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Distance to pig farms as risk factor for community-onset livestock-associated MRSA CC398 infection in persons without known contact to pig farms—A nationwide study

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Summary

MRSA CC398 is an emerging MRSA strain found in livestock, mainly in pigs. Direct occupational livestock contact is the principal risk factor for human MRSA CC398 infection. Nonetheless, in recent years, an increasing number of MRSA CC398 cases has been observed in persons without known pig contact. Such cases, referred to as MRSA CC398 of unknown origin (MUO CC398), have, like livestock-onset (LO) MRSA CC398 cases, been found concentrated in rural, livestock-producing areas. The presence of MUO CC398 cases indicates alternative and unknown MRSA CC398 transmission pathways into the community. We performed a nationwide study in Denmark of the geographic distributions of MRSA cases in general and persons with MUO CC398 or LO MRSA CC398 infections (1 January 2006–11 February 2015), with the Danish population as background population. Place of living of study persons was mapped using the ArcGIS software, and information on pig farms was retrieved from the Central Husbandry Register. The incidence of MUO CC398 infections was clearly higher in rural than in urban areas, and such cases lived on average closer to pig farms than the general population. However, within three pig-farming-dense municipalities, patients with MUO CC398 infections did not live closer to pig farms than population controls. This shows that direct environmental spread from neighbouring pig farms of MRSA CC398 is unlikely. Instead, community spread through other means of transmission than direct spread from farms may more likely explain the clustering of MUO CC398 in livestock-dense areas.

KEYWORDS
CC398, Geographic Information Systems, livestock, MRSA, pigs, risk factors

1 | INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) are staphylococci resistant to beta-lactam antibiotics including methicillin. MRSA can cause minor and life-threatening infections (Larsen et al., 2015), and the antibiotic resistance makes MRSA infection treatment difficult, prolonged and sometimes unsuccessful, demanding specific types of antibiotics.

In 2005, a new type of MRSA with reservoir in livestock and transmission to humans was reported (Armand-Lefevre, Ruimy, & Andremont, 2005; Voss, Loeffen, Bakker, Klaassen, & Wulf, 2005). The MRSA isolates of these cases belonged to the clonal complex 398 (CC398), rare in humans at that time. Livestock-associated MRSA CC398 lineages have been found in various livestock including pigs, horses, poultry and mink (Larsen et al., 2016). In Denmark, pigs represent the main source of livestock-associated MRSA CC398 with 88% of Danish pig farms being MRSA CC398 colonized by the year 2016 (Danish Veterinary and Food Administration, 2017), while other types of livestock are colonized at substantially lower proportions (Larsen et al., 2016).

Despite the fact that MRSA CC398 only accounted for a minor proportion of human European MRSA cases (colonized or infected) (van Cleef et al., 2011), today MRSA CC398 is a prevailing type of new human MRSA cases in many European countries (DANMAP, 2012). Denmark has a developed pig industry with 12.5 million pigs and 3,700 pig farms by 2015 (Statistics Denmark, 2015). In 2015, MRSA CC398 accounted for 39% of new human MRSA cases in Denmark (colonized and infected) (Petersen et al., 2016).

Work involving direct livestock contact is the primary mode of MRSA CC398 acquisition (Larsen et al., 2015; Lewis et al., 2008). In Denmark, the highest rates of MRSA CC398 colonization are found among people with direct livestock contact or their household members. Such MRSA CC398 cases are termed livestock-onset (LO) MRSA CC398. However, an increasing number of CC398 cases without known contact with livestock occurs (Larsen et al., 2015; Petersen et al., 2016) (in this study termed MRSA CC398 of unknown origin, MUO CC398). This indicates alternative and unknown MRSA CC398 transmission pathways into the community, which can be described as spill over to the neighbouring community that is almost proportional to the number of LO MRSA CC398 cases (Larsen et al., 2015).

MUO CC398 cases have been found concentrated in rural, livestock-producing areas suggesting a connection between such cases and surrounding livestock density (Carrel, Schweizer, Sarrazin, Smith, & Perencevich, 2014; Casey, Curriero, Cosgrove, Nachman, & Schwartz, 2013; Feingold et al., 2012; Larsen et al., 2015). However, these studies had limitations as they did not take into account either direct distance to pig farms on an individual level, livestock contact, other aspects of exposure history, or MRSA type. One recent study found that living near livestock farms increased the risk for MRSA CC398 carriage (Zomer et al., 2017).

It is therefore debated whether the emergence of MUO CC398 infections observed in rural livestock-producing areas is associated with direct pig contact, with distance between households and pig-producing farms (suggesting environmental pathways of transmission), or simply with living in an area with pig farming and possible person-to-person spread through the community.

The purpose of this study was to determine the spatial distribution of MRSA in Denmark with particular focus on MUO CC398 infections and to estimate whether living in a pig-dense area and/or living close to a pig farm increases the risk of MUO CC398 infections.

Impacts

- MRSA CC398 (livestock-associated MRSA) is mainly seen in persons with direct contact with pigs. In recent years, an increasing number of persons infected or colonized with MRSA CC398 without known contact with pigs has been observed, indicating unknown transmission pathways in the community.
- In this Danish study, persons with infection with MRSA CC398 without known contact with pigs lived closer to pig farms than population controls; but within three pig-farming-dense municipalities, there was no such difference.
- These results do not support that MRSA CC398 is transmitted through direct environmental spread from neighbouring pig farms.

2 | MATERIALS AND METHODS

2.1 | Study population

The study population consisted of all persons notified with MRSA colonization or infection in Denmark (1 January 2006–11 February 2015), with the Danish population in the same period as background population.

2.2 | Data sources

Since 2006, MRSA has been a notifiable condition in Denmark. Following identification at regional laboratories, the first MRSA isolate from any given person irrespectively of age and possible risk factors for MRSA besides the first annual isolates for the subsequent years are sent to Statens Serum Institut for typing. Hereof are the first MRSA isolate and possible first isolates of new MRSA types reported to the MRSA notification system. By 2016, 39% of notified cases were infected, and 61% were colonized (Petersen et al., 2016).

Every Danish citizen is assigned a unique civil person registry (CPR) number that follows the person throughout life. The CPR contains information of all Danish citizens with regularly updated information of vital status and historical and current addresses. We used this data set to geocode all patients based on address at time of sampling.

Information on pig farms was retrieved from the Central Husbandry Register (CHR), a database for livestock and herds in Denmark administrated by the Danish Veterinary and Food Administration (Ministry of Environment and Food of Denmark, Danish Veterinary and Food Administration, n.d.). The register contains information on the exact geographical location of the main livestock housing and type and number of livestock.

2.3 | Case definitions and classifications

In the Danish notification system, MRSA cases are classified according to information on, among others, travel and contact to hospitals and/or livestock. A case of MRSA is coded as livestock-associated if the person or a household member has livestock contact, and if there is no indication that the case is travel-related.

In Denmark, almost all livestock-associated MRSA cases are caused by MRSA CC398. The CC398 lineage consists of two different sublineages, a PVL-negative sublineage associated with livestock and a PVL-positive sublineage not associated with livestock. Almost all MRSA CC398 sublineages in Denmark are PVL-negative. To ensure that we only addressed livestock-associated MRSA CC398, we excluded PVL-positive MRSA CC398 cases. Thus, in this study, an MRSA CC398 case denotes a PVL-negative case of MRSA CC398.

In 2012, the Danish MRSA screening procedures changed so that persons with pig contact are mandatorily screened in case of hospital contact. As this results in geographic screening bias, we only included patients with MRSA CC398 infections (a person with a clinical infection from which MRSA is cultured; a "clinical case") and not screened persons in incidence and distance analyses.

Clinical MRSA CC398 cases were classified as livestock-onset (LO) MRSA CC398, if the case had direct or indirect (through household members) livestock contact. Else, the case was termed MRSA CC398 of unknown origin (MUO CC398) irrespectively of possible route of transmission.

2.4 | Geographical analyses

MRSA cases in Denmark as identified in the MRSA database were mapped using the ARCGIS software (ArcGIS Desktop, 2011). The home address of each MRSA case at time of positive MRSA test was represented by an exact set of coordinates.

Cumulative incidence by municipality was calculated for clinical LO and MUO CC398 cases, with the total population by municipality as identified in the CPR as denominator.

Possible clustering of incidence (spatial autocorrelation), that is that incidence is not randomly distributed across the municipalities of Denmark, was tested for LO MRSA CC398 and MUO CC398 infections using Global Moran's Index (Mitchell, 2009).

To test whether the risk of MUO CC398 infection was associated with the number of pig farms with more than 10 pigs and/or the incidence of LO MRSA CC398 infections in the municipality of residence, we carried out a multivariable linear regression analysis with both number of pig farms and LO MRSA CC398 cases included in the model. The ordinary least squares (OLS) method was used to test for significance.

Finally, to test whether clinical MUO CC398 cases lived closer to pig farms and/or clinical LO MRSA CC398 cases than the general population, we plotted the cumulative numbers of clinical MUO CC398 cases and the general population (controls), respectively, against distances to the nearest pig farm and the nearest LO MRSA CC398 case. Distances were measured by road and not by Euclidian distance (direct distance through air) to reflect the actual travelled distance between points, as distance by road may often be substantially longer than the direct distance.

2.5 | Ethical considerations

The study was reported to the Danish Data Protection Agency. In Denmark, scientific ethical approval is not required for register-based studies as the present.

3 | RESULTS

In total, 11,174 MRSA cases with exact addresses were identified in the MRSA database, of which 2,706 (24%) were MRSA CC398 (Figure 1). Hereof had 632 (23% of MRSA CC398 cases) clinical infection. Of the 632 clinical cases, 440 (70%) were LO MRSA CC398 and 192 (30%) were MUO CC398.

Figure 1 shows that MRSA cases as a whole were spread over the entire country with high numbers, among others, around the largest cities in Denmark, which coincides with high population densities in these areas. For MRSA CC398 cases, irrespectively of carriage or clinical infection, a relatively smaller proportion lived around the larger cities indicating that MRSA cases observed in urban areas were mainly non-CC398. Except for the absence of MRSA CC398 clusters in Northern Jutland and on the island of Funen, the distribution of clinical MRSA CC398 seems, by visual inspection, to be similar with the distribution of all MRSA CC398 cases in Denmark. Likewise, the distribution of MUO CC398 cases seems to be overall similar to that of all MRSA CC398 cases in Denmark.

Figure 2 shows the incidence of clinical cases of MRSA CC398, overall and divided into LO or MUO CC398, and the number of pig farms by municipality. The incidence of clinical MRSA CC398 cases, both overall and by type, was not evenly distributed throughout Denmark, but was much higher in Jutland and the island of Funen compared with the island of Zealand with the Copenhagen metropolitan area, where the incidence was very low. The distributions of LO and MUO CC398 incidence seemed to reflect that of the number of pig farms by municipality, although there was a higher visual agreement between number of pigs and incidence of LO than of MUO CC398.

The Global Moran's *z*-score underpinned the visual inspection suggesting that the incidence of clinical cases of MUO CC398 by municipality was geographically clustered throughout Denmark (*z*-score 11.03, $p < .001$).

The multivariate OLS analysis showed a borderline statistically significant association between number of pig farms by municipality and the incidence of clinical cases of MUO CC398 ($p = .057$). There was no significant association between the incidence of clinical cases of LO MRSA CC398 and MUO CC398 by municipality ($p = .13$).

Figure 3 shows the cumulative percentage of distance for clinical MUO CC398 cases and population controls to nearest pig farm with 10 livestock or more, and to nearest clinical LO MRSA CC398 case. The distribution curves show that clinical MUO CC398 cases in Denmark lived closer both to pig farms (median distance 2,500 m) and to clinical LO cases (median distance 4,500 m) than controls did (median distances 3,500 m and 6,000 m, respectively). The median difference in distance between addresses of cases and population controls was to nearest pig farm 1,010 m and to nearest LO MRSA CC398 case 1,350 m.

However, as pig farms are not evenly distributed across Denmark, we repeated this analysis using data for only three municipalities (all in Jutland; *Hedensted*, *Horsens* and *Vejle* municipalities) with high densities of pig farms (Figure 4). The cumulative percentage of distance to pig farms was largely identical for clinical MUO CC398 cases and population controls (distribution lines largely overlapping), and likewise for the cumulative percentage of distance to nearest LO MRSA CC398 case. There were small differences between cases and controls in median distance to pig farms and nearest LO MRSA CC398 cases (median distance to pig farm 2,600 m for clinical MUO CC398 cases

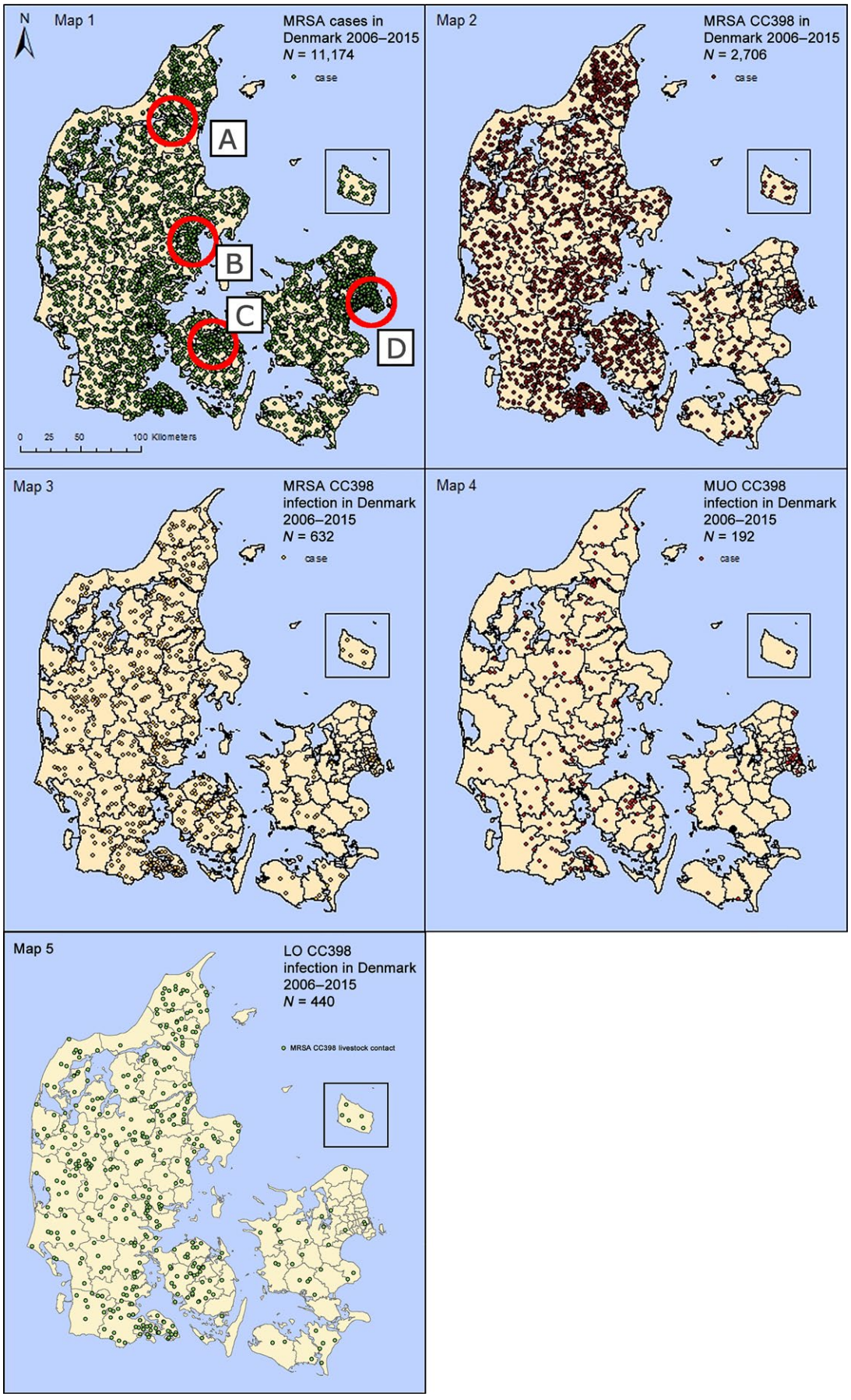
N
Map 1
MRSA cases in Denmark 2006–2015
N = 11,174
case
A
B
C
D
0 25 50 100 Kilometers
Map 2
MRSA CC398 in Denmark 2006–2015
N = 2,706
case
Map 3
MRSA CC398 infection in Denmark 2006–2015
N = 632
case
Map 4
MUO CC398 infection in Denmark 2006–2015
N = 192
case
Map 5
LO CC398 infection in Denmark 2006–2015
N = 440
MRSA CC398 livestock contact

FIGURE 1 Place of living in Denmark (2006–2015) for each notified human case of (1) MRSA infection or carriage (red circles largest cities in Denmark; A: Aalborg (peninsula Jutland), B: Aarhus (Jutland), C: Odense (island of Funen), D: Copenhagen (capital, island of Sealand); (2) MRSA CC398 infection or carriage; (3) MRSA CC398 infection; (4) MRSA CC398 of unknown onset (MUO CC398) infection; and (5) livestock-onset (LO) MRSA CC398 infection

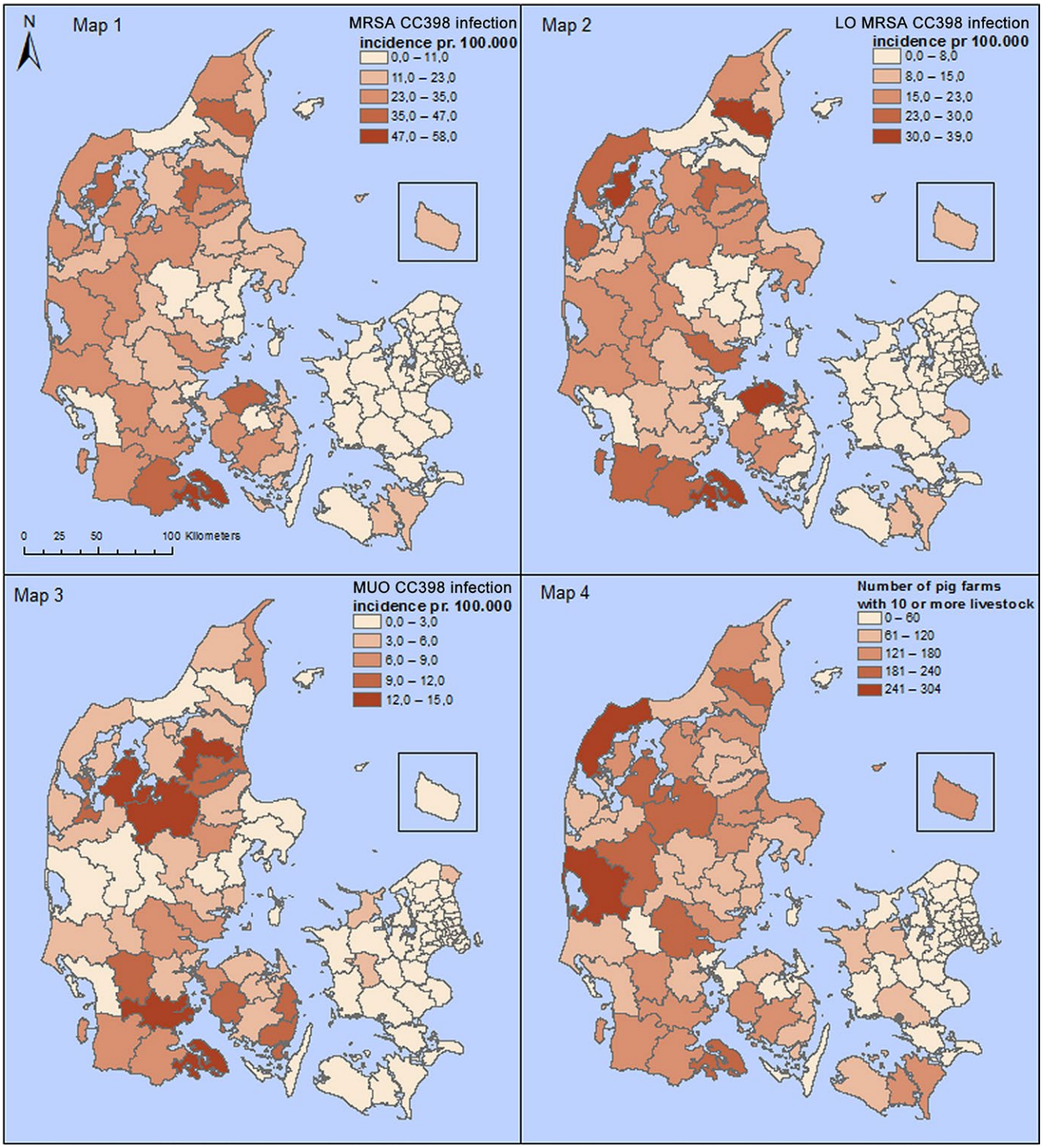

FIGURE 2 Maps 1–3: Incidence per 100,000 by municipality in Denmark (2006–2015) of human MRSA CC398 infection (Map 1); human livestock-onset (LO) MRSA CC398 infection (Map 2); human MRSA CC398 of unknown onset infection (MUO CC398, Map 3); and number of pig farms with 10 or more livestock (Map 4)

and 2,900 m for population controls; and to nearest clinical case of LO MRSA CC398 4,800 m for clinical MUO CC398 cases and 5,000 m for population controls) but the differences were smaller than for the country as a whole. In fact, none of the clinical MUO CC398 cases in the three municipalities lived any closer than 800 m to a LO MRSA CC398 case or a pig farm.

4 | DISCUSSION

This population-based study shows that the incidence of clinical MUO CC398 cases in Denmark is clearly higher in rural than in urban areas and that such cases on average live closer to pig farms than the background population. However, in municipalities with high densities of pig farms, such cases do not live closer to pig farms than the general population. The same applies to distance to nearest known case of LO MRSA CC398 that, like pig farms, represent a possible known source of environmental exposure of MRSA CC398. This information provides clues to the understanding of transmission of MRSA CC398 among residents of rural communities and will be discussed in the following.

As MRSA infection and colonization may be hospital-associated or community-acquired, domestically or abroad, it is not surprising to find high numbers of MRSA cases in the larger cities compared with rural areas, simply as a result of the higher population numbers in urban areas.

Likewise, given the well-known association between MRSA CC398 and contact with pigs (Huijsdens et al., 2006; Lewis et al., 2008), it is not surprising that a much smaller number of MRSA CC398 cases are seen in the major urban areas compared with rural areas. The different distribution patterns of MRSA in general and that of MRSA CC398 might reflect different screening activities in rural and urban areas. However, the distribution of clinical MRSA CC398 cases reflects that of MRSA CC398 in general. In Denmark, it is a common practice to do microbiological sampling in case of infection, irrespectively of place of living and livestock contact. Although we cannot completely rule out that sampling procedures may nevertheless vary though out Denmark, the findings indicate that MRSA CC398 truly occurs mainly in rural farming areas in Denmark.

In recent years, an increasing number of MUO CC398 cases has emerged. Possible routes of infection in such cases are unknown, and the emergence has caused a lot of concerns for public health. Some studies have found association between MUO CC398 cases and surrounding livestock density (Carrel et al., 2014; Casey et al., 2013; Feingold et al., 2012).

As MRSA CC398 is so closely related to pig farming, three explanations for clustering of MUO CC398 cases in livestock-dense areas seem likely: (i) direct, but unrecorded, livestock exposure; (ii) direct spread from farms through the environment (e.g., water effusion, downwind by dust and other particles, small animals and insects, or through manure); or (iii) spread in the community from livestock though known modes of transmission, including contact with colonized or infected persons, and to a lesser extent fomites.

We do not believe misclassification of exposure explains our findings. All MUO CC398 cases in Denmark are checked by personal contact between the Staphylococcal laboratory at Statens Serum Institut and the MUO CC398 case or the reporting doctor who is often the patient's family doctor with thorough knowledge of the patient and

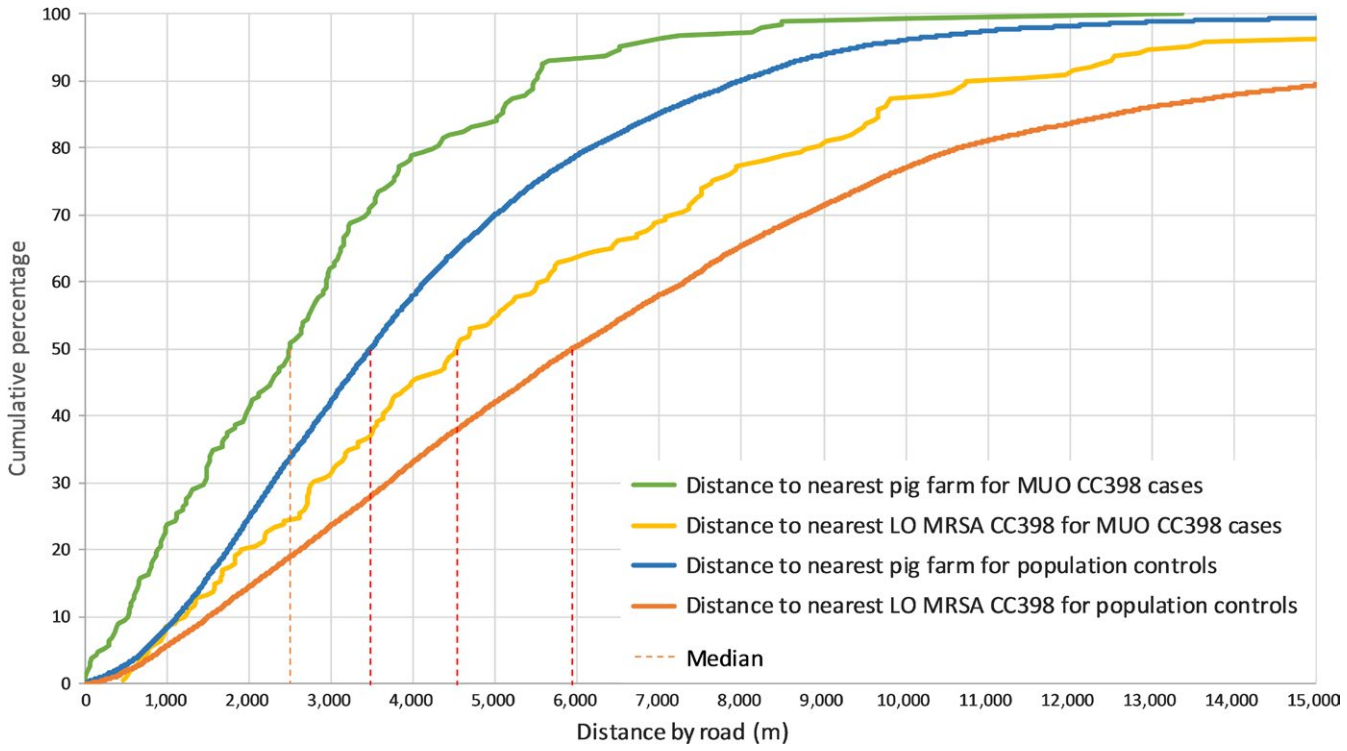

FIGURE 3 Cumulative percentage of distance by road to nearest pig farm and livestock-onset (LO) MRSA CC398 case for human MRSA CC398 of unknown onset infection (MUO CC398) and population controls, Denmark overall, 2006–2015

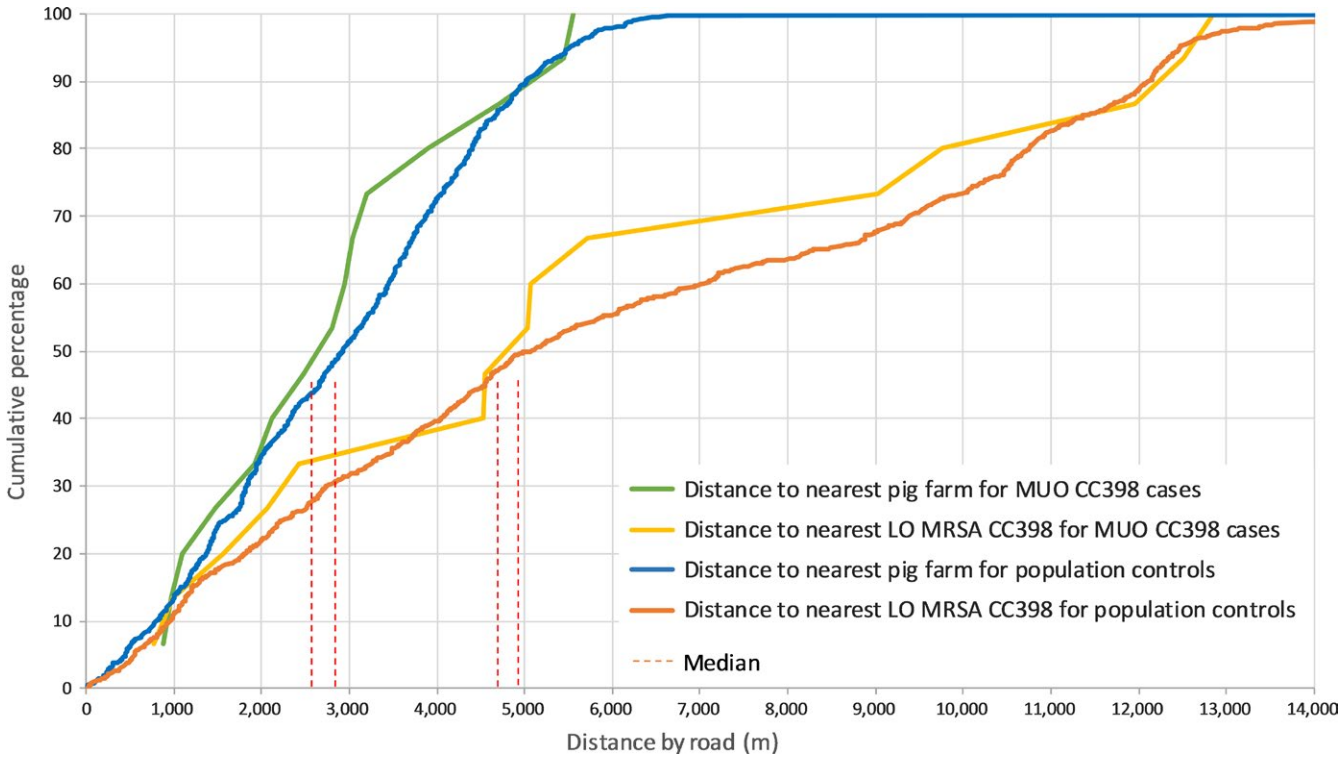

FIGURE 4 Cumulative percentage of distance by road to nearest pig farm and livestock-onset (LO) MRSA CC398 case for human MRSA CC398 of unknown onset infection (MUO CC398) and population controls, three pig-farming-dense municipalities in Jutland, west Denmark, 2006–2015

his/hers family, to ensure that the case is not misclassified. There is much awareness in Denmark of pig contact as a risk factor for MRSA CC398 acquisition, as, according to Danish regulations, a MRSA-positive person with regular contact with pigs will not undergo attempts to eradicate MRSA, unless for medical reasons, for example elective surgery. We therefore consider it unlikely that the reporting doctor would not report known livestock contact or contacts to persons with livestock contact.

Direct MRSA spread from pig farms may occur. Possible vectors include effluent and surface water run-off (Singer, Ward, & Maldonado, 2006), wind (Gibbs et al., 2006; Schulz et al., 2012) and/or manure (Friese et al., 2013; Friese et al., 2012). Resistant bacteria, both bacteria with multiple antibiotic resistance or multidrug resistance and LA-MRSA, have been found both in air in low concentrations and in soil at least up to 150 m downwind from barns with LA-MRSA (Gibbs et al., 2006; Schulz et al., 2012), with significantly lower bacterial concentration in soil upwinds than downwinds (Schulz et al., 2012). Indications of such direct spread are found by two studies that showed MUO CC398 cases to be concentrated in rural, livestock-producing areas (Feingold et al., 2012; Larsen et al., 2015), but these studies addressed distance to farms in zones only and not distance to farms on individual levels. Other studies have tried to account for this using an exact georeferenced residential address of each case (Carrel et al., 2014; Casey et al., 2013), but did not take into account direct contact with livestock or people with livestock contact, and did not report MRSA lineages. Thus, as persons who had actual pig contact might not have been excluded from these studies, it is not possible to determine whether the observed living distance in itself was associated with increased risk of MRSA CC398.

One recent study from the Netherlands screened 2,492 persons living in livestock-dense areas, but without living or working on a farm, for MRSA carriage, and found 10 to be carriers of CC398 LA-MRSA (Zomer et al., 2017). These lived significantly closer to the nearest farm than non-carriers. However, in contrast to our study, the Dutch study only included few MRSA-positive persons, addressed carriage while we addressed infection and included any type of farm while we only included pig farms. These methodological differences may explain the diverging results.

In contrast to most of the studies above, we determined MRSA lineage, livestock contact, as well as exact distance by road to pig farms on an individual basis for each case of MUO CC398. Hereby we found no significant difference in distance between MUO CC398 cases and controls within areas with high densities of pig farms, neither to nearest pig farm or nearest LO MRSA CC398 case. This suggests that for persons without livestock contact, but living within a pig-farming area, the actual distance to pigs or to nearest LO MRSA CC398 case does not increase the risk of MRSA CC398 infection.

This leaves spread in the community through other means of transmission than direct spread from farms as the most likely explanation for clustering of MUO CC398 cases in pig-farming-dense areas. The main *S. aureus* transmission route is through contact with a person who has a purulent lesion or is an asymptomatic *S. aureus* carrier, mainly in the anterior nares (Heymann, 2015). Hands are the most important vehicles for staphylococcal transmission that has also been demonstrated via fomites or through air. Human-to-human MRSA

CC398 transmission has been observed in hospitalized patients (Wulf et al., 2008), and a recent Dutch study showed that genetically, MRSA CC398 isolates from persons without known contact with livestock resembled LO MRSA CC398 as found in pigs, but not MSSA CC398 of human origin (Lekkerkerk et al., 2015). Therefore, an explanation for the increased occurrence of MUO CC398 observed in rural areas could be that transmission of MUO CC398 could take place by spread from MRSA CC398 carriers in their neighbourhood such as pig farmers, veterinarians, their household members and other occupationally exposed persons, rather than as an environmental spread from pig farms or households of MRSA CC398-positive persons. However, as the MRSA notifications did not render systematic information about other possible risk factors for MRSA infection including contact to actually MRSA-infected persons, we could not further characterize the increased risk posed by living in a pig-farming-dense area.

As MRSA CC398 is also found in other livestock than pigs, it might be of interest to estimate the risk of MRSA CC398 for persons living close to such farms. We cannot rule out that distance to such farms would pose a risk to humans. However, with the substantially higher proportion of pig farms infected than other types of farms in Denmark, we believe that pig farms represent the main source of livestock exposure for humans in Denmark. Distance to other types of farms was therefore outside of the scope of this paper.

What is the public health impact of these findings? Living in a pig-farming-dense area in itself seems to be a risk factor for MRSA CC398 infection, but the absolute risk is small as less than 15% of all cases and 30% of infections have community onset. Furthermore, community onset is not a function of living distance to nearest farm, and this may ease some of the concern that has been expressed by families who are neighbours to pig farms or live in a downwind direction. At present, the unknown size of risk associated with living in such an area makes firm public health recommendations a bit premature, but awaits further knowledge of precise risk factors for MRSA transmission.

The strengths of this study include a nationwide MRSA register with information of all known MRSA cases in Denmark since 2006; mandatory reporting of MRSA cases and molecular typing of MRSA isolates; and exact calculations of distances to pig farms and known cases of LO MRSA CC398 infections. We used a conservative estimate of MRSA CC398 infection by only including clinical cases that are less prone to screening bias. However, there are also weaknesses. As we used a clinical definition of MRSA CC398 infection, we cannot exclude that there could be difference in distance to nearest MRSA CC398 carrier for MUO CC398 cases than controls. However, this would imply different distributions of carriers and infected persons by pig-farming-dense areas which we consider unlikely. We did not estimate the distance to actually MRSA-infected pig farms, as we did not have such information at time of MRSA identification, but rather to any pig farm. This misclassification might affect the actual risk of MRSA CC398 associated with living close to a pig farm, but as the misclassification applies equally to cases and controls, we do not believe this biases our results. The number of clinical MUO CC398 cases in the three pig-farming-dense municipalities was limited (n = 15). However, this would mainly be an issue if there were differences in distances between MUO CC398 cases and controls (Figure 4). As there were no differences, we do not believe a higher sample number would change our findings. It could be argued that direct environmental spread of MRSA does not follow physical roads, but rather straight lines or environmental routes (streams, etc.). However, as people do not travel in straight lines but through infrastructure, distance by road better reflects contact patterns and thereby human exposure to known point sources of LO MRSA CC398 than air distance.

In conclusion, in this population-based study, we found that while more MRSA cases occurred in the larger cities compared with rural areas, MRSA CC398 cases were clearly more often seen in rural areas than in cities. Overall, clinical MUO CC398 cases without known pig contact lived closer to pig farms and known clinical cases of MRSA CC398 than population controls did, but within three pig-farming-dense municipalities, there was no such difference between cases and controls. This shows that direct environmental spread from neighbouring pig farms of MRSA CC398 is unlikely. Instead, spread in the community through other means of transmission than direct spread from farms may more likely explain the clustering of MUO CC398 in livestock-dense areas.

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