Swine Farming Is a Risk Factor for Infection With and High Prevalence of Carriage of Multidrug-Resistant *Staphylococcus aureus*

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Background. Livestock-associated *Staphylococcus aureus* (LA-SA) has been documented worldwide. However, much remains unknown about LA-SA colonization and infection, especially in rural environments.

Methods. We conducted a large-scale prospective study of 1342 Iowans, including individuals with livestock contact and a community-based comparison group. Nasal and throat swabs were collected to determine colonization at enrollment, and skin infection swabs over 17 months were assessed for *S. aureus*. Outcomes included carriage of *S. aureus*, methicillin-resistant *S. aureus* (MRSA), tetracycline-resistant *S. aureus* (TRSA), multidrug-resistant *S. aureus* (MDRSA), and LA-SA.

Results. Of 1342 participants, 351 (26.2%; 95% confidence interval [CI], 23.8%–28.6%) carried *S. aureus*. MRSA was isolated from 34 (2.5%; 95% CI, 1.8%–3.5%) and LA-SA from 131 (9.8%; 95% CI, 8.3%–11.5%) of the 1342 participants. Individuals with current swine exposure were significantly more likely to carry *S. aureus* (prevalence ratio [PR], 1.8; 95% CI, 1.4–2.2), TRSA (PR, 8.4; 95% CI, 5.6–12.6), MDRSA (PR, 6.1; 95% CI, 3.8–10.0), and LA-SA (PR, 5.8; 95% CI, 3.9–8.4) than those lacking exposure. Skin infections (n = 103) were reported from 67 individuals, yielding an incidence rate of 6.6 (95% CI, 4.9–8.9) per 1000 person-months.

Conclusions. Current swine workers are 6 times more likely to carry MDRSA than those without current swine exposure. We observed active infections caused by LA-SA. This finding suggests that individuals with livestock contact may have a high prevalence of exposure to, and potentially infection with, antibiotic-resistant *S. aureus* strains, including LA-SA strains.

Keywords. *Staphylococcus aureus*; multidrug resistance; swine; colonization; livestock-associated *Staphylococcus aureus*.

Staphylococcus aureus colonizes approximately 30% of Americans and causes a range of infections [1]. An estimated 1.5% of the US population is colonized with methicillin-resistant *S. aureus* (MRSA) [2, 3]; emergence of multidrug-resistant strains increases this burden [4]. *Staphylococcus aureus* epidemiology has changed considerably in recent decades. Livestock-associated *S. aureus* (LA-SA) strains, including sequence type (ST) 398 and ST9, are often associated with swine, cattle, and poultry exposure [5], but little is known regarding LA-SA carriage and infection in the United States [6, 7].

ST398 carriage has been reported in areas with a high density of swine [8–12]. ST398 is the dominant MRSA strain on European farms [6, 13] and has been documented in the United States [11, 14]. It is unknown if ST398 colonizes a broader population of livestock workers or if additional strains may be zoonotic and

spreading on US farms. Common human strains of t002/ST5 and t008/ST8 have been found in live pigs in North America [15–19]. Invasive human disease caused by ST398 has been reported, even in those without animal contact, suggesting that bidirectional spread of these strains is possible [6].

Many studies have investigated *S. aureus* colonization and infection in the healthcare setting [20]. Fewer have assessed its ecology and transmission in the community [21], and most of these have been conducted in urban areas [22, 23]. In a rural state like Iowa, which ranks third nationally in overall livestock production and first in swine production, transmission of *S. aureus* between pigs and farmers and into the broader community could complicate efforts to control *S. aureus* transmission statewide, and could have effects nationally due to movement of colonized pigs or travel by colonized humans.

In this study, we report the prevalence of *S. aureus* colonization and infection among a population of Iowans, along with molecular characteristics, antimicrobial resistance profiles, and risk factors for carriage. We identified potential transmission within households and associations between duration of livestock exposure and LA-SA carriage.

MATERIALS AND METHODS

Subject Enrollment

Participants were enrolled May–September 2011, with 4723 and 2882 recruitment letters mailed to members of the Agricultural Health Study (AHS) [24] and Iowa Voter Registry (IVR), respectively. AHS participants were eligible for participation if they were actively farming at the most recent cohortwide interview (2005–2010). Spouses and children >6 months old were also invited to participate. Enrollment occurred at 32 county extension offices around the state. All participants signed informed consent documents approved by the University of Iowa and the National Institutes of Health institutional review boards.

Sample Collection and Culture

Nasal and pharyngeal samples were collected by sterile cotton swabs. Minors were only asked to provide a nasal swab, and adult nasal swabs were self-collected. All samples were maintained in Stuart medium at 4°C and processed within 24 hours. Participants were given mailing kits with ice packs to swab for potential or diagnosed staphylococcal infections during the 17-month follow-up period. Additional information is described in the Supplementary Data.

Susceptibility Testing

Using the Clinical and Laboratory Standards Institute methodology [25], isolates were tested for susceptibility to a panel of antibiotics (Supplementary Table 1). Isolates showing resistance

to ≥3 classes of antibiotics were classified as multidrug-resistant *S. aureus* (MDRSA) [26].

Molecular Testing

Genomic DNA was extracted using the Wizard Genomic DNA kit (Promega). Polymerase chain reaction was performed for the following: PVL, *mecA*, *scn*, protein A-encoding gene (*spa*) typing, and multilocus sequence typing (MLST) (Supplementary Data). LA-SA was defined based on *spa* typing and MLST. Strains belonging to *spa* types within 6 steps of t034 or t337 using the based upon repeat pattern algorithm [27], or ST398 or ST9 via MLST, were considered LA-SA. Isolates not belonging to those STs were considered putative LA-SA if they were *scn* negative.

Questionnaire Data

Each adult participant and parents of minors filled out an enrollment questionnaire that included demographic information and *S. aureus* risk factor data. Participants with occupational livestock exposure (work on a farm or in a processing plant) or healthcare exposure completed an additional questionnaire (Supplementary Data). Each family filled out an infection questionnaire monthly for 17 months, answering "no" to having potential or diagnosed staphylococcal infections, or "yes" and detailing the infection and treatment methods.

Statistical Methodology

Associations between variables were addressed using Fisher exact test for categorical variables and the Cochran-Armitage test for trend. Outcomes included carriage of *S. aureus*, MRSA, tetracycline-resistant *S. aureus* (TRSA), MDRSA, and LA-SA. Age-adjusted prevalence ratios (PRs) were calculated by log-binomial regression and adjusted for clustering within households using generalized estimating equations in PROC GENMOD (SAS version 9.3; SAS Institute, Cary, North Carolina). Incidence rates were estimated using Poisson regression with confidence intervals adjusted for repeated measures among participants in PROC GENMOD. Statistical significance was set at α = .05. No adjustments were made for multiple comparisons.

RESULTS

Cohort Descriptions and Demographic Characteristics

Of 4723 AHS cohort members who were contacted, 1101 (23.3%) agreed to participate. Of 2882 subjects who were contacted through the IVR, 188 participated (6.5%). In total, 1342 individuals participated, including 53 minors. More than 85% (1151/1342) of participants completed at least 1 month of follow-up; 64.2% (861/1342) completed all 17 months. The average age of participants was 60.5 years (median, 62 years; range, 1–88). The proportion of males was similar between the 2

Table 1. Risk Factors for *Staphylococcus aureus* Carriage Among Adult Participants

Risk Factor	Any *Staphylococcus aureus*, No. (%)	MRSA, No. (%)	TRSA, No. (%)	MDRSA, No. (%)	LA-SA, No. (%)
Any livestock exposure	*P* = .001	*P* = .79	*P* < .001	*P* < .001	*P* < .001
None[a] (n = 693)	156 (22.5)	19 (2.7)	26 (3.8)	22 (3.2)	46 (6.6)
Past or current (n = 596)	181 (30.3)	14 (2.3)	75 (12.6)	46 (7.7)	82 (13.8)
Swine exposure	*P* < .001	*P* = .75	*P* < .001	*P* < .001	*P* < .001
None (n = 939)	211 (22.5)	26 (2.8)	36 (3.8)	31 (3.3)	58 (6.2)
Past (n = 187)	56 (30.0)	3 (1.6)	9 (4.8)	4 (2.1)	12 (6.4)
Current (n = 163)	70 (42.9)	4 (2.5)	56 (34.4)	33 (20.3)	58 (35.6)
Cattle exposure	*P* = .001	*P* = .78	*P* < .001	*P* = .053	*P* = .004
None (n = 839)	192 (22.9)	22 (2.6)	48 (5.7)	36 (4.3)	68 (8.1)
Past (n = 86)	28 (32.6)	3 (3.5)	9 (10.5)	8 (9.3)	15 (17.4)
Current (n = 364)	117 (32.1)	8 (2.2)	44 (12.1)	24 (6.6)	45 (12.4)
Chicken exposure	*P* = .019	*P* = 1.0	*P* = .69	*P* = .85	*P* = .54
None (n = 1160)	290 (25.0)	30 (2.6)	89 (7.7)	61 (5.3)	113 (9.7)
Past (n = 47)	16 (34.0)	1 (2.1)	4 (8.5)	3 (6.4)	4 (8.5)
Current (n = 82)	31 (37.8)	2 (2.4)	8 (9.8)	4 (4.9)	11 (13.4)
Current swine and/or cattle exposure	*P* = .004	*P* = .48	*P* < .001	*P* < .001	*P* < .001
Current swine and cattle (n = 75)	35 (46.7)	3 (4.0)	27 (36.0)	15 (20.0)	27 (36.0)
Current swine only (n = 88)	35 (39.8)	1 (1.1)	29 (33.0)	18 (20.5)	31 (35.2)
Current cattle only (n = 289)	82 (28.4)	5 (1.7)	17 (5.9)	9 (3.1)	18 (6.2)

Categories may have differing numbers of participants owing to incomplete questionnaires. *P* values are based on Fisher exact test.

Abbreviations: LA-SA, livestock-associated *Staphylococcus aureus*; MDRSA, multidrug-resistant *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; TRSA, tetracycline-resistant *Staphylococcus aureus*.

[a] No self-report of past or current occupational exposure to any livestock.

cohorts (61.3% [AHS] vs 63.1% [IVR]). Most participants were white (98.9% [1318/1333]; 9 did not respond). Participants were recruited from 53 of Iowa's 99 counties, with a median of 22 per county (range, 1–87; Supplementary Figure 1). The majority of adult AHS participants reported residing in a rural area (96.6% [973/1085]; 16 did not respond), whereas the majority of IVR participants reported residence in small towns (58.8% [110/187]; 1 did not respond).

Overall, 46.2% of adults reported past or current occupational exposure to livestock. Specifically, 27.2%, 34.9%, and 10.0% reported exposure to swine, cattle, and chickens, respectively (Table 1). Most individuals with current livestock exposure (exposure to 1 or more types of livestock) reported working directly with the livestock (95.2% [457/480]).

**Staphylococcus aureus Carriage and Antibiotic Susceptibility**

Overall, 351 of 1342 (26.2%; 95% confidence interval [CI], 23.8%–28.6%) participants carried *S. aureus* in their nose (16.0% [215]), throat (4.0% [54]), or both (6.1% [82]). Most were colonized by methicillin-sensitive *S. aureus* (MSSA) (23.6% [317/1342]; 95% CI, 21.4%–26.0%); fewer were colonized by MRSA (2.5% [34/1342]; 95% CI, 1.8%–3.5%). There was no significant difference in colonization rates between

males (27.6% [226/820]) and females (24.2% [124/513]) (*P* = .12 [9 did not respond]).

More than half of colonized participants (51.3% [180/351]) carried *S. aureus* that was resistant to 1 or more antibiotics tested (Supplementary Table 1). MDRSA was found in 19.4% (68/351) of colonized individuals. Based on the presence of *mecA* and/or phenotypic resistance to oxacillin, 9.7% (34/351) of colonized individuals carried MRSA. The spatial distribution of drug resistance in *S. aureus*–colonized participants varied, with TRSA and MDRSA appearing more than MRSA in northwestern and central southeast Iowa, areas with high numbers of swine concentrated animal feeding operations (CAFOs) (Figure 1A–D).

Molecular Data

In total, 434 *S. aureus* isolates were collected from 351 participants (Supplementary Figure 2). PVL prevalence was low (3.5% [15/434]). A total of 118 *spa* types were identified; 6 isolates were nontypeable. The most common *spa* types were t002 (9.4%), t034 (8.1%), t012 (7.8%), t338 (5.1%), and t216 (5.1%). Other *spa* types were identified in <5% of participants. Based on *spa* typing, MLST, and/or absence of *scn*, 9.8% (131/1342) of participants carried LA-SA. Of these, 50.4% (66/131) were ST398 and 11.5% (15/131) were ST9. Both strains display
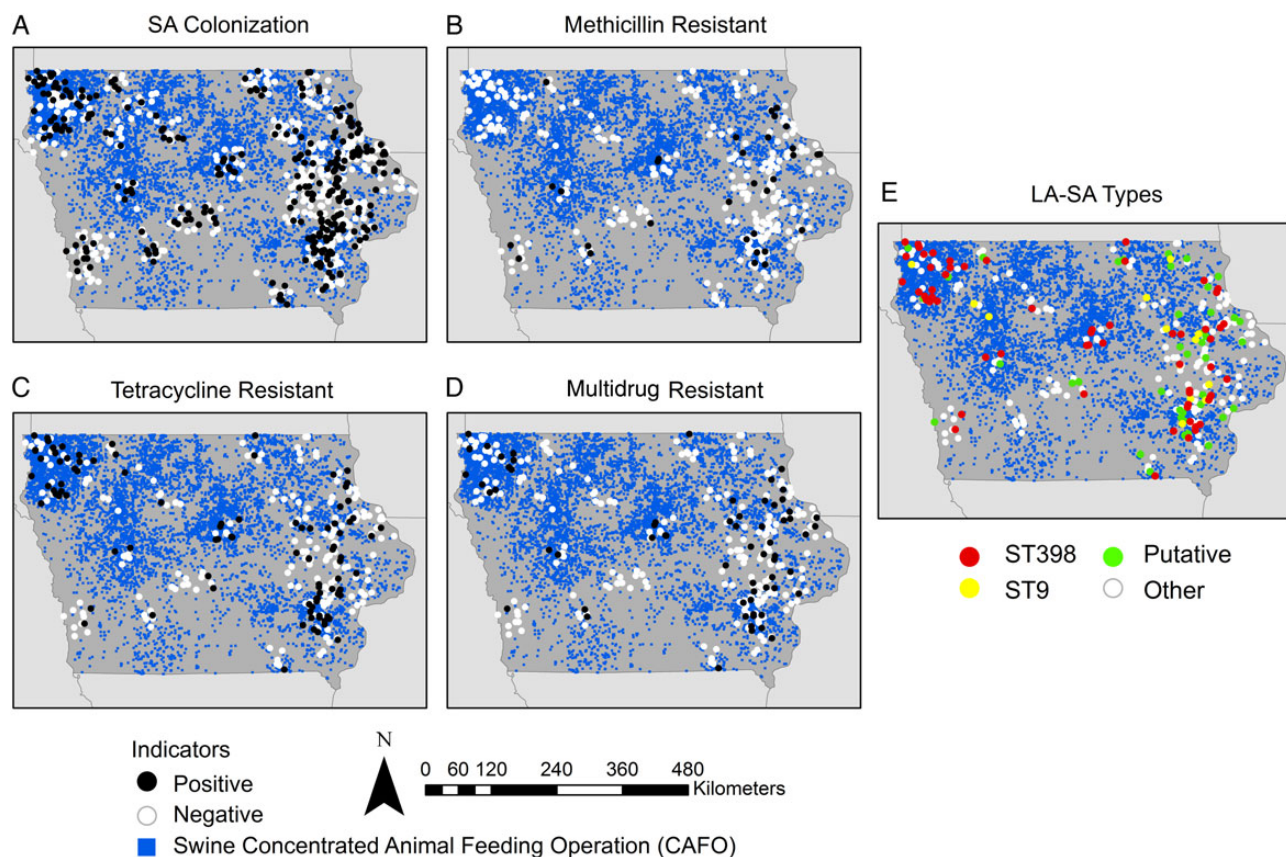
Figure 1. Distribution of *Staphylococcus aureus* (SA) compared to concentrated animal feeding operations (CAFOs) in Iowa. *A*, Locations of participants with positive *S. aureus* colonization (red). SA strains testing positive for drug resistance by type: methicillin (*B*), tetracycline (*C*), and multidrug (*D*). *E*, Locations of livestock-associated *S. aureus* (LA-SA) strains. All panels include distribution of swine CAFOs within Iowa.

broad distribution across Iowa (Figure 1*E*). LA-SA strains were more often tetracycline resistant (65.7% [86/131]) and multidrug resistant (33.6% [44/131]) than were non–LA-SA strains (7.3% [16/220] and 10.9% [24/220], respectively).

### Livestock Occupation Risk Factors for *S. aureus* Carriage

To determine the impact of occupational livestock exposure on *S. aureus* carriage, we compared colonization prevalence among adults reporting no exposure, past exposure, and current exposure. Approximately 22% of individuals reporting no occupational exposure to livestock were colonized with *S. aureus* (Table 1), with low prevalence of antibiotic resistance (<4% for MRSA, TRSA, and MDRSA). Although *S. aureus* carriage was elevated among individuals with current livestock contact, there was no evidence for increased risk of MRSA colonization. In contrast to unexposed individuals, those with current exposure to swine had a higher rate of TRSA (PR, 8.4; 95% CI, 5.6–12.6), MDRSA (PR, 6.1; 95% CI, 3.8–10.0), and LA-SA (PR, 5.8; 95% CI, 3.9–8.4) colonization (Table 1; Figure 2). Past exposure to swine was not associated with significantly higher prevalence of TRSA, MDRSA, or LA-SA (Figure 2).

We also noted a small but significant increase in the prevalence of *S. aureus*, TRSA, and LA-SA among cattle workers (Table 1). Many livestock workers reported contact with both swine and cattle: 20.6% [75/364] of cattle workers also reported current work with swine. In the absence of current swine exposure, the rates of *S. aureus*, TRSA, MDRSA, and LA-SA colonization were greatly reduced. Among swine workers without current cattle work, the decrease in *S. aureus*, TRSA, MDRSA, and LA-SA prevalence was less pronounced (Table 1).

Risk Factors Among Individuals With Occupational Exposure to Swine

Occupational risk factors for *S. aureus* colonization among individuals reporting current exposure to swine were evaluated. *Staphylococcus aureus*, TRSA, and MDRSA colonization fell off rapidly with longer time since most recent swine contact (Table 2). Individuals working directly with live swine were at higher risk for colonization than individuals without direct contact. We observed a general trend of increased prevalence among individuals having contact with a larger number of swine (Table 2). Individuals with ≤10 hours of reported direct
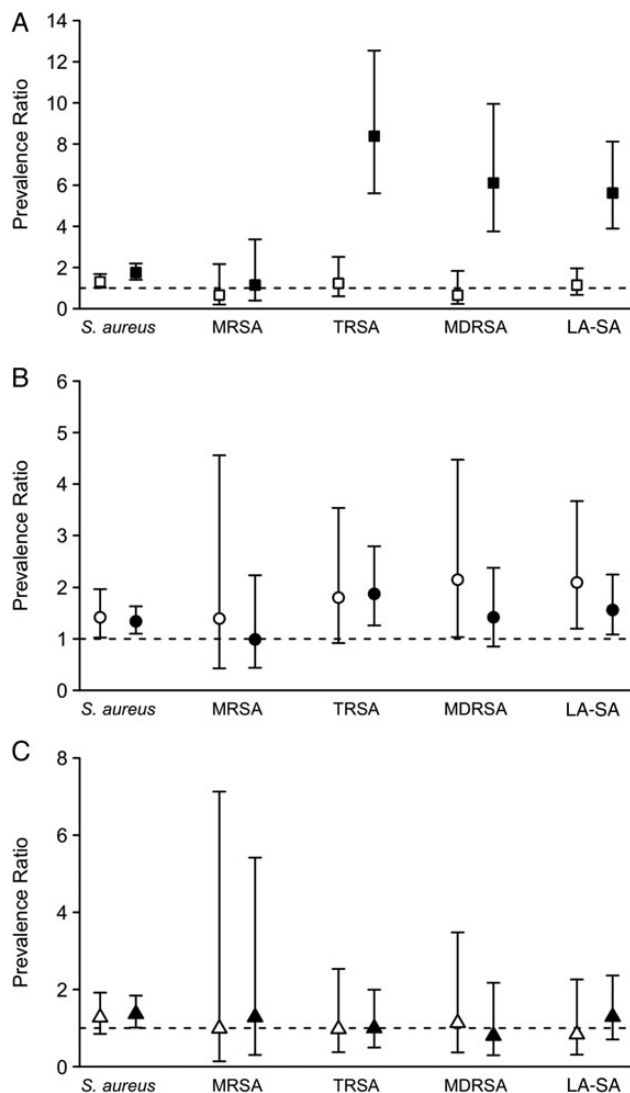
Figure 2. Prevalence ratios for colonization by any *Staphylococcus aureus* or by methicillin-resistant *S. aureus* (MRSA), tetracycline-resistant *S. aureus* (TRSA), multidrug-resistant *S. aureus* (MDRSA), or livestock-associated *S. aureus* (LA-SA) specifically, based on occupational exposure to swine (*A*), cattle (*B*), or chickens (*C*). The prevalence of colonization among participants without livestock exposure was selected as the reference for each group. Prevalence ratios are adjusted for age and clustering within households. Open and closed symbols represent past and current occupational livestock exposure, respectively. Error bars indicate 95% confidence intervals. Dashed lines indicate a prevalence ratio of 1.

contact each week had a lower prevalence than those with >10 hours (mean weekly contact with swine, 9.8 hours [standard deviation, 12.4 hours]).

Risk for *S. aureus* Colonization Among Household Members

We examined whether secondary transmission was evident among household members of individuals currently working with swine, cattle, or chickens (Supplementary Table 2). We

focused on *S. aureus*, TRSA, MDRSA, and LA-SA for swine, and *S. aureus* for cattle and chickens because of the observed patterns of increased carriage (Table 1). Adult household members were included if they did not report current occupational exposure to livestock. For comparison, we calculated the prevalence of *S. aureus* carriage among participants who did not report a household member who currently works with livestock. *Staphylococcus aureus* prevalence was not substantially affected by having a household member with current livestock exposure (Supplementary Table 2). MDRSA and LA-SA carriage were elevated among household members of swine workers, but differences were not statistically significant and comparisons are constrained by limited sample size.

Although the prevalence was low, individuals without current livestock exposure did carry TRSA, MDRSA, and LA-SA. To determine if we could identify instances consistent with household transmission of LA-SA, we examined household clustering of LA-SA *spa* types. We identified 10 instances where spousal pairs carried *S. aureus* with the same *spa* type and similar antibiotic susceptibility patterns (Supplementary Table 3), including 2 pairs with t034 (ST398), 2 pairs with t571 (ST398), 2 pairs with t012 (*scn* negative), and 1 pair each of t337 (ST9), t9418 (ST398), t073 (*scn* negative), and t338 (*scn* negative). For 4 of the pairs, 1 spouse had current occupational exposure to livestock, whereas the others did not, suggesting potential transmission events.

Staphylococcus aureus Infections

Study participants were followed to examine skin and soft tissue infections (SSTIs) consistent with *S. aureus* infection for a total of 15 631 person-months. In total, 103 SSTIs were reported by 67 individuals (incidence rate of 6.6 [95% CI, 4.9–8.9] per 1000 person-months). Of these, 42 were confirmed *S. aureus* infections, either by the participants' physician or based on a swab sample sent to investigators (2.7 [95% CI, 1.8–3.9] per 1000 person-months). Swabs were received from 22 participants; 10 participants had at least 1 swab that was culture positive for *S. aureus* (Supplementary Table 4). Three participants were infected by ST398; all had occupational exposure to livestock. Two other participants were infected with non-ST398/*scn*-negative *S. aureus*. The percentage of participants with SSTIs and confirmed *S. aureus* infections reporting recent livestock exposure for themselves or a family member during the month of infection (58% for participants with SSTIs and 52% for participants with confirmed *S. aureus* infections) was similar to the study population overall (54%).

DISCUSSION

This study represents the largest prospective examination of *S. aureus* infection in a cohort of livestock workers worldwide, and

Table 2. Risk Factors for *Staphylococcus aureus* Carriage Among Participants With Current (Within ≤30 Days) Occupational Exposure to Swine

Risk Factor	*Staphylococcus aureus*, No. (%)	TRSA, No. (%)	MDRSA, No. (%)	LA-SA, No. (%)
Days since last contact	*P* = .04	*P* = .02	*P* = .14	*P* = .004
≤2 (n = 105)	50 (47.6)	41 (39.1)	23 (21.9)	44 (41.9)
3–10 (n = 29)	12 (41.4)	8 (27.6)	4 (13.8)	9 (31.0)
11–30 (n = 13)	2 (15.4)	1 (7.7)	1 (7.7)	0 (0.0)
Type of work	*P* = .08	*P* = .01	*P* = .53	*P* = .004
No direct contact (n = 18)	4 (22.2)	1 (5.6)	2 (11.1)	1 (5.5)
Direct contact (n = 145)	67 (46.1)	55 (37.9)	31 (21.4)	57 (39.3)
No. of swine	*P* = .06	*P* = .04	*P* = .09	*P* = .17
≤100 (n = 57)	20 (35.1)	16 (28.1)	8 (14.0)	16 (28.1)
101–500 (n = 59)	26 (44.1)	20 (33.9)	13 (22.0)	24 (40.7)
501–1000 (n = 22)	11 (50.0)	10 (45.5)	7 (31.8)	10 (45.5)
≥1001 (n = 15)	9 (60.0)	8 (53.3)	4 (26.7)	6 (40.0)
Hours per week	*P* = .03	*P* = .002	*P* = .01	*P* = .006
≤10 (n = 89)	30 (33.7)	21 (23.6)	10 (11.2)	23 (25.8)
11–20 (n = 33)	20 (60.6)	17 (51.5)	13 (39.4)	17 (51.5)
21–30 (n = 26)	14 (53.9)	13 (50.0)	8 (30.8)	13 (50.0)
≥31 (n = 8)	4 (50.0)	4 (50.0)	2 (25.0)	4 (50.0)

Categories may have differing numbers of participants owing to incomplete questionnaires. *P* values are based on the Cochran-Armitage test for trend, with the exception of the variable "type of work," which is based on Fisher exact test.

Abbreviations: LA-SA, livestock-associated *Staphylococcus aureus*; MDRSA, multidrug-resistant *Staphylococcus aureus*; TRSA, tetracycline-resistant *Staphylococcus aureus*.

the first such study in the United States. We found that farmers with livestock exposure, particularly swine exposure, are more likely to carry MDRSA, TRSA, and LA-SA than those without exposure in a manner that positively relates with increased exposure to swine. Carriage prevalence negatively correlates with increased time since last exposure. Although we examined carriage at a single time point, previous studies have reported a strong link between duration of livestock exposure and persistence of carriage, especially for LA-MRSA [28, 29].

TRSA was found in 34% of our current swine-exposed population, compared to 3.8% in our unexposed group. In terms of both prevalence and discrepancy between populations, our findings are lower than those of Oppliger et al, who found 50% and 0% carriage of TRSA in Swiss individuals with or without swine exposure, respectively [30]. Although MRSA prevalence unexpectedly did not differ between groups, MDRSA carriage was significantly higher in our current swine-exposed cohort (20.3% vs 3.3%).

Livestock-associated *S. aureus* strains were most often carried by those with livestock exposure. Additionally, a number of "human" types of *S. aureus* displayed markers of livestock association, such as loss of the *scn* gene [31] and/or tetracycline resistance. Additional screening tests to distinguish livestock-adapted strains from human-origin strains are necessary.

We found that spatial patterns of drug resistance in *S. aureus* vary according to resistance type. In particular, the northwestern

region of Iowa exhibited high numbers of TRSA and MDRSA-positive samples, whereas no MRSA was found in residents of this region. This region is also home to a large number of swine CAFOs, although swine are raised in operations across Iowa.

A limitation of this study is that most farmers were owners/operators of family farms with a median of 355 pigs; they were not highly exposed livestock confinement workers, as were sampled in a previous US study [11]. Iowa farms average approximately 2300 hogs [32]; as such, our cohort is likely at the low end of MRSA prevalence, which has been associated with higher pig exposure and density [28, 29]. Samples were not collected from animals on the farms, so transmission of antibiotic resistance and strains between farmers and animals cannot directly be addressed. Farming practices, such as antibiotic usage, were not available. The majority of participants were older white males, so the results may not be generalizable to other populations.

A major strength of this study is our enrollment of participants from across Iowa, including areas of high and low livestock and human density. Additionally, we followed participants for 17 months postenrollment to estimate infection incidence, and obtained biological samples in addition to self-reported infection information. Our study was prospective, minimizing recall and selection bias that may have been present in a previous US study of *S. aureus* infections [33], in which 5 of 135 (3.7%) participating pork producers reported a MRSA

infection. In our study, 67 of 1342 (5.0%) participants reported a potential or confirmed SSTI. Our incidence rate of 6.6 SSTIs per 1000 person-months was also higher than that reported in a population of military Tricare beneficiaries (1.5 SSTIs per 1000 person-months) [34].

Although we did not detect elevated *S. aureus* prevalence among participants sharing a household with an individual having current livestock or poultry exposure, MDRSA and LA-SA carriage were elevated among family members of swine workers. These differences were not statistically significant, which may be due to limited sample size. We did observe 10 instances of clustering within families; 4 of these clustered pairs had a family member with livestock exposure. Studies from the Netherlands and Germany have reported that LA-SA colonization depends strongly on direct exposure to swine [29, 35]. Our results provide further support for this conclusion.

Staphylococcus aureus colonization in humans is difficult to prevent; a third of Americans carry MSSA and 1.5% carry MRSA [2]. For LA-SA, there are further challenges. *Staphylococcus aureus* is not an economic issue for swine farmers, as pigs are not commonly infected symptomatically. No licensed vaccine against *S. aureus* exists for humans or animals. There is no method to decolonize animals that carry *S. aureus;* therefore, constant reexposure and, possibly, transmission can occur between livestock and caretakers. As such, occupational exposure to livestock should be considered a significant risk factor when examining *S. aureus* colonization or treating infections in rural areas.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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