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Emergence of Livestock-Associated Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections in Denmark

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Background. Livestock-associated methicillin-resistant *Staphylococcus aureus* clonal complex 398 (LA-MRSA CC398) is causing an increasing number of skin and soft tissue infections (SSTIs) in Denmark and other European countries with industrial pig production. Yet, its impact on MRSA bloodstream infections (BSIs) has not been well studied.

Methods. We investigated the clinical epidemiology of all human cases of LA-MRSA CC398 BSI during 2010–2015. Cases of LA-MRSA CC398 BSI were compared to cases of BSI caused by other types of MRSA and cases of SSTI caused by LA-MRSA CC398. Whole-genome sequence analysis was used to assess the phylogenetic relationship among LA-MRSA CC398 isolates from Danish pigs and cases of BSI and SSTI.

Results. The number of LA-MRSA CC398 BSIs and SSTIs increased over the years, peaking in 2014, when LA-MRSA CC398 accounted for 16% (7/44) and 21% (211/985) of all MRSA BSIs and SSTIs, corresponding to 1.2 and 37.4 cases of BSI and SSTI per 1 000 000 person-years, respectively. Most patients with LA-MRSA CC398 BSI had no contact to livestock, although they tended to live in rural areas. LA-MRSA CC398 caused 24.3 BSIs per 1000 SSTIs among people with no livestock contact, which is similar to the ratio observed for other types of MRSA. Whole-genome sequence analysis showed that most of the BSI and SSTI isolates were closely related to Danish pig isolates.

Conclusions. This study demonstrates that the increasing number of LA-MRSA CC398 BSIs occurred in parallel with a much larger wave of LA-MRSA CC398 SSTIs and an expanding pig reservoir.

Keywords. MRSA; humans; livestock; zoonosis; bacteremia.

Since the early 2000s, zoonotic transmission of livestock-associated methicillin-resistant *Staphylococcus aureus* clonal complex 398 (LA-MRSA CC398) has led to an increasing number of human infections in Denmark and other European countries with industrial pig production [1, 2]. LA-MRSA CC398 is primarily associated with skin and soft tissue infections (SSTIs) among otherwise young and healthy livestock workers but also in the general population, which includes elderly and immunocompromised people with an elevated risk of developing invasive staphylococcal illnesses [1]. Yet, its impact on MRSA bloodstream infections (BSIs) is poorly understood. In Denmark, the first case of LA-MRSA CC398 BSI was identified

in November 2010 in an 11-year-old boy with leukemia. The patient's father owned a pig farm and was found to be colonized with LA-MRSA CC398. Subsequently, LA-MRSA CC398 has been described as a sporadic cause of BSIs and deaths in patients with no connection to pigs or pig farmers [3].

The objectives of this study were to: (1) investigate the clinical epidemiology of cases of LA-MRSA CC398 BSI; (2) compare cases of LA-MRSA CC398 BSI to cases of BSI caused by other types of MRSA and cases of SSTI caused by LA-MRSA CC398; and (3) infer the phylogenetic relationship among LA-MRSA CC398 isolates from Danish pigs and cases of BSI and SSTI.

METHODS

The study population included all Danish patients who were registered as having had an episode of MRSA BSI or SSTI between 1 January 2010 and 31 December 2015. Detailed data on the characteristics of MRSA isolates from each episode of BSI and information on the patients at the time of diagnosis were extracted from the national *S. aureus* bacteremia (SAB) database. For comparative purposes, the national MRSA database was reviewed to identify and abstract information on patients with MRSA SSTIs. The MRSA database contains strain typing results and information about all individuals colonized or infected with MRSA

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but only at the time when a given MRSA CC is first detected, except from subsequent episodes of BSI, which are recorded in the SAB database. The regional clinical microbiology laboratories performed *S. aureus* identification and established methicillin resistance by use of standard laboratory methods and forwarded the isolates to the National Reference Laboratory for Staphylococci at Statens Serum Institut. LA-MRSA CC398 was identified using a 3-step procedure. First, MRSA identification was confirmed by polymerase chain reaction (PCR) detection of *mecA* and *spa* [4]. Second, MRSA CC398 was differentiated from other types of MRSA using *spa* typing and PCR detection of the *S. aureus* CC398-specific *sau1-hsdS1* variant. Third, LA-MRSA CC398 was distinguished from the human variant of MRSA CC398 using a dual-probe real-time PCR assay [1]. The following data were collected for each patient's medical record: sex, age, livestock contact (only available for patients with LA-MRSA CC398 BSI or SSTI), residential address, hospitalization dates, and Charlson comorbidity score (only available for patients with MRSA BSI) [5]. An episode of MRSA BSI was defined as community-onset if the patient had a positive blood culture within the first 48 hours after admission or hospital-onset if the first positive blood culture was obtained ≥ 48 hours after admission. Data collection was approved by the Danish Data Protection Agency (protocol number 2001-14-0021). Incidence rates for LA-MRSA CC398 BSIs and SSTIs were calculated by using all cases identified in 2014 and Danish census population estimates for 2014 [6]. Pearson correlation coefficient (r) was used to evaluate temporal trends, and patient variables were compared between groups using Student's t test for continuous data and Fisher's exact test for categorical data (GraphPad Prism software, version 5, GraphPad, La Jolla, California). The significance level was set at $\alpha = .05$. Whole-genome phylogenetic tools were used to study the relationship among the following *S. aureus* CC398 isolates: (1) all 17 BSI isolates collected between 2010 and 2015; (2) a subset of 66 SSTI isolates, including all 36 isolates from 2010 and every third isolate according to isolation date from 2015; (3) a subset of 50 LA-MRSA CC398 isolates collected from Danish pig production farms (1 isolate per farm) in 2010 and 2014 by the Danish Veterinary and Food Administration [7, 8]; and (4) 89 international *S. aureus* CC398 isolates from humans and various animal species [9]. Six LA-MRSA CC398 isolates from the international collection (2007-70-91-4-SPA, 2008-60-970, 9B, 3-S-1, 2008-60-3254, and 7_2007-70-77-4) originated from Danish pigs and were categorized as such in the analysis. Methodological details are provided in the Supplementary Materials.

RESULTS AND DISCUSSION

LA-MRSA CC398 accounted for 17 cases of BSI, 700 cases of SSTI, and 76 cases with other infections between 2010 and 2015, whereas other types of MRSA caused a total of 145 BSIs,

3897 SSTIs, and 570 other infections during the study period. Cases of LA-MRSA CC398 BSI (cases A–Q) and laboratory findings are described in Table 1. The number of LA-MRSA CC398 BSIs and SSTIs increased over the years, peaking in 2014, where LA-MRSA CC398 accounted for 16% (7/44) and 21% (211/985) of all MRSA BSIs and SSTIs, corresponding to 1.2 and 37.4 cases of BSI and SSTI per 1 000 000 person-years, respectively (Figure 1). The correlation between the annual numbers of LA-MRSA CC398 BSIs and SSTIs was statistically significant ($r = 0.88$, $P = .02$).

Thirty-two percent (221/700) of the LA-MRSA CC398 SSTIs occurred in people with no livestock contact, confirming previous findings that LA-MRSA CC398 is spreading into the community [1]. This is worrisome because the general population includes a higher proportion of elderly and immunocompromised people at elevated risk of developing invasive staphylococcal illnesses, compared to people with livestock contact who consist primarily of healthy adults of working age. In fact, 59% (10/17) of patients with LA-MRSA CC398 BSI had no contact to livestock, although they tended to live in rural areas where livestock is raised (Table 1). In addition, LA-MRSA CC398 caused 45.2 BSIs per 1000 SSTIs (10/221) among people with no livestock contact, compared to only 14.6 BSIs per 1000 SSTIs (7/449) among livestock workers and their family members. Death attributable to LA-MRSA CC398 BSI was also more common in the general population in that none of the 6 patients, who died within 30 days after diagnosis of LA-MRSA CC398 BSI, had contact to livestock (Table 1).

LA-MRSA CC398 lacks many of the adhesion and virulence-associated determinants found in other types of MRSA, which has raised questions about its pathogenicity in humans [10, 11]. However, we found no differences between cases of LA-MRSA CC398 BSI and cases with other types of MRSA BSI with regard to age (mean, 56 years vs 61 years; $P = .3$), Charlson comorbidity score (mean, 2.4 vs 2.2; $P = .8$), the total number of BSIs per 1000 SSTIs (24.3 vs 37.2; $P = .1$), or the 30-day case-fatality rate (35% [6/17] vs 21% [31/145]; $P = .2$). Although the small numbers make it difficult to draw definitive conclusions, these findings indicate that LA-MRSA CC398 may be as capable as other types of MRSA of causing serious illness and even death in elderly and immunocompromised people.

Pigs are the primary host of LA-MRSA CC398 in Denmark [12]. During the study period, the prevalence of Danish pig farms that tested positive for LA-MRSA CC398 increased from 16% in 2010 to >60% in 2014 [7, 8]. Thus, pigs constitute a likely source of both LA-MRSA CC398 BSIs and SSTIs in Denmark. However, LA-MRSA CC398 can also spread between countries, for example via contaminated meat products and colonized individuals [12, 13]. We used whole-genome phylogenetic tools to determine whether LA-MRSA CC398 isolates from cases of BSI and SSTI were most closely related to each other, to LA-MRSA CC398 isolates from Danish

Table 1. Danish Patients With Livestock-Associated Methicillin-Resistant *Staphylococcus aureus* CC398 Bloodstream Infection and Laboratory Findings

Case/ Isolate	Sex	Age,y	Isolation Date	Charlson Comorbidity Score	Residence	Disease Onset	Outcome ^a	Livestock Exposure	Other Epidemiologic Findings	<i>spa</i> Type	Shortest Distance to a Danish Pig LA-MRSA CC398 Isolate, SNPs
A	M	11	10 Sept 2010	6	Rural	Community		Yes		t034	7
B	F	57	7 Apr 2012	5	Urban	Community		No	Possibly foodborne transmission [12]	t899	90
C	F	51	6 Oct 2012	4	Rural	Community	Died	No		t034	22
D	M	65	10 June 2013	1	Rural	Community		Yes		t034	8
E	M	63	11 Nov 2013	3	Rural	Community	Died	No	Hospital outbreak A [14]	t011	16
F	F	86	23 Nov 2013	3	Rural	Community	Died	No		t034	7
G	F	0	4 Dec 2013	0	Rural	Community		Yes		t034	9
H	F	60	8 Apr 2014	2	Rural	Community		Yes		t034	15
I	M	74	14 Apr 2014	4	Rural	Community	Died	No	Nursing home out- break [14]	t034	19
J	M	69	9 June 2014	1	Rural	Community		No		t034	13
K	M	72	5 July 2014	0	Rural	Hospital	Died	No		t571	16
L	M	31	14 Sept 2014	6	Rural	Community		Yes		t034	10
M	M	48	30 Dec 2014	0	Rural	Community		Yes		t034	11
N	M	49	31 Dec 2014	0	Rural	Community		Yes		t034	13
O	F	67	6 Mar 2015	3	Rural	Community		No		t034	8
P	F	68	4 Sept 2015	0	Rural	Hospital		No	Hospital outbreak B	t034	14
Q	M	77	11 Oct 2015	2	Rural	Hospital	Died	No	Hospital outbreak B	t034	14

Abbreviations: CC, clonal complex; LA-MRSA, livestock-associated methicillin-resistant *Staphylococcus aureus*; SNP, single-nucleotide polymorphism.

^aDied within 30 days after diagnosis of LA-MRSA CC398 bloodstream infection.

pigs, or to *S. aureus* CC398 isolates from the international collection. The maximum-likelihood phylogenetic tree showed that LA-MRSA CC398 isolates from Danish pigs and cases of SSTI and BSI often grouped together in several distinct clusters (Figure 2 and Supplementary Figure 1). The average single-nucleotide polymorphism (SNP) distance between the 17 BSI isolates and their closest SSTI and Danish pig LA-MRSA CC398 counterparts was 18 (range, 8–86 SNPs) and 17 (range, 7–90

SNPs), respectively, whereas the average shortest SNP distance to an *S. aureus* CC398 isolate from the international collection was 48 SNPs (range, 32–58 SNPs) ($P < .0001$). Likewise, the 66 SSTI isolates had significantly shorter average SNP distances to Danish pig isolates than to *S. aureus* CC398 isolates from the international collection (18 SNPs [range, 2–61] vs 42 SNPs [range, 15–75]; $P < .0001$). In total, 16 of the 17 BSI isolates and 59 of the 66 SSTI isolates were more closely related to LA-MRSA CC398 isolates from Danish pigs than to isolates from the international collection (Figure 2 and Supplementary Figure 1). Thus, Danish pigs and cases of BSI and SSTI seem to share a common pool of LA-MRSA CC398 isolates, which supports that the increasing number of SSTIs and BSIs is a result of zoonotic transmission from the expanding pig reservoir. The remaining BSI isolate originated from a 57-year-old urban-dwelling woman with no history of livestock exposure (case B). It had *spa* type t899 and was most closely related to a *spa* type t899 pig MRSA isolate from France (Figure 2 and Supplementary Figure 1). This isolate from case B was analyzed in a recent study, which showed that it belongs to a poultry-adapted genotype that consists of a CC398 chromosomal backbone and a smaller CC9 region [12]. The CC9/CC398 genotype has never been found in Danish livestock, whereas it occurs with some frequency in poultry and poultry meat produced in other European countries as well as in chicken meat products imported to Denmark [12]. These findings support

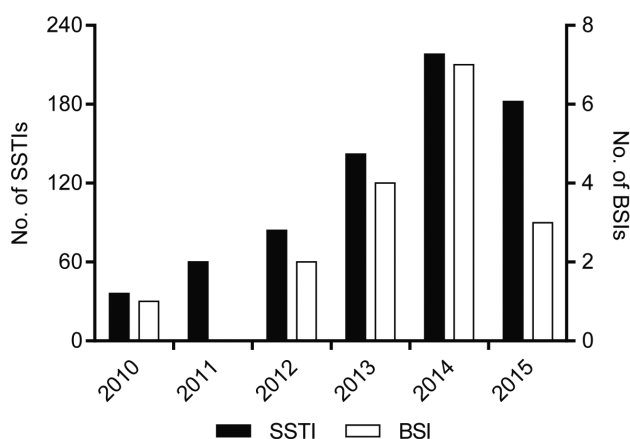


Figure 1. Temporal trends of livestock-associated methicillin-resistant *Staphylococcus aureus* CC398 bloodstream infections (BSIs) and skin and soft tissue infections (SSTIs) in Denmark.

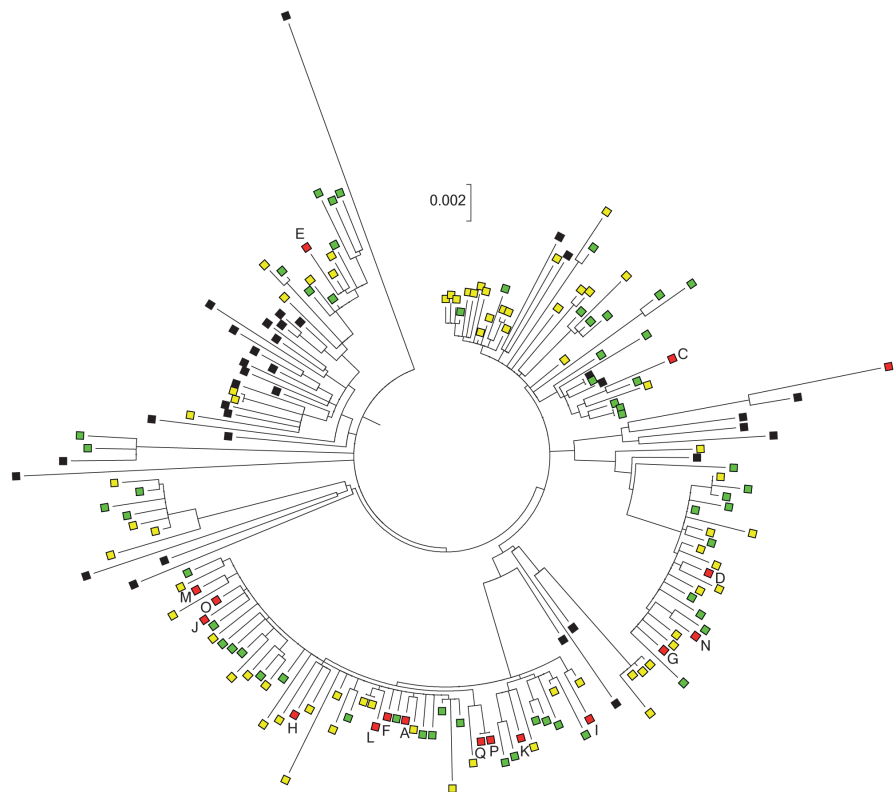


Figure 2. Part of the maximum-likelihood phylogeny containing the bloodstream infection (BSI) and skin and soft tissue infection (SSTI) isolates (see Supplementary Figure 1 for a full version of the phylogeny, including bootstrap values). Red boxes, BSI isolates; yellow boxes, SSTI isolates; green boxes, Danish pig livestock-associated methicillin-resistant *Staphylococcus aureus* CC398 isolates, including 6 isolates from the international collection; black boxes, other livestock-associated *Staphylococcus aureus* CC398 isolates from the international collection. Scale bar represents the number of nucleotide substitutions per site.

that the isolate from case B originates from a poultry reservoir outside Denmark, rather than from Danish pigs.

Three patients (cases K, P, and Q) had hospital-onset LA-MRSA CC398 BSI, 2 of whom, a 68-year-old woman (case P) and a 77-year old man (case Q), were epidemiologically linked to a nosocomial outbreak in 2015 (Table 1). Pairwise SNP comparison showed that the isolates were identical to each other (Figure 2 and Supplementary Figure 1), which supports transmission between these patients or acquisition from a common hospital source. In addition, 2 patients with community-onset LA-MRSA CC398 BSI, a 63-year-old man receiving outpatient dialysis (case E) and a 74-year-old male nursing home resident (case I), were previously reported to be part of 2 distinct healthcare outbreaks [14]. All 5 isolates from cases E, P, and Q were closely related to Danish pig isolates (range, 14–16 SNPs). These observations substantiate those of previous studies from the Netherlands showing that LA-MRSA CC398 is able to migrate into healthcare facilities where it can cause outbreaks among high-risk patients [15–17].

The findings of our study pertain to CC398, which is the dominant LA-MRSA strain type in pigs in Denmark and other European countries. Other LA-MRSA strain types are dominant in pigs elsewhere, such as CC9 in Asia and some areas of

the United States [18, 19], and their impact on human health is currently less well described.

In summary, this study demonstrates that the increasing number of LA-MRSA CC398 BSIs observed in Denmark between 2010 and 2015 occurred in parallel with a much larger wave of LA-MRSA CC398 SSTIs and an expanding pig reservoir with increased spread into the community and healthcare settings. However, Denmark is still considered to have low-endemic levels of MRSA compared to other European countries [20]. This is illustrated by the fact that MRSA accounted for only 44 of 1964 episodes of *S. aureus* BSI in Denmark in 2014, when the number of LA-MRSA CC398 BSIs peaked at 7 [21]. Nonetheless, the number of serious infections and deaths is expected to increase in the near future if LA-MRSA CC398 is allowed to spread into the general population. Thus, it is important to identify and implement effective control measures to prevent transmission of LA-MRSA CC398 between pig farms and from pigs to humans.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author contributions. J. L., A. P., A. R. L., M. S., A. K., and R. L. S. were members of the MRSA surveillance team. J. L., M. S., L. B. P., and R. L. S. designed the study and prepared the initial manuscript. A. P., A. R. L., R. N. S., A. K., and F. M. A. contributed to the subsequent editorial revisions. J. L., A. P., and A. K. performed epidemiological investigations. J. L., R. N. S., and M. S. conducted whole-genome sequencing and phylogenetic analysis of the isolates. F. M. A. performed initial genotypic characterization of the Danish pig isolates collected in 2010 and 2014. The Danish MRSA Study Group collected and shared isolates and patient data and commented on the manuscript. All authors proofread the article.

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