Livestock-Associated Methicillin-Susceptible *Staphylococcus aureus* Bacteremia, Denmark, 2007–2023

Claire L. Raisen,[1] Anna B. Pedersen,[1] Anders Dalsgaard, Kåre Mølbak, Andreas Petersen, Anders R. Larsen, Jesper Larsen

Livestock-associated *Staphylococcus aureus* caused 200 human bloodstream infections in Denmark during 2007–2023; two thirds were caused by methicillin-susceptible isolates. Risk for death was comparable to that associated with human *S. aureus* clones. Industrial pig population size correlated strongly with disease prevalence. Seventeen percent of isolates showed signs of human adaptation.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a leading cause of difficult-to-treat infections, causing an estimated 130,000 deaths worldwide in 2021, and is classified as a high-priority pathogen by the World Health Organization (*1*,*2*). The emergence of livestock-associated (LA) MRSA clonal complex (CC) 398 (LA-MRSA CC398) in the early 2000s has led to increasing numbers of human infections in countries in Europe with industrial pig production, including Denmark, where LA-MRSA CC398 accounted for 12% (241/1,993) of all human MRSA infections in 2024 (*3*,*4*). LA *S. aureus* CC398 isolates are descendants of a human *S. aureus* CC398 variant but have lost the ΦSa3int prophage and the associated immune evasion cluster (IEC), which encodes immune modulators that protect human *S. aureus* clones from the human innate immune system (*5*). LA-MRSA CC398 is poorly adapted for human-to-human transmission (*6*) but nonetheless can spread from pigs to the community and healthcare facilities (*7*).

Previous efforts to assess the prevalence of LA *S. aureus* CC398 disease have focused almost exclusively on LA-MRSA CC398, including a study in Denmark (*8*), but overlooked that pigs also constitute a reservoir of methicillin-susceptible *S. aureus* (MSSA) CC398 (*9*) and that most *S. aureus* bloodstream infections are caused by MSSA isolates (*10*). For example, the incidence rate of MSSA bacteremia is ≈10 times higher than that of MRSA bacteremia in countries of the European Union and European Economic Area (37.9 vs. 4.43 cases/100,000 population) (*10*).

We conducted a nationwide study of LA *S. aureus* CC398 bacteremia in Denmark during January 1, 2007–December 31, 2023 (Appendix https://wwwnc.cdc.gov/EID/article/32/12/26-1261-App1.pdf). The objectives were to determine the relative prevalence of LA-MRSA CC398 and LA-MSSA CC398 bacteremia in Denmark, estimate the relative risk for death in patients with bacteremia caused by LA *S. aureus* CC398 and human *S. aureus* clones, evaluate whether the number of LA *S. aureus* CC398 bloodstream infections correlates with the size of the industrial pig population across regions of Denmark, and investigate whether IEC is associated with increased risk for death among patients with LA *S. aureus* CC398 bacteremia.

The Study

LA *S. aureus* CC398 caused 200 human bloodstream infections in Denmark during 2007–2023 (Figure). We summarized results by strain characteristics and patient demographic information (Table 1). In brief, 36% of patients were female and 64% male, median age was 69 years, median Charlson comorbidity index (CCI) score was 1, and the all-cause 30-day case-fatality rate (CFR) was 27%.

The percentage of methicillin-resistant isolates was 34.5% (69/200) for LA *S. aureus* CC398 bacteremia isolates, compared with 1.71% (567/33,123) for

Author affiliations: Statens Serum Institut, Copenhagen, Denmark (C.L. Raisen, A.B. Pedersen, K. Mølbak, A. Petersen, A.R. Larsen, J. Larsen); University of Copenhagen, Frederiksberg, Denmark (A.B. Pedersen, A. Dalsgaard, K. Mølbak, J. Larsen)

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[1]These first authors contributed equally to this article.

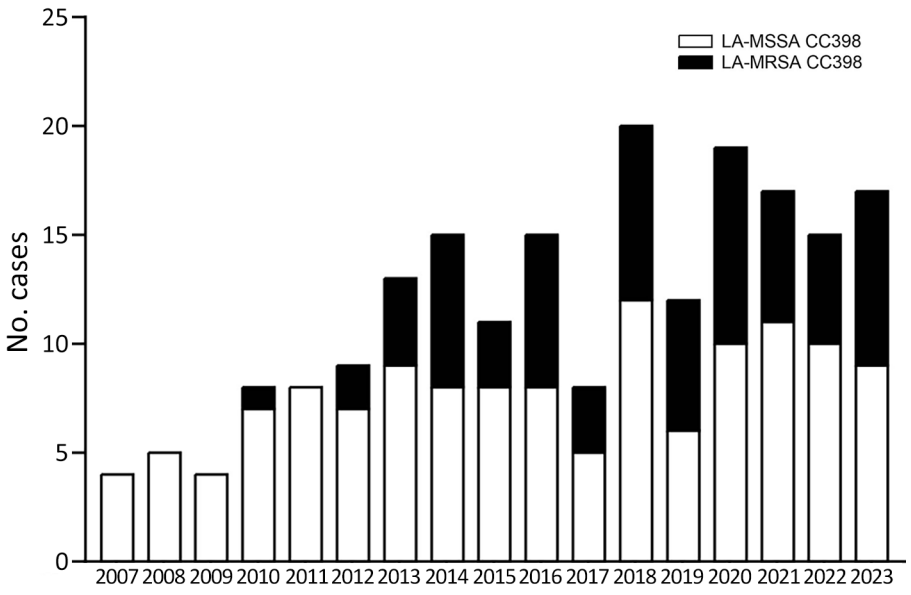


Figure. Temporal changes in livestock-associated *Staphylococcus aureus* clonal complex 398 bacteremia, Denmark, 2007–2023. CC, clonal complex; LA, livestock-associated; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

all *S. aureus* bacteremia isolates (p<0.0001 by 2-sided Fisher exact test). The first case of LA-MRSA CC398 bacteremia was identified in 2010, whereas LA-MSSA CC398 was a sporadic cause of bacteremia throughout the study period (Figure). That finding is consistent with the fact that most porcine *S. aureus* CC398 isolates collected during 1993–2007 were methicillin-susceptible and that the prevalence of LA-MRSA CC398 in pig farms was relatively low until 2010 (*9*,*11*). The high percentage of LA-MRSA CC398 bacteremia isolates might reflect that LA-MRSA CC398 is better adapted than LA-MSSA CC398 in industrial pig production. The type V(5C2&5)c staphylococcal cassette chromosome *mec* element is enriched in LA-MRSA CC398 isolates in Denmark, where it encodes resistance to several antimicrobial agents commonly used in pigs in Denmark, including β-lactams, tetracyclines, and zinc (*11*).

Table 1. Strain characteristics and demographics of patients with livestock-associated *Staphylococcus aureus* clonal complex 398 bacteremia, Denmark, 2007–2023*

Characteristic	Value
Sex	
F	72 (36.0)
M	128 (64.0)
Age group, y	
<40	20 (10.0)
40–59	37 (18.5)
60–69	45 (22.5)
70–79	49 (24.5)
≥80	49 (24.5)
Median (IQR)	69 (57–79)
CCI score	
0	67 (35.8)
1–2	70 (37.4)
≥3	50 (26.7)
Median (IQR)	1 (0–3)
CFR	
Survived	146 (73.4)
Died	53 (26.6)
Region	
Capital Region	14 (7.0)
Zealand	21 (10.5)
Southern Denmark	60 (30.0)
Central Denmark	70 (35.0)
North Denmark	35 (17.5)
Methicillin resistance	
MSSA	131 (65.5)
MRSA	69 (34.5)
IEC	
Negative	167 (83.5)
Positive	33 (16.5)

*Values are no. (%) patients except as indicated. CCI, Charlson comorbidity index; CFR, all-cause 30-day case-fatality rate; IEC, immune evasion cluster; IQR, interquartile range; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

LA *S. aureus* CC398 accounted for 12.17% (69/567) of all MRSA bloodstream infections and 0.40% (131/32,556) of all MSSA bloodstream infections during the study period. In total, only 0.60% (200/33,123) of all *S. aureus* bloodstream infections were caused by LA *S. aureus* CC398 isolates. Average annual incidence rates were 0.20 (range 0.07–0.35) cases/100,000 population for LA *S. aureus* CC398 bacteremia and 34.06 (range 24.61–43.97) cases/100,000 population for *S. aureus* bacteremia. The discrepancy between the relative disease prevalence of LA-MRSA CC398 alone (12.17% of all MRSA bloodstream infections) and the combined relative disease prevalence of LA-MRSA CC398 and LA-MSSA CC398 (0.60% of all *S. aureus* bloodstream infections) underscores that conclusions drawn narrowly from MRSA surveillance data may not accurately reflect the overall prevalence of LA *S. aureus* CC398 disease.

LA *S. aureus* CC398 is adapted to livestock and lacks many adhesion and virulence-associated determinants found in human *S. aureus* clones (*12*), providing a rationale for investigating whether these differences are associated with clinical outcome. We therefore conducted a case–control study involving 187 LA *S. aureus* CC398 bloodstream infections and 18,521 bloodstream infections caused by human *S. aureus* clones to estimate the relative risk for death in Denmark by using multivariable logistic regression (Appendix). With adjustment for sex, age, CCI score, and region, LA *S. aureus* CC398 was not associated with decreased risk for death (adjusted odds ratio 1.23 [95% CI 0.86–1.73]) (Table 2). We observed higher CFRs with increasing age and CCI score and for female compared with male patients (Table 2), consistent with a study of *S. aureus* bacteremia in Denmark during 2008–2015 (*13*). We observed similar findings in a sensitivity analysis with further adjustment for methicillin resistance and IEC (Appendix Table 1). Those findings suggest that the risk for death is comparable to that associated with human *S. aureus* clones.

The number of LA *S. aureus* CC398 bloodstream infections correlated with the size of the industrial pig population at the regional level (r = 0.97; p = 0.0053) but not with the size of the human population (r = −0.039; p = 0.95) (Appendix Figure, panels A, B). In contrast, the number of bloodstream infections caused by human *S. aureus* clones in each region correlated with the number of inhabitants (r = 0.97; p = 0.0053) but not with the size of the industrial pig population (r = −0.45; p = 0.44) (Appendix Figure, panels C, D). Those findings indicate that industrially raised pigs are an important source of zoonotic transmission to farmers, with subsequent spread to the general public through human-to-human transmission.

IEC was present in 17% of the LA *S. aureus* CC398 bacteremia isolates (Table 1). Reacquisition of IEC has been linked to longer chains of human-to-human transmission and an increased number of LA-MRSA CC398 infections in persons without livestock exposure (*14*). To test whether IEC also is associated with increased risk for death, we conducted a case–control study involving 29 bloodstream infections caused by IEC-positive LA *S. aureus* CC398 isolates and 158 bloodstream infections caused by IEC-negative LA *S. aureus* CC398 isolates by using multivariable logistic regression (Appendix). With adjustment for sex, age, CCI score, and region, IEC was not associated with increased risk for death (adjusted odds ratio 0.57 [95% CI 0.19–1.63]) (Table 3). We confirmed this finding in a sensitivity analysis with further adjustment for methicillin resistance (Appendix Table 2). We therefore propose that IEC is involved in asymptomatic colonization and sustained human-to-human transmission of LA *S. aureus* CC398, which in turn would increase the number of human infections and associated deaths.

Table 2. Risk factors for death in patients with bacteremia caused by livestock-associated *Staphylococcus aureus* clonal complex 398 and human *S. aureus* clones, Denmark, 2010–2023*

Characteristic	Patients†	CFR	aOR (95% CI)	p value‡
S. aureus				0.26
Human *S. aureus* clones§	18,521	23.8	Referent	
LA *S. aureus* CC398	187	26.2	1.23 (0.86–1.73)	
Sex				0.003
F	6,969	25.7	Referent	
M	11,739	22.8	0.90 (0.83–0.96)	
Age group, y				<0.0001
<40	1,821	3.7	Referent	
40–59	3,298	12.8	3.15 (2.44–4.14)	
60–69	3,657	17.8	4.45 (3.46–5.81)	
70–79	4,802	25.1	6.88 (5.38–8.94)	
≥80	5,130	41.2	14.96 (11.75–19.39)	
CCI score				<0.0001
0	6,172	16.3	Referent	
1–2	6,986	23.5	1.37 (1.25–1.51)	
≥3	5,550	32.7	2.23 (2.03–2.45)	
Region				0.16
Capital Region	6,218	23.2	Referent	
Zealand	3,008	24.7	1.02 (0.92–1.14)	
Southern Denmark	3,944	24.9	1.04 (0.94–1.15)	
Central Denmark	3,666	22.2	0.94 (0.85–1.04)	
North Denmark	1,872	25.5	1.11 (0.98–1.26)	

*aOR, adjusted odds ratio; CC, clonal complex; CCI, Charlson comorbidity index; CFR, all-cause 30-day case-fatality rate; LA, livestock-associated.
†Patients with incomplete data were excluded from analysis, including all patients with cases recorded before CCI scores became available in 2010.
‡p values were determined by 2-sided likelihood-ratio tests.
§CC1, CC5, CC7, CC8, CC15, CC22, CC30, and CC45.

Table 3. Risk factors for death in patients with livestock-associated *Staphylococcus aureus* clonal complex 398 bacteremia, Denmark, 2010–2023*

Characteristic	Patients†	CFR	aOR (95% CI)	p value‡
IEC				0.284
Negative	158	27.2	Referent	
Positive	29	20.7	0.57 (0.19–1.63)	
Sex				0.25
F	68	23.5	Referent	
M	119	27.3	1.55 (0.71–3.38)	
Age group, y				0.037
<60	52	15.4	Referent	
60–69	41	17.1	1.04 (0.33–3.31)	
70–79	47	23.4	1.64 (0.57–4.76)	
≥80	47	48.9	5.72 (2.09–15.64)	
CCI score				0.203
0	67	17.9	Referent	
1–2	70	27.1	1.52 (0.62–3.72)	
≥3	50	36.0	3.24 (1.27–8.27)	
Region				0.952
Capital Region	13	30.8	Referent	
Zealand	20	35.0	1.12 (0.21–5.97)	
Southern Denmark	57	19.3	0.59 (0.14–2.50)	
Central Denmark	66	27.3	0.83 (0.21–3.35)	
North Denmark	31	29.0	0.91 (0.20–4.26)	

*aOR, adjusted odds ratio; CCI, Charlson comorbidity index; CFR, all-cause 30-day case-fatality rate; IEC, immune evasion cluster; LA, livestock-associated.
†Patients with incomplete data were excluded from analysis, including all patients with cases recorded before CCI scores became available in 2010.
‡p values were determined by 2-sided likelihood-ratio tests.

Conclusions

Our study shows that pigs are an underrecognized source of LA-MSSA CC398 bacteremia and associated deaths in Denmark, underscoring that enhanced clinical and epidemiologic recognition of methicillin-susceptible isolates is fundamental when estimating the absolute number of LA *S. aureus* CC398 infections and the relative disease prevalence of LA *S. aureus* CC398 versus human *S. aureus* clones. The ability of *S. aureus* to adapt to new hosts through gene exchange, as demonstrated in our study and corroborated by the broader literature (*5*,*14*,*15*), highlights the importance of systematic surveillance at the human–animal interface.

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Short-read sequence data for the 200 LA *S. aureus* CC398 isolates are available in the European Nucleotide Archive and the National Center for Biotechnology Information Sequence Read Archive (https://www.ncbi.nlm.nih.gov/sra; BioProject no. PRJEB115597).

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About the Author

Dr. Raisen is a senior scientist at Statens Serum Institut, Copenhagen. Her research interests are the evolution and epidemiology of *Staphylococcus aureus* at the human–animal interface. Ms. Pedersen is a master's student at Statens Serum Institut and University of Copenhagen. Her research focuses on statistical analysis of risk factors for death in patients with *S. aureus* bacteremia.

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Address for correspondence: Jesper Larsen, Department of Bacteria, Parasites and Fungi, Statens Serum Institut, Artillerivej 5, DK-2300 Copenhagen S, Denmark; email: JRL@ssi.dk

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