufficient.

The observed difference in transmission capacity remains unexplained. Molecular studies have identified differences between ST398 MRSA and both healthcare-associated MRSA and community-acquired MRSA strains, such as the absence of important virulence genes (e.g. the Panton–Valentine leukocidin gene, *tst* and *LukM*) and antimicrobial resistance genes (19th European Congress of Clinical Microbiology and Infectious Diseases, Abstracts P1372 and P1376) [4,9,10]. Furthermore, differences in transmission capacity may also result from different characteristics among patients carrying different MRSA strains. Although length of hospital stay, number of contacts with HCWs and number of post-exposure screenings in intensive-care units were comparable between the two different patient groups in our study, other relevant information, such antibiotic use, was not available.

We made the assumption that all index patients were already colonized at the day of admission. This assumption is probably more accurate for ST398 MRSA, as the risk of contracting non-ST398 MRSA carriage is higher in the hospital environment, which implies that some non-ST398 index cases might, in fact, have been secondary cases originating from an index case that was never identified. As a result, the true number of days without isolation measures might be lower for non-ST398 index patients, implying that the observed difference between transmission of ST398 and non-ST398 MRSA is underestimated, which actually strengthens our conclusion.

In another, much smaller, Dutch surveillance study, ST398 MRSA carriage was detected in 1/77 (1%) HCWs who were considered to have frequent contacts with pigs and veal calves in their home situation [11]. That study was performed in an area with a high density of pig farms. Our study also included areas with low pig farm densities, yielding a prevalence of 0.06% of ST398 MRSA carriage among HCWs. We therefore conclude that the MRSA prevalence in Dutch HCWs is low for all types of MRSA, and that they do not represent a serious risk of introducing MRSA into hospitals.

Our study has several limitations. First, we did not collect clinical and demographic data from index patients, the secondary cases and screened individuals, and were therefore unable to identify specific risk factors for transmission or to differentiate the transmission potential of individual non-ST398 MRSA strains. In fact, much larger patient populations would be needed for such analyses. Community-associated Panton–Valentine leukocidin-containing MRSA isolates are still infrequently encountered in The Netherlands, and our findings are therefore not generalizable to these types of MRSA. Second, we could not compare ST398 MRSA isolates at the molecular level, and therefore cannot be completely sure that transmission really originated from the index case. Again, in this respect, our findings might represent an underestimation of the true difference in transmission capacity of ST398 and non-ST398 MRSA strains.

In conclusion, nosocomial transmission of ST398 MRSA to HCWs and patients is 72% less likely than that of non-ST398 MRSA strains. As the global emergence of ST398 MRSA in the animal reservoir, with subsequent spill-over to frequently exposed individuals, may put a burden on hospitals in regions with high densities of agricultural industry, infection control guidelines should consider less stringent control measures for ST398 MRSA carriers.

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Transparency Declaration

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