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SHORT REPORT
Proximity to animal or crop operations may be associated with *de novo* daptomycin-non-susceptible *Enterococcus* infection

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SUMMARY

Daptomycin-non-susceptible enterococci (DNSE) are emerging pathogens. We have previously reported *de novo* DNSE isolates in patients with agricultural activities and exposure to livestock. We studied the geographical distribution of the residencies of 34 patients with DNSE infections described in a tertiary centre over a 5-year period in an effort to explore the association between patients' residential locations and agricultural and farm lands. Nine patients had no prior exposure to daptomycin (*de novo*) and seven of these lived in areas with animal or crop operations. Of those living near an animal or crop operation, the mean number of operations in the proximity of the residence of patients with daptomycin-exposed DNSE was 13·8 (range 1–67) compared to 98·6 (3–529) for those patients with *de novo* DNSE ($P = 0{\cdot}0486$). These data are consistent with previous reports that the transport of daptomycin resistance genes between animals and humans may be a possible mechanism for development of *de novo* daptomycin resistance in enterococci.

Key words: Daptomycin, *Enterococcus*, non-susceptibility, resistance.

Daptomycin-non-susceptible enterococci (DNSE) are emerging pathogens [1] that may pose both treatment and infection control challenges [2]. We have recently reported DNSE infections that developed in the absence of any prior use of daptomycin therapy [1, 2]. Little is known about how these *de novo* DNSE infections develop or the risk factors associated with them. Determining risk factors associated with *de novo* DNSE infections will aid in understanding the mechanisms of daptomycin non-susceptibility. Development of daptomycin resistance in enterococci has recently been associated with mutations in genes encoding proteins involved in cell envelope homeostasis (LiaFSR system; putative histidine kinase YycG) and cell membrane phospholipid metabolism (glycerophosphoryl diester phosphodiesterase and cardiolipin synthase) [3]. We have recently suggested that transport of daptomycin resistance genes between animals and humans may be a possible mechanism for development of *de novo* daptomycin resistance in enterococci [4].

Zoonoses that can be transmitted from livestock to humans have increasingly been reported [5] and humans in contact with animals worldwide are at risk for carriage of multidrug-resistant bacteria [6]. Spread of these bacteria to humans from agricultural

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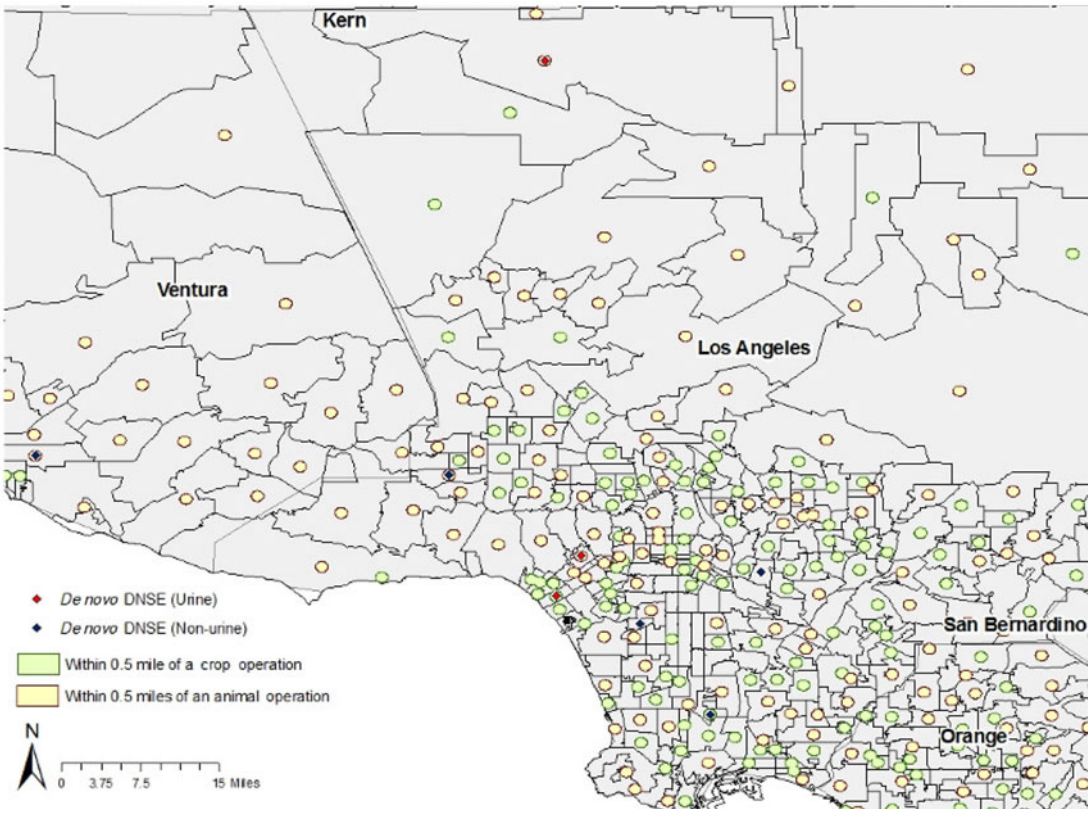

Fig. 1 [*colour online*]. Proximity of daptomycin-non-susceptible enterococci cases to animal and crop operations in Los Angeles County and vicinity.

practices via the food chain may be one mechanism by which DNSE are emerging [7, 8]. We have previously reported *de novo* and community-acquired DNSE isolates in patients exposed to agricultural activities and livestock [2].

Studying home address data from electronic medical records may provide useful epidemiological information regarding emerging infections [9]. We used this approach to study the geographical distribution of the residencies of 34 patients with at least one positive culture for DNSE described in a tertiary centre over a 5-year period (2007–2012) in an effort to identify an epidemiological link between these cases.

DNSE were defined by the criteria of the Clinical Laboratory Standards Institute criteria as enterococci with a daptomycin MIC >4 μg/m1 as determined by reference broth microdilution testing in cation-adjusted Mueller–Hinton broth (MHB) supplemented with 50 mg/l calcium [1]. Daptomycin non-susceptibility was also confirmed by Etest (bioMérieux, USA) on MHA (BBL, Sparks USA). Using the residential address zip codes of patients with DNSE infections, we explored the association between patients' residential locations and agricultural and farm lands, and examined their proximity to agricultural and farming activities. The U.S. Department of Agriculture (USDA)'s 2007 census data on the total number of animal and crop operations by zip code was used for the analyses [10]. ArcGIS 9·3 (ESRI, USA) was used to process patients' home addresses and USDA census data, and geocoded to state and county maps. Differences in agricultural and farming exposures between *de novo* and daptomycin-exposed DNSE cases were compared by Fisher's exact test.

Of the 34 patients with DNSE isolates, 25 had prior exposure to daptomycin and nine had no prior exposure to daptomycin (*de novo*); 26/33 (79%) patients who had addresses in the state of California resided in Los Angeles County. Twenty-one (84%) of 25 patients with prior daptomycin exposure and 7/9 (78%) patients with *de novo* DNSE infections lived in areas with at least one animal or crop operation. The latter group included three and four patients with urinary and non-urinary infections, respectively. For patients living near an animal or crop operation, the mean number of operations in the proximity of the residence of patients with daptomycin exposure was 13·8 (range 1–67) compared

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to 98·6 (3–529) for those with *de novo* DNSE ($P=0·0486$) (Fig. 1). To further compare any significant exposure to animal or crop operations (as defined by USDA) between the two groups, we focused our analysis on residences with proximity to >50 operations. Two (9·5%) of 21 in the prior daptomycin exposure group had lived in the proximity of >50 operations compared to three (42·9%) patients with *de novo* DNSE ($P=0·0825$). These data suggest that patients with *de novo* DNSE were significantly more likely to be exposed to an animal or crop operation than patients with daptomycin-exposed DNSE, due to the density of operations in the proximity of their residences. A proximity analysis of patients' residences using ring buffers of 0·5 miles around animal and crop operations [11] revealed that the 6/8 (75%) patients with *de novo* DNSE infections who resided in Los Angeles County lived within a half-mile radius of such operations.

To further investigate the significance of the association between *de novo* DNSE and residential proximity to an agricultural property, we compared the length of hospital stay prior to isolation of DNSE (defined as the time from admission to the hospital to the date of culture of DNSE) between patients with *de novo* DNSE isolates and those with daptomycin exposure. In 5/9 (55·6%) patients in the *de novo* group, DNSE was isolated on the first day of admission to the hospital whereas the median length of hospital stay for the remaining four patients (median 24 days, range 17–47 days) was significantly lower ($P<0·05$) than the median length of hospital stay for the 25 patients with daptomycin-exposed DNSE (median 89·5 days, range 10–230 days). These data are consistent with possible acquisition of the majority of the *de novo* DNSE isolates from the community. However, for four cases with *de novo* DNSE isolates hospital exposure or hospital transmission may be more likely especially since the duration of hospital stay prior to isolation of DNSE was more than 1 week in these cases. Although two of the patients with *de novo* DNSE had not been previously hospitalized or seen a physician [2], nosocomial acquisition of DNSE for most patients cannot be entirely ruled out due to lack of information on enterococci from other clinical sites that may have previously colonized the patients and persisted for years [12].

Linkage of patient home addresses from electronic health records to USDA's census data may provide useful information for the epidemiological investigations into potential sources of emerging infections such as DNSE and may facilitate early identification of community-acquired *de novo* DNSE infections. Due to the limited number of these cases, the study was underpowered to show an association between exposure to animal and agricultural activities and *de novo* DNSE infection. Further, our study is limited by the retrospective observational design, the small number of cases, and the lack of a comparator group. Nonetheless, our data showed that the 78% of *de novo* DNSE-infected individuals lived in areas with animal or crop operations and this may be consistent with previous reports that suggest the transport of daptomycin resistance genes between animals and humans may be a possible mechanism for development of *de novo* daptomycin resistance in enterococci [2, 4].

Consistent with our hypothesis that *de novo* DNSE may have been transmitted to humans in the setting of agricultural exposures, daptomycin resistance genes such as an inducible daptomycin hydrolase were recently found in a culture collection of isolates from an ecosystem that has been isolated for over 4 million years [13]. We have also identified nucleotide mutations in DNSE isolates in genes that have also been described in many soil bacteria [14]. The potential development of environmental reservoirs of antibiotic resistance in farmland is concerning and transfer of resistance between soil bacteria and enterococci has previously been documented [15].

Linkage of readily available patients' residence addresses from electronic health records to USDA's animal and agriculture census data provides promising opportunities for use in the epidemiological investigations into potential sources of emerging infections such as DNSE. This information may form the basis for further studies that could possibly facilitate early identification of community-acquired *de novo* DNSE infections.

DECLARATION OF INTEREST

None.

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