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Swine exposure and methicillin-resistant *Staphylococcus aureus* infection among hospitalized patients with skin and soft tissue infections in Illinois: A ZIP code-level analysis

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ABSTRACT

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA), a bacterial pathogen, is a predominant cause of skin and soft tissue infections (SSTI) in the United States. Swine-production facilities have been recognized as potential environmental reservoirs of MRSA. To better understand how swine production may contribute to MRSA infection, we evaluated the association between MRSA infection among SSTI inpatients and exposure measures derived from national swine inventory data.

Methods: Based on adjusted odds ratios from logistic regression models, we evaluated the association between swine exposure metrics and MRSA infections among all Illinois inpatient hospitalizations for SSTI from January 2008 through July 2011. We also assessed if swine exposures had greater association with suspected community-onset MRSA (CO-MRSA) compared to suspected hospital-onset MRSA (HO-MRSA). Exposures were estimated using the Farm Location and Agricultural Production Simulator, generating the number of farms with greater than 1000 swine per residential ZIP code and the residential ZIP code-level swine density (swine/km^2).

Results: For every increase in 100 swine/km^2 within a residential ZIP code, the adjusted OR (aOR) for MRSA infection was 1.36 (95% CI: 1.28 − 1.45). For every additional large farm (i.e., > 1000 swine) per ZIP code, the aOR for MRSA infection was 1.06 (95% CI: 1.04 − 1.07). The aOR for ZIP codes with any large farms compared to those with no large farms was 1.24 (95% CI: 1.19 − 1.29). We saw no evidence of an increased association for CO-MRSA compared to HO-MRSA with either continuous exposure metric (aORs = 0.99), and observed inconsistent results across exposure categories.

Conclusions: These publicly-available, ecological exposure data demonstrated positive associations between swine exposure measures and individual-level MRSA infections among SSTI inpatients. Though it is difficult to draw definitive conclusions due to limitations of the data, these findings suggest that the risk of MRSA may increase based on indirect environmental exposure to swine production. Future research can address measurement error related to these data by improving exposure assessment precision, increased specification of MRSA strain, and better characterization of specific environmental exposure pathways.

1. Introduction

Over the last two decades, Methicillin-resistant *Staphylococcus aureus* (MRSA) has garnered increased attention, with a shift from a largely nosocomial etiology, affecting individuals with preexisting health conditions to that of community origin, affecting populations

Abbreviations: MRSA, Methicillin-resistant Staphylococcus aureus; IHA, Illinois Hospital Association; OR, odds ratios; aOR, adjusted odds ratios; CA-MRSA, community-acquired MRSA; HA-MRSA, hospital acquired MRSA; LA-MRSA, livestock-associated MRSA; SSTI, skin and soft tissue infection; CO-MRSA, community-onset MRSA; HO-MRSA, hospital-onset MRSA; IHA, Illinois Hospital Association; IHD, Illinois Hospital Discharge Database; ICD-9, International Classification for Diseases coding 9th revision; CDC, Centers for Disease Control and Prevention; USDA, U.S. Department of Agriculture; RUCC, rural-urban continuum code; FLAPS, farm location and agricultural production simulator; ArcGIS, aeronautical reconnaissance coverage geographic information system; ESRI, Environmental Systems Research Institute; SAS, Statistical Analysis System; ETS, Econometrics and Time Series; COPD, chronic obstructive pulmonary disease; NASS, National Agricultural Statistics Service; COL, colonization; Std Dev, standard deviation; CI, confidence interval; N/E, not able to estimate, PHE, previous healthcare exposure; POA, present on admission; HIV, human immunodeficiency virus; CAFO, concentrated animal feeding operation

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with limited healthcare exposures (Grundmann et al., 2006; Levy, 2010; Mediavilla et al., 2012). The first cases of community-acquired MRSA (CA-MRSA) were documented in the 1990s (Herold et al., 1998) and have since increased dramatically (Dukic et al., 2013). Because asymptomatic MRSA colonization is a risk factor for MRSA infection (Davis et al., 2004), active surveillance for MRSA carriers is a potential preventive practice in hospital settings (Diekema and Edmond, 2007). Likely due to improvements in hospital surveillance and biosecurity, hospital acquired MRSA (HA-MRSA) cases have decreased, leading to a higher relative proportion of CA-MRSA overall (Dantes et al., 2013; Lowy, 2013; David et al., 2014). This change in incidence and disease dynamics highlight the need to identify and characterize community-level risk factors for MRSA infection.

Swine production facilities have been identified as environmental reservoirs of MRSA (Silbergeld et al., 2008b; Gilchrist et al., 2007). The first livestock-associated (LA)-MRSA strain, ST398, was traced to swine farms and contact with livestock in Europe (Voss et al., 2005; van Loo et al., 2007; Feingold et al., 2012). More recently, other LA-MRSA strains have been identified (Monecke et al., 2011; Molla et al., 2012; Frana et al., 2013), and those found in the US appear to differ regionally (Casey et al., 2013; Smith et al., 2013). Using whole genome sequencing data, Price et al. (2012) first demonstrated jump of LA-MRSA from humans to swine and back, and multiple studies have shown an elevated prevalence of MRSA colonization in swine farmers and swine veterinarians (Smith et al., 2009, 2013; van Cleef et al., 2011, 2014; Frana et al., 2013; Huang et al., 2014; Nadimpalli et al., 2015; Rinsky et al., 2013). The spread of antibiotic resistance has been a major concern since the introduction of non-therapeutic antibiotics for growth promotion into conventional livestock production systems (Starr and Reynolds, 1951; Levy et al., 1976). Exposing microorganisms to consistent nontherapeutic levels of antibiotics may accelerate the formation of antimicrobial-resistant bacteria (Akwar et al., 2007; Silbergeld et al., 2008a). These bacteria can colonize and infect swine, contaminate their containment facilities and be excreted in waste. Further selective pressure by excreted and dispersed residual antibiotics (Hamscher et al., 2003; Dolliver and Gupta, 2008; Manzetti and Ghisi, 2014) and horizontal transfer of antimicrobial-resistant genes (Witte, 2000; Gilchrist et al., 2007; Marshall and Levy, 2011) can result in additional proliferation of both exogenous and endogenous antimicrobial-resistant bacteria in swine waste and the environment.

The shift of swine production to larger confinement operations has increased the volume of waste and may amplify the selection of antimicrobial-resistant bacteria and antimicrobial-resistant genes (Silbergeld et al., 2008b). Swine facility-level fate and transport studies have shown MRSA colonization of buildings and immediate surroundings (Leedom Larson et al., 2011) and the environmental dispersion of MRSA and their genetic markers via aerosolization and deposition (Chapin et al., 2005; Gibbs et al., 2006; Schulz et al., 2012), spills and discharges from waste storage, direct land application for fertilizing crops (Chee-Sanford et al., 2009; Heuer et al., 2011), runoff into surface waters (Pruden et al., 2012), and groundwater leaching (Chee-Sanford et al., 2001). Previous research shows that even indirect exposure may increase MRSA colonization risk among neighboring communities (Bisdorff et al., 2011; van Rijen et al., 2014; Feingold et al., 2012; Carrel et al., 2014) and shows the increase in livestock-associated strains in humans in areas devoid of livestock (Larsen et al., 2015). However, the relative importance of different environmental media and specific exposure pathways is not completely understood (Appendix A, Fig. A.2). To our knowledge, only one other published study has investigated the relationship of non-occupational swine exposure to non-LA-MRSA-specific MRSA infection in the United States (Casey et al., 2013).

To better understand how swine production may contribute to MRSA infection, we analyzed routinely-collected administrative hospitalization data and national swine inventory data to evaluate the association between community-level swine exposure and individual MRSA infection among skin and soft tissue infection (SSTI) inpatients from 2008 to 2011 in Illinois. Illinois offers a unique study opportunity as it was the fourth highest swine producing state in the country throughout the study period, had sufficient variability in the concentration of production across the state, and by comparison is a low producer of other livestock that might confound study results (USDA, 2007, 2012, 2014). We hypothesized that there would be increased risk of MRSA infections and colonization for individuals living in ZIP codes with increasing numbers of swine/km^2 and increasing numbers of large-scale facilities housing greater than 1000 swine. Additionally, we hypothesized that swine exposure would be more strongly associated with community-onset (CO-) MRSA compared to hospital-onset (HO-) MRSA.

2. Methods

2.1. Case ascertainment and outcome definitions

We utilized the Illinois Hospital Association's (IHA) Hospital Discharge Database (IHD) to identify MRSA infection among all statewide SSTI inpatient hospitalizations from January 2008 through July 2011. The IHA membership includes 97% of Illinois hospitals; the remaining nonmember hospitals treat 7% of all hospitalizations in Cook County, a primarily urban area encompassing the city of Chicago, IL (Illinois Department of Public Health, 2015). Records stored in this database include all diagnoses identified and procedures reported using the 9th revision of the International Classification for Diseases coding (ICD-9) for up to 24 diagnostic positions. Although residential address is not available, the database included several relevant individual-level covariates, including ZIP code and county of residence, admission date, age, sex, type of health insurance and other comorbid risk factors (Appendix A, Table A.2).

Study inclusion criteria required records to contain ICD-9 codes 680 – 686, indicating an SSTI, and to have a residential ZIP code and Federal Information Processing Standard County code within Illinois. Presence of MRSA was determined primarily using specified codes for MRSA infection, 041.12, 038.12, or 482.42, which were introduced to ICD-9 in the 2008 update (CDC/NCHS, 2013). To account for any outdated coding, we also included records with the code assignment for MRSA infection used prior to 2008, which requires both one code for *Staphylococcus aureus* infection (038.11, 482.41 or 041.11) along with the supplementary V09.0 code indicating resistance to penicillins (CDC/NCHS, 2013).

In addition to the main analysis, we also evaluated the association of ZIP-based swine exposure and MRSA colonization, the results of which are included in Tables 1, 3, as well as expanded results in the Appendix. The primary supplementary code used to identify MRSA colonization was V02.54. This specified colonization code was added to ICD-9 in 2008; thus, we also included the pre-2008 unspecified colonization code V02.59. For the MRSA infection analysis, MRSA-positive SSTI inpatients were compared to those without MRSA coding. For the MRSA-colonization analysis, MRSA-positive SSTI with MRSA colonization coding were compared to those without colonization coding (Table 2).

2.1.1. HO- and CO-MRSA coding designation

To assess the difference in risk from swine exposure for hospital-acquired and community-acquired MRSA, we assigned all MRSA infections as either HO- or CO- based on a modified version of the Centers for Disease Control and Prevention's (CDC) definitions for hospital-acquired and community-acquired MRSA. The CDC's definitions characterize these categories based on epidemiological criteria, rather than molecular specification. CDC case definition defines a community-