Original Investigation

High-Density Livestock Operations, Crop Field Application of Manure, and Risk of Community-Associated Methicillin-Resistant *Staphylococcus aureus* Infection in Pennsylvania

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IMPORTANCE Nearly 80% of antibiotics in the United States are sold for use in livestock feeds. The manure produced by these animals contains antibiotic-resistant bacteria, resistance genes, and antibiotics and is subsequently applied to crop fields, where it may put community members at risk for antibiotic-resistant infections.

OBJECTIVE To assess the association between individual exposure to swine and dairy/veal industrial agriculture and risk of methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

DESIGN, SETTING, AND PARTICIPANTS A population-based, nested case-control study of primary care patients from a single health care system in Pennsylvania from 2005 to 2010. Incident MRSA cases were identified using electronic health records, classified as community-associated MRSA or health care–associated MRSA, and frequency matched to randomly selected controls and patients with skin and soft-tissue infection. Nutrient management plans were used to create 2 exposure variables: seasonal crop field manure application and number of livestock animals at the operation. In a substudy, we collected 200 isolates from patients stratified by location of diagnosis and proximity to livestock operations.

MAIN OUTCOMES AND MEASURES Community-associated MRSA, health care–associated MRSA, and skin and soft-tissue infection status (with no history of MRSA) compared with controls.

RESULTS From a total population of 446 480 patients, 1539 community-associated MRSA, 1335 health care-associated MRSA, 2895 skin and soft-tissue infection cases, and 2914 controls were included. After adjustment for MRSA risk factors, the highest quartile of swine crop field exposure was significantly associated with community-associated MRSA, health care-associated MRSA, and skin and soft-tissue infection case status (adjusted odds ratios, 1.38 [95% CI, 1.13-1.69], 1.30 [95% CI, 1.05-1.61], and 1.37 [95% CI, 1.18-1.60], respectively); and there was a trend of increasing odds across quartiles for each outcome ($P \leq .01$ for trend in all comparisons). There were similar but weaker associations of swine operations with community-associated MRSA and skin and soft-tissue infection. Molecular testing of 200 isolates identified 31 unique *spa* types, none of which corresponded to CC398 (clonal complex 398), but some have been previously found in swine.

CONCLUSIONS AND RELEVANCE Proximity to swine manure application to crop fields and livestock operations each was associated with MRSA and skin and soft-tissue infection. These findings contribute to the growing concern about the potential public health impacts of high-density livestock production.

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The US Food and Drug Administration reports that 80% of antibiotics in the United States are used in food animals, mainly to promote growth of livestock in high-density production.[1,2] In this industrial model, thousands of livestock animals are housed together and fed subtherapeutic doses of antimicrobial agents.[3] This can select for antibiotic-resistant bacteria like methicillin-resistant *Staphylococcus aureus* (MRSA).[4] About 75% of administered antibiotics are not absorbed by the animal and end up in manure.[5] In addition to antibiotics, antibiotic-resistant bacteria and resistance genes have been isolated from manure and are known to persist in the environment.[6] Application of manure to crop fields close to human dwellings may lead to increased risk of antibiotic-resistant infections.[7]

High prevalence of MRSA colonization among pig farmers was first noted in the Netherlands in 2005.[8] Transmission of MRSA among cows, calves, and humans has also been reported.[9,10] A US study reported that 45% of swine workers were colonized, which is 30 times the national average.[11,12] Few studies have assessed risk of MRSA infection. A Danish case-control study (21 cases) found that living or working on a farm was a risk factor for MRSA infection.[13] Other studies of MRSA infection have described the spread of infection within pig farming families.[14,15] To our knowledge, the impact of proximity to high-density livestock production on risk of MRSA infection has not been evaluated. Two studies assessed community livestock density and found no association with MRSA colonization.[16,17] Most studies have implicated clonal complex 398 (CC398) as the most common variant harbored by swine.[9,12-15,17,18]

In the United States, community-associated MRSA (CA-MRSA) now accounts for more than half of all noninvasive MRSA infections.[19-22] CA-MRSA often occurs as a skin and soft-tissue infection (SSTI) in young, otherwise healthy individuals who lack common health care risk factors.[23-25] In contrast, health care–associated MRSA (HA-MRSA) generally occurs in older individuals with comorbidities. Now, the epidemiology and microbiology of 2 epidemics previously considered distinct are merging.[26-28]

The possible contribution of high-density livestock production to these epidemics has been inadequately studied.[29] US data are needed to evaluate which livestock species pose risk, what aspects of the operations and manure handling are involved, and the magnitude of the risk. We conducted a population-based, nested case-control study using electronic health record (EHR) data from the Geisinger Health System, an integrated health services organization with 4 hospitals and 41 outpatient clinics. We evaluated residential proximity to swine and dairy/veal high-density livestock operations and manure-applied crop fields in relation to CA-MRSA, HA-MRSA, and SSTI (without a history of MRSA infection or colonization) case status.

Methods

Data Sources

To select cases and controls, we used EHR data from January 1, 2005, to February 9, 2010, from 446 480 patients with a Gei-

singer primary care provider. Geisinger's primary care patients represent the general population in the region.[30] The study area comprised the health system's primary care market and bordering counties totaling 38 counties in Pennsylvania (**Figure 1**); approximately 3.8 million people resided in these counties according to the 2000 US Census. The study was approved by institutional review boards at the Geisinger Health System and the Johns Hopkins Bloomberg School of Public Health.

Pennsylvania Act 38 of 2005 requires high-density livestock operations to develop and implement nutrient management plans (NMPs) for manure handling. We defined *high-density livestock operations* as agricultural operations where animal density exceeded 2 animal equivalent units (AEUs, 1000 pounds of live weight) per acre and where total AEUs exceeded 8; or operations that exceeded 300 AEUs. When livestock operations have insufficient land for manure application, manure is exported to other areas and applied to crop fields. We focused on swine and dairy/veal operations because of previously identified links with MRSA.[8-10,13-15] The NMPs provided data on livestock operation location, animal type, livestock quantity (AEUs), amount of manure applied to crop fields by season, and crop field area and location. We obtained NMPs from the Pennsylvania Department of Environmental Protection and County Conservation Districts.
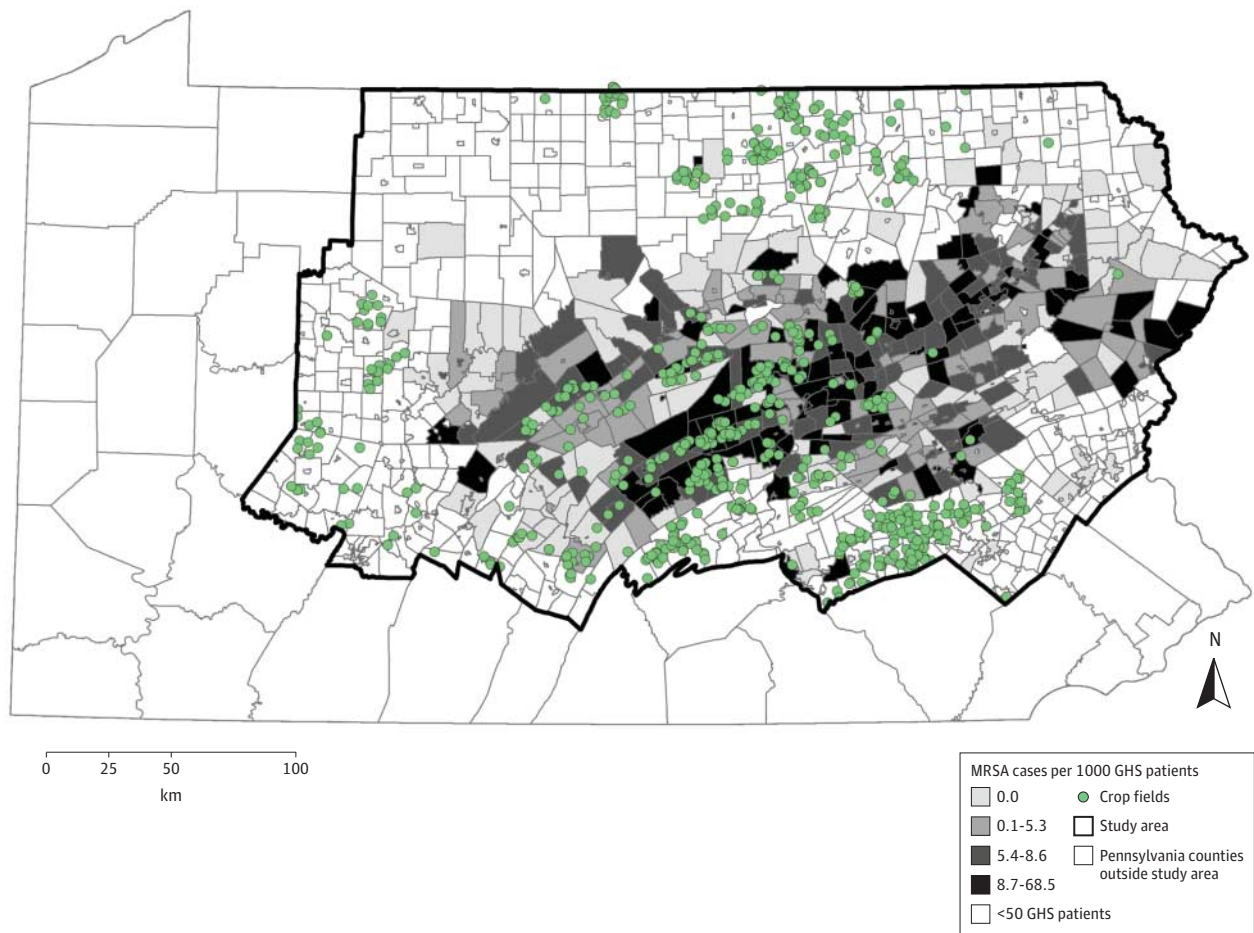
Case Ascertainment and Control Selection

Incident MRSA cases were identified primarily using laboratory cultures and secondarily by diagnosis codes (eg, *International Classification of Diseases, Ninth Revision* [*ICD-9*]) that indicated MRSA infection, as previously described.[22] Cases were then classified as either CA-MRSA or HA-MRSA based on presence of health care risk factors (eg, hospitalization, surgery, dialysis, nursing home residence, indwelling device)[22,31] or diagnosis more than 2 days after hospital admission using *ICD-9* codes[21,23,32] and *Current Procedural Terminology* codes. We then randomly selected patients with SSTI but no history of MRSA using 29 *ICD-9* codes (eg, carbuncle, furuncle, abscess)[22] and controls with no history of MRSA, and we frequency matched both groups with case patients by age (0-6, 7-18, 19-45, 46-62, 62-74, ≥75 years), sex, and diagnosis or an outpatient encounter in the same year as MRSA diagnosis. The SSTI cases were evaluated as a separate case group because some SSTIs occurring during the study period were likely to have been caused by MRSA but not diagnosed as such, and high-density livestock production could cause SSTIs from other bacteria. Therefore, we selected patients with SSTIs without reference to any specific pathogen. If a control had multiple outpatient encounters during the year, a single encounter was randomly selected as the date for exposure assignment.

Geographic Location of Patients, Livestock Operation, and Crop Fields

We identified the latitude and longitude of patient addresses using ArcGIS, version 10 (Esri),[33] and calculated MRSA rates by community (Figure 1). The latitude and lon-

Figure 1. Crop Field Locations and Methicillin-Resistant *Staphylococcus aureus* (MRSA) Rates

Crop field locations and rates of MRSA per 1000 Geisinger Health System (GHS) primary care patients in townships, boroughs, and cities. Rates in communities with fewer than 50 GHS patients were not estimated. The map demonstrates that crop fields were often located in areas with a range of human population densities.

gitude of livestock operation addresses were located using Google Earth with visual confirmation of the presence of a barn at the address. Three different methods were used to locate crop fields because 131 fields (17.3%) were missing address data (**Figure 2**). In the absence of an address, we used the county and community of the field from the NMP to locate the crop field.

Exposure Assessment

We estimated each individual's exposure to livestock operations and to manure-applied crop fields, for swine and dairy/veal, using an inverse distance-squared approach[34] in R, version 2.14.2 (R Foundation for Statistical Computing). For livestock operations, we used the equation

$$\text{Exposure for patient j} = \sum_{i=1}^{n} \frac{a_i}{d_{ij}^2}$$

where n is the number of operations, a_i is AEUs of livestock at operation I, and d_{ij}^2 is the squared distance (in meters) be-

nure application during the season of diagnosis or visit, we used the equation

$$\text{Exposure for patient j} = \sum_{i=1}^{n} \frac{c_i}{d_{ij}^2}$$

where n is the number of crop fields, c_i is the concentration of manure (gallons per square meter) applied during the season of diagnosis or visit at field i, and d_{ij}^2 is the squared distance (in meters) between the crop field centroid i and patient j. This resulted in exposure units of gallons per quartic meter (m^4). For missing seasonal application data (40% of fields), we used the regional seasonal average. Exposure variables were modeled as quartiles because they were not normally distributed.

Genetic Typing of MRSA Isolates

In a prospective substudy that occurred from January to December 2012, we identified all primary care patients with a culture-confirmed MRSA infection. We then randomly selected isolates from patients stratified by location of diagnosis (in-

Figure 2. Three Methods Used to Identify and Locate Crop Fields

A, Aerial photograph (top) or map (bottom) were located using Google Earth (n = 135). B, Operation addresses known and located using ArcGIS, version 10 (Esri) (n = 420). C, County and township known and addresses were located by identifying cropland, hay land, and pastureland on a land use map and randomly selecting a point within the eligible land use types (n = 131).

patient or outpatient) and presence or absence of a livestock operation or crop field in their zip code of residence. We over-sampled outpatient isolates from zip codes with high-density livestock production. All isolates were characterized by DNA sequence analysis of the protein A gene variable repeat region (*spa* typing).[35] The *spa* types were also assigned a Ridom StaphType, using the Ridom SpaServer database (available at http://www.spaserver.ridom.de).[36] Panton-Valentine leukocidin (*PVL*) genes were detected by polymerase chain reaction.[37]

Statistical Analysis

To compare the 4 study groups, we used Kruskal-Wallis tests for comparisons of means and χ^2 tests for comparisons of proportions. We used multilevel multinomial (2 MRSA groups and controls) and multilevel logistic regression (SSTI cases and controls) to assess the association between exposure and case status. We adjusted models for predictors obtained from the EHR: age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other); ever-smoking status

using *ICD*-9 codes[22]; antibiotic order in the 2 years preceding diagnosis; and Medical Assistance for health insurance, residential community (city, borough, or township), and community socioeconomic deprivation.[33] *Medical Assistance* is a means-tested program, which we used as a surrogate indicator for low socioeconomic status.[38,39] It was identified for each encounter by 1 of 24 codes and modeled as ever received (if received for >2 encounters) vs never received. The livestock operation model was additionally adjusted for season of infection or visit. Final models were selected based on associations reported in our group's earlier article,[22] and adequate model fit was confirmed using Pearson goodness-of-fit tests and likelihood ratio tests. Semivariograms were used to determine that spatial autocorrelation did not account for the results.[40] We used a 2-sided type 1 error rate of 0.05 as the threshold for statistical significance and made no adjustments for multiple comparisons. Logistic and multinomial logistic regression analyses were completed using Stata statistical software version 11.2 (StataCorp Inc) and the GLLAMM program (www.gllamm.org).

We calculated population attributable fraction (PAF) for CA-MRSA and SSTI cases by using the adjusted odds ratios (AORs) for the third and fourth quartile of crop field swine manure exposure obtained from the final multivariable logistic regression model using the formula PAF = (AOR − 1)/ AOR × (proportion of cases exposed to risk factor).[41] The PAF for the third and fourth quartiles were summed to calculate the final PAF. Confidence intervals were computed using the delta method with the postestimation command *nlcom* in Stata.

We performed several sensitivity analyses. First, we evaluated 2 other time windows for crop field manure exposures: a 1-year and a 30-day window before either the date of MRSA diagnosis or the date of a preceding SSTI diagnosis. Second, models were repeated using different methods to identify crop fields (Figure 2). Third, we evaluated effect modification by community type and season. Fourth, analysis was performed to evaluate whether distance to nearest crop field, independent of manure application, was associated with disease outcomes. Finally, we repeated analyses using only culture-confirmed MRSA cases.

Results

Patients, Farms, and Crop Fields Included in the Study
A total of 1734 CA-MRSA and 1519 HA-MRSA cases were identified between January 2005 and February 2010. Most cases (72.3%) were identified by a positive MRSA culture. We frequency matched 3336 SSTIs and 3336 controls to the cases. Of the 9925 patients, we were able to identify latitude and longitude coordinates for home addresses for 87.5%. Thirty-one patients (0.35%) were excluded because they did not reside in counties for which we collected NMPs. This resulted in a total of 1539 CA-MRSA, 1335 HA-MRSA, and 2895 SSTI cases and 2914 controls with residences in 32 counties and 574 communities defined by *minor civil divisions*, ie, census-designated divisions of a county.

We collected NMPs and identified the location of 326 high-density livestock operations, 123 swine and 203 dairy/veal operations, in 27 counties and 168 townships. Ninety-eight of the swine operations (79.7%) and 71 of the dairy/veal farms (35.0%) exported at least a portion of their manure to a total of 424 crop fields. Crop fields were located in 29 counties, 8 boroughs, and 218 townships, for an average of 3.4 crop fields per township. A reported 637 266 595 gallons of manure was applied to crop fields annually. Among those in the highest quartiles of swine livestock operation exposure and swine crop field manure exposure, the median (IQR) distance to the nearest farm or field was 4.6 km (3.1-6.7 km) and 4.0 km (2.6-7.5 km), respectively. The Pearson *r* correlation between the individual-level exposure assignments from the 2 models was 0.59 (both log transformed).

Demographic Characteristics of Cases and Controls
There were no differences in demographic characteristics between patients included in the study and those excluded because we could not map their home address (n = 1211), except

that patients with SSTIs who were included were significantly more likely to have ever smoked than were those who were excluded (eTable 1 in the Supplement). Compared with controls, patients in the CA-MRSA group were significantly younger; they were more likely to be black, to smoke, and to receive Medical Assistance; and they lived in communities with greater socioeconomic deprivation (Table 1). White race/ ethnicity (95.3% of the study population) was associated with higher levels of swine and dairy/veal crop field manure exposure (Table 2). Exposures to manure were also the lowest among those who had not received an antibiotic prescription in the 2 years prior to diagnosis or visit, those who had received Medical Assistance, and those residing in cities.

Association of Crop Field Manure Exposure With Case Status
After adjusting for potential confounding variables, we found a significantly increased odds of CA-MRSA, HA-MRSA, and SSTI with higher swine manure exposure (fourth vs first quartile AORs, 1.38 [95% CI, 1.13-1.68], 1.30 [95% CI, 1.05-1.61], and 1.37 [95% CI, 1.18-1.60], respectively; P = .01, P < .001, and P < .001 for trend, respectively) (Table 3). The fourth quartile (vs first quartile) of dairy/veal exposure was also associated with increased odds of CA-MRSA (AOR, 1.24 [95% CI, 1.01-1.52]). The PAFs (95% CI) for the highest 2 quartiles of swine crop field manure exposure for CA-MRSA infection and SSTI were 10.7% (5.0-16.4%) and 11.5% (7.0-16.0%), respectively.

Association of High-Density Livestock Operations With Case Status
The fourth quartile vs first quartile of swine livestock operation exposure was associated with increased odds of CA-MRSA and SSTI (AORs, 1.25 [95% CI, 0.99-1.58] and 1.27 [95% CI, 1.08-1.50], respectively; P = .04 and P = .002, respectively) but not HA-MRSA (Table 3). No associations were seen with dairy/veal operations. Receipt of Medical Assistance remained independently associated with MRSA and SSTI outcomes in all adjusted analyses.

MRSA Isolate Substudy
A total of 200 isolates were randomly selected from 1128 patients with isolates (Table 4). Of these, 133 (66.5%) were common community strains (*spa* types t008, t024, t064, t206, t211); 33 (16.5%) were common health care strains (t002, t010, t062, t105); and the remainder were divided among 22 additional types. Notably, none was a *spa* type associated with CC398. A total of 27 community-onset isolates were *PVL*-negative.

Sensitivity Analyses
Evaluation of the 2 other time windows for manure application revealed slightly attenuated but otherwise similar results, except in the case of annual dairy/veal exposure, where the association strengthened for both CA-MRSA and SSTI cases (fourth vs first quartile AORs, 1.41 [95% CI, 1.13-1.77] and 1.26 [95% CI, 1.08-1.48], respectively; P = .01 and P = .02, respectively) (eTable 2 in the Supplement). Exclusion of crop fields without aerial photographs and/or addresses, including interaction terms for community type

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Study Participants, No. (%)			
	CA-MRSA (n = 1539)	HA-MRSA (n = 1335)	SSTI With No History of MRSA (n = 2895)[a]	Control (n = 2914)
Male	715 (46.5)	673 (50.4)	1412 (48.8)	1430 (49.1)
Age at infection or visit, median (IQR), y	23.5 (10-47)[b]	60.9 (39-77)[b]	41.5 (16-66)	41.9 (16-66)
Race/ethnicity[c]				
Non-Hispanic white	1446 (94.0)	1285 (96.5)	2772 (95.8)	2770 (95.1)
Non-Hispanic Black	49 (3.2)[d]	26 (2.0)	46 (1.6)	57 (2.0)
Hispanic	31 (2.0)	13 (1.0)[d]	52 (1.8)	52 (1.8)
Other	13 (0.8)	7 (0.5)[d]	25 (0.9)	34 (1.2)
Smoking[e]				
Never	1288 (83.7)[b]	952 (71.3)[b]	2334 (80.6)[b]	2649 (90.9)
Season of onset[f]				
Winter	352 (22.9)[g]	327 (24.5)	683 (23.6)[g]	786 (27.0)
Spring	269 (17.5)[b]	292 (21.9)	646 (22.3)	702 (24.1)
Summer	412 (26.8)[d]	342 (25.6)	819 (28.3)[b]	686 (23.5)
Fall	506 (32.9)[b]	374 (28.0)	747 (25.8)	740 (25.4)
Any antibiotic prescription in 2 years prior[h]	1125 (73.1)[b]	1024 (76.7)[b]	2018 (69.7)[b]	1499 (51.4)
Medical assistance[i]				
Never	1056 (68.6)[b]	1067 (79.9)[g]	2307 (79.7)[b]	2450 (84.1)
Community type				
City	250 (16.2)[b]	238 (17.8)[b]	371 (12.8)[d]	316 (10.8)
Borough	550 (35.7)[b]	393 (29.4)	870 (30.1)	839 (28.8)
Township	739 (48.0)[b]	704 (52.7)[b]	1654 (57.1)[d]	1759 (60.4)
Community socioeconomic deprivation[j]				
Quartile 1	347 (22.6)[b]	269 (20.1)[b]	723 (25.0)[g]	835 (28.7)
Quartile 2	392 (25.5)	316 (23.6)	741 (25.6)	725 (24.9)
Quartile 3	395 (25.7)	361 (27.0)[d]	722 (24.9)	691 (23.7)
Quartile 4	405 (26.3)[c]	389 (29.1)[b]	709 (24.5)	663 (22.8)

Abbreviations: CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus*; CPT, *Current Procedural Terminology*; HA-MRSA, health care-associated MRSA; ICD-9, *International Classification of Diseases, Ninth Revision*; IQR, interquartile range; SSTI, skin and soft-tissue infection.

[a] Based on 29 *ICD-9* codes: 680.0-680.9, 681.00-681.02, 681.9-681.11, 682.0-682.9, 035, 684, and 686.9.

[b] P < .001. vs control.

[c] Race/ethnicity was missing for 4 HA-MRSA cases and 1 control.

[d] P < .05 vs control.

[e] Based on presence of *ICD-9* codes 305.1 (tobacco use disorder), V15.82 (history of tobacco use), or 649.0 (tobacco use complicating pregnancy) or *CPT* codes 99406 or 99407 (smoking cessation counseling).

[f] Spring, March through May; summer, June through August; fall, September through November; and winter, December through February.

[g] P < .01. vs control.

[h] Indicates receipt of antibiotic prescription in the 730 to 14 days prior to diagnosis or visit.

[i] Based on the health insurance carrier for each encounter; identified with 24 separate codes, and "ever" was defined as more than 2 encounters with Medical Assistance.

[j] Community socioeconomic deprivation was assigned at the township, borough, or census tract level and was based on 6 indicators (all percentages) derived from US Census 2000 data: combined less than high school education, not in the labor force, in poverty, on public assistance, civilian unemployment, and does not own a car; a higher score represents a more deprived community; quartile 1 values, less than −2.22; quartile 2 values −2.23 through 0.46; quartile 3 values, 0.47 through 3.05; and quartile 4 values 3.06 or greater.

or season, and restricting analysis to culture-confirmed MRSA cases did not alter results. Distance to nearest crop field, independent of manure application, was not associated with MRSA or SSTI.

Discussion

High-density swine production was an independent risk factor for CA-MRSA and HA-MRSA infection and SSTI in patients without a history of MRSA. There was evidence that both a crop field manure application model that incorporated distance, swine manure volume, season of application, and field area, as well as a livestock operation model that incorporated distance and swine count, were each associated with increased risk of infection. Exposure assignments from these 2 models were moderately correlated, suggesting 2 independent sources of risk. Furthermore, while livestock operations are easily identifiable and fixed, manure-applied crop fields are not necessarily easily identifiable, are scattered, and may change from year to year. Associations with dairy/veal operations were less consistent and weaker than those for swine operations, which

Table 2. Characteristics of CA-MRSA Group by Crop Field Manure Exposure Quartiles (n=1539)

Characteristic	Individual Seasonal Crop Field Exposure, gal/m⁴, No. (%)									
	Swine Quartiles[a]					Dairy/Veal Quartiles[b]				
	1	2	3	4	P Value[c]	1	2	3	4	P Value[c]
Sex										
Female	185 (51.0)	217 (55.8)	205 (54.1)	217 (53.2)	.61	176 (49.3)	206 (56.1)	203 (55.2)	239 (53.5)	.27
Male	178 (49.0)	172 (44.2)	174 (45.9)	191 (46.8)		181 (50.7)	161 (43.9)	165 (44.8)	208 (46.5)	
Race/ethnicity										
Non-Hispanic white	336 (92.6)	353 (90.8)	367 (96.8)	390 (95.6)	<.001	322 (90.2)	347 (94.6)	345 (93.8)	432 (96.6)	.005
Non-Hispanic black	17 (4.7)	18 (4.6)	5 (1.3)	9 (2.2)		21 (5.9)	9 (2.5)	8 (2.2)	11 (2.5)	
Hispanic	6 (1.7)	17 (4.4)	5 (1.3)	3 (0.7)		11 (3.1)	9 (2.5)	9 (2.5)	2 (0.5)	
Other	4 (1.1)	1 (0.3)	2 (0.5)	6 (1.5)		3 (0.8)	2 (0.5)	6 (1.6)	2 (0.5)	
Smoking[d]										
Never	291 (80.2)	326 (83.8)	320 (84.4)	351 (86.0)	.17	303 (84.9)	308 (83.9)	296 (80.4)	381 (85.2)	.26
Ever	72 (19.8)	63 (16.2)	59 (15.6)	57 (14.0)		54 (15.1)	59 (16.1)	72 (19.6)	66 (14.8)	
Age group, y										
<25	174 (47.9)	216 (55.5)	186 (49.1)	217 (53.2)	.13	198 (55.5)	187 (51.0)	198 (53.8)	210 (47.0)	.08
≥25	189 (52.1)	173 (44.5)	193 (50.9)	191 (46.8)		159 (44.5)	180 (49.1)	170 (46.2)	237 (53.0)	
Antibiotic order in prior 2 years										
No	108 (29.8)	120 (30.9)	102 (26.9)	84 (20.6)	.005	115 (32.2)	108 (29.4)	92 (25.0)	99 (22.2)	.007
Yes	255 (70.3)	269 (69.2)	277 (73.1)	324 (79.4)		242 (67.8)	259 (70.6)	276 (75.0)	348 (77.9)	
Medical Assistance[e]										
Never	245 (67.5)	246 (63.2)	278 (73.4)	287 (70.3)	.02	235 (65.8)	260 (70.8)	239 (65.0)	322 (72.0)	.08
Ever	118 (32.5)	143 (36.8)	101 (26.7)	121 (29.7)		122 (34.2)	107 (29.2)	129 (35.1)	125 (28.0)	
Community										
City	90 (24.8)	75 (19.3)	53 (14.0)	32 (7.8)	<.001	75 (21.0)	66 (18.0)	66 (17.9)	43 (9.6)	<.001
Borough	121 (33.3)	151 (38.8)	131 (34.6)	147 (36.0)		136 (38.1)	123 (33.5)	153 (41.6)	138 (30.9)	
Township	152 (41.9)	163 (41.9)	195 (51.5)	229 (56.1)		146 (40.9)	178 (48.5)	149 (40.5)	266 (59.5)	
Community socioeconomic deprivation[f]										
Quartile 1	75 (20.7)	64 (16.5)	105 (27.7)	103 (25.3)	.001	61 (17.1)	93 (25.3)	74 (20.1)	119 (26.6)	<.001
Quartile 2	99 (27.3)	91 (23.4)	95 (25.1)	107 (26.2)		73 (20.5)	99 (27.0)	84 (22.8)	136 (30.4)	
Quartile 3	108 (29.8)	117 (30.1)	83 (21.9)	87 (21.3)		111 (31.1)	90 (24.5)	95 (25.8)	99 (22.2)	
Quartile 4	81 (22.3)	117 (30.1)	96 (25.3)	111 (27.2)		112 (31.4)	85 (23.2)	115 (31.3)	93 (20.8)	

Abbreviations: CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus*; CPT, Current Procedural Terminology; ICD-9, International Classification of Diseases, Ninth Revision; IQR, interquartile range; m⁴, quartic meters; SSTI, skin and soft-tissue infection.

[a] Quartile 1 values, less than 7549 gal/m²/km²; quartile 2 values, 7650 through 18 846 gal/m²/km²; quartile 3 values, 18 847 through 39 047 gal/m²/km²; quartile 4 values, 39048 gal/m²/km² or greater.

[b] Quartile 1 values, less than 29 205 gal/m²/km²; quartile 2 values, 29 206 through 60 623 gal/m²/km²; quartile 3 values, 60 624-104 717 gal/m²/km²; quartile 4 values, 104 718 gal/m²/km² or greater.

[c] Calculated using χ^2 test.

[d] Based on presence of ICD-9 codes 305.1 (tobacco use disorder), V15.82 (history of tobacco use), or 649.0 (tobacco use complicating pregnancy) or

CPT codes 99406 or 99407 (smoking cessation counseling).

[e] Based on the health insurance carrier for each encounter; identified with 24 separate codes, and "ever" was defined as more than 2 encounters with Medical Assistance.

[f] Community socioeconomic deprivation was assigned at the township, borough, or census tract level and was based on 6 indicators (all percentages) derived from US Census 2000 data: combined less than high school education, not in the labor force, in poverty, on public assistance, civilian unemployment, and does not own a car; a higher score represents a more deprived community; quartile 1 values, less than −2.22; quartile 2 values, −2.23 through 0.46; quartile 3 values, 0.47 through 3.05; quartile 4 values, 3.06 or higher.

was not surprising, given the limited number studies on the topic. Our data also suggest that approximately 11% of CA-MRSA and SSTI cases in the study population could be attributed to crop field application of swine manure.

The association with SSTIs is notable because there were more than 50 000 such cases, compared with 4000 MRSA cases, in the region since 2001.[22] Crop field manure application may lead to SSTI either by causing MRSA infection that goes undiagnosed as such or by exposure to other bacteria that cause SSTI.

We cannot attribute these infections to any single pathogen. Subanalysis of 258 SSTI cases (9%) identified from culture data as methicillin-susceptible *S aureus* (MSSA) revealed an association with swine livestock exposure (AOR, 1.70 [95% CI, 1.15-2.52]) that was stronger than for all SSTIs together. The public health burden of SSTIs[25,42] warrants future study of links to high-density livestock production. Concerning the association with HA-MRSA, this finding does not imply that livestock-associated strains are in hospitals. Rather, these older patients

Table 3. Association of Seasonal Crop Field Manure Exposure and Livestock Operation Exposure With CA-MRSA, HA-MRSA, and SSTI From Full Multilevel Multivariate Model[a]

| | Odds Ratio (95% CI) | | | | | |
| | CA-MRSA | | HA-MRSA | | SSTI | |
Characteristic	Univariate	Adjusted	Univariate	Adjusted	Univariate	Adjusted
Seasonal Crop Field Manure Exposure						
Swine[b]						
Quartile 1	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Quartile 2	1.11 (0.93-1.32)	1.09 (0.90-1.31)	1.15 (0.96-1.38)	1.21 (0.98-1.48)	1.03 (0.89-1.20)	1.03 (0.88-1.20)
Quartile 3	1.12 (0.94-1.33)	1.26 (1.04-1.52)	1.09 (0.90-1.31)	1.27 (1.03-1.57)	1.15 (1.00-1.33)	1.22 (1.05-1.41)
Quartile 4	1.34 (1.13-1.60)	1.38 (1.13-1.69)	1.26 (1.05-1.51)	1.30 (1.05-1.61)	1.34 (1.16-1.55)	1.37 (1.18-1.60)
P value[c]	.002	<.001	.04	.01	<.001	<.001
Dairy/veal[d]						
Quartile 1	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Quartile 2	0.93 (0.78-1.12)	0.95 (0.78-1.16)	0.76 (0.64-0.92)	0.82 (0.67-1.02)	0.90 (0.78-1.04)	0.90 (0.77-1.05)
Quartile 3	0.94 (0.79-1.13)	0.90 (0.74-1.09)	0.94 (0.79-1.12)	0.92 (0.76-1.13)	0.84 (0.72-0.97)	0.85 (0.73-0.99)
Quartile 4	1.25 (1.05-1.48)	1.24 (1.01-1.52)	0.74 (0.62-0.90)	0.78 (0.62-0.98)	1.02 (0.88-1.18)	1.01 (0.87-1.19)
P value[c]	.01	.06	.03	.08	.96	.92
Livestock Operation Exposure						
Swine[e]						
Quartile 1	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Quartile 2	0.85 (0.72-1.02)	0.96 (0.77-1.20)	0.78 (0.65-0.94)	0.96 (0.76-1.21)	0.91 (0.79-1.06)	1.00 (0.85-1.18)
Quartile 3	0.91 (0.77-1.09)	1.05 (0.84-1.32)	0.83 (0.69-0.99)	0.88 (0.70-1.12)	0.95 (0.82-1.10)	1.05 (0.89-1.23)
Quartile 4	1.03 (0.87-1.23)	1.25 (0.99-1.58)	1.04 (0.87-1.25)	1.18 (0.93-1.50)	1.19 (1.03-1.38)	1.27 (1.08-1.50)
P value[c]	.60	.04	.57	.19	.01	.002
Dairy/veal[f]						
Quartile 1	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Quartile 2	0.80 (0.67-0.95)	0.90 (0.72-1.12)	0.79 (0.66-0.94)	0.83 (0.66-1.05)	1.02 (0.88-1.18)	1.10 (0.93-1.30)
Quartile 3	1.04 (0.88-1.24)	1.18 (0.94-1.48)	0.95 (0.79-1.13)	1.00 (0.79-1.26)	1.07 (0.92-1.24)	1.17 (0.99-1.39)
Quartile 4	0.86 (0.73-1.03)	1.07 (0.85-1.35)	0.62 (0.52-0.75)	0.80 (0.62-1.02)	0.99 (0.87-1.15)	1.12 (0.95-1.32)
P value[c]	.51	.21	<.001	.24	.97	.18

Abbreviations: AEU, animal equivalent unit; CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus*; HA-MRSA, health care-associated MRSA; SSTI, skin and soft-tissue infection.

[a] For multinomial models, n = 5783, and for binomial model, n = 5808; crop field model adjusted for sex, age, race/ethnicity, ever-smoking status, antibiotic prescription in the prior 2 years, receipt of Medical Assistance, residential minor civil division, and community socioeconomic deprivation; livestock model further adjusted for season of infection or visit.

[b] Quartile 1 values, less than 7549 gal/m²/km²; quartile 2 values, 7650 through 18 846 gal/m²/km²; quartile 3 values, 18 847 through 39 047 gal/m²/km²; quartile 4 values, 39 048 gal/m²/km² or greater.

[c] P value for linear trend (quartiles included as a single variable with values 1, 2, 3, and 4).

[d] Quartile 1 values, less than 29 205 gal/m²/km²; quartile 2 values, 29 206 through 60 623 gal/m²/km²; quartile 3 values, 60 624 through 104 717 gal/m²/km²; quartile 4 values, 104 718 gal/m²/km² or greater.

[e] Quartile 1 values, less than 6.3 AEU/km²; quartile 2 values, 6.4 through 7.8 AEU/km²; quartile 3 values, 17.9-34.7 AEU/km²; quartile 4 values, 34.8 AEU/km² or greater.

[f] Quartile 1 values, less than 7.1 AEU/km²; quartile 2 values, 7.2 through 21.0 AEU/km²; quartile 3 values, 21.1 through 44.9 AEU/km²; quartile 4 values, 44.9 AEU/km² or greater.

may have been colonized in the community with livestock strains and then had health care contact (eg, hospitalization, surgery, dialysis, indwelling device) before infection.

To our knowledge, no studies have examined the association between high-density livestock operations and MRSA infection in the community, and only 2 studies have assessed risk of colonization.[16,17] Study of colonization may not be useful when evaluating the risk of MRSA infection associated with industrial agriculture because, first, environmental exposure or direct contact may more often lead to CA-MRSA infection than does colonization[43] and second, MRSA colonization may not persist for more than 24 hours after livestock exposure.[44] Prior studies limited their ability to identify risk from high-density livestock exposure by including only patients with CC398,[13,45] by studying only people who lived or worked on farms,[9,12,46-48] and by not including crop field manure exposure.

A unique aspect of this study is the consideration of risk from manure application to crop fields. Sensitivity analyses across time (eg, annual, seasonal, and 30-day exposure) and across space (eg, restricting analysis to fields with aerial photographs or maps) did not substantively change results. Our findings are likely not an artifact of rural residents in the study popu-

Table 4. Summary of MRSA Genetics

Characteristic	spa Types, No. (%)		Other Types, No. (%) (n = 34)[c]	P Value
	Community (n = 133)[a]	Healthcare (n = 33)[b]		
Age at infection, median (IQR), y	29 (13-48)	65 (45-77)	46 (14-61)	<.001
Location of onset				
Inpatient[d]	8 (6.0)	20 (60.1)	7 (20.6)	<.001
Outpatient[e]	125 (94.0)	13 (39.9)	27 (79.4)	
Community type				
City	18 (13.5)	1 (3.0)	5 (14.7)	
Borough	34 (25.6)	13 (39.4)	12 (35.3)	.25
Township	81 (60.9)	19 (57.6)	17 (50.0)	
PVL-positive	131 (98.5)	1 (3.0)	17 (50.0)	<.001
Swine operation exposure, fourth quartile[f]	27 (20.3)	10 (30.3)	13 (38.2)	.36

Abbreviations: AEU, animal equivalent unit; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; PVL, Panton-Valentine leukocidin genes.

[a] Includes spa types t008 (n = 123), t024 (n = 7), t064, t206, and t211.

[b] Includes spa types t002 (n = 27), t105 (n = 3), t010 (n = 2), and t062.

[c] Includes spa types t121 (n = 4), novel varieties (n = 3), t088 (n = 3), t622

(n = 3), t045 (n = 2), t068 (n = 2), t012, t125, t216, t304, t306, t316, t437, t539, t681, t692, t856, t948, t1154, t1610, t6614, t9964, and unknown.

[d] Inpatient isolates collected more than 2 days after hospital admission.

[e] Isolates collected in the outpatient setting or within the first 2 days of hospitalization.

[f] Quartile 4 values, 33.4 AEU/km^2 or greater.

lation because, while manure-applied crop fields were associated with risk, residence in a township (where 98.5% of crop fields are located) and distance to nearest crop field independent of manure application were not associated with the 3 outcomes.

Previous studies have used community-level livestock density as a marker of livestock exposure.[16,17,45] We estimated exposure at the individual level, incorporating several features of these operations and fields. Operation and field sites were confirmed using Google Earth rather than physical inspection of the area, which may have led to some misclassification. Additional exposure misclassification may have occurred since the exposure assessment did not capture all smaller farms. In Pennsylvania, only large operations, specifically concentrated animal feeding operations, or operations with greater than 2 AEUs per acre are required to produce NMPs. The 2007 US Census of Agriculture revealed that our exposure models included 89% of swine AEUs present in the study area. Because characteristics of high-density livestock practices differ by and within states, our results may not apply in full to other areas with these operations.

A limitation of this study is that we did not measure how livestock-associated pathogens may reach individuals in a community, but several ways have been considered in prior studies. Aerosolized MRSA has been isolated from the air up to 150 m downwind and from the soil up to 300 m downwind of swine operations.[49,50] Studies have also reported that tetracycline, the most commonly used antimicrobial agent used in food-producing animals in the United States,[1] was found at concentrations sufficient to select for resistant bacteria in both swine manure and manure-fertilized soil.[51] These studies provide biologic plausibility for our findings, but more research is needed to establish sources, media, routes, and behaviors that may lead to infection. Other animals,[52] slaughterhouses,[53] and meat consumption[54] may be involved.

We did not find any spa types associated with clonal complex CC398. Most MRSA found on farms or in farmers has been characterized as CC398, though other types have been identified.[9,12,13,45,55,56] However, few studies have assessed MRSA infection, instead focusing on MRSA carriage, and those that do come from Europe[14,15,57,58] and/or deal exclusively with CC398 MRSA.[58-60] The most common strains on US farms are not well known. In Ohio, the closest state to Pennsylvania for which there are data, common health care strains were most often isolated from swine; CC398 was secondary.[53] We were limited in that genetic data did not come from the same time period as the main study, and isolate strains could have changed over time.

We used *ICD-9* codes to classify MRSA cases as CA or HA and to derive the predictor variables used in the analysis. The primary HA epidemiologic factors[31] are well captured by the EHR. Ever-smoking status can also be effectively obtained using *ICD-9* codes.[61] Unfortunately, the EHR did not directly capture data on individual-level socioeconomic status or occupation, so our results could have been due to these variables. To evaluate this potential confounding, we adjusted the final models for 2 surrogates for socioeconomic status: Medical Assistance at the individual level and community socioeconomic deprivation at the community level. As expected, patients with CA-MRSA were more likely to receive Medical Assistance and more likely to live in more deprived communities than controls, associations that persisted in the adjusted models.[62,63] Previous literature has suggested increased prevalence of MRSA colonization in livestock workers.[8] However, given the low prevalence of this employment (1% of population in any agricultural work, according to US Census data) even in townships and boroughs in the study area, it seems unlikely that farming occupation could account for the reported associations. Moreover, inclusion of community-level percentage of agri-

cultural workers in the multilevel model did not change associations.

In conclusion, proximity to and size of high-density livestock production were associated MRSA infection and SSTI, and the population-attributable fraction of crop field manure application exceeded 10% for CA-MRSA and SSTI. The findings contribute to the growing concern about the potential public health impacts of high-density livestock production.

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