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# Livestock associated MRSA: What are the risks to human health?

Peter Davies, BVSc, PhD; , DVM
Department of Veterinary Population Medicine, University of Minnesota

Methicillin resistant *Staphylococcus aureus* (MRSA) was first isolated from people in 1961 and rapidly became endemic in hospitals in many countries (hospital associated MRSA, or HA-MRSA). Later, in the 1990s, MRSA emerged worldwide to become a prevalent cause of infections in the general community (termed community associated MRSA, or CA-MRSA). Clones associated with hospital infections have generally been different from clones involved in infections in the general community, and different clones have been predominant in different geographical regions.[1,2]

MRSA were first isolated from animals (cattle with mastitis) in 1972. However, prior to 2004 animals were not considered to have any significant role in the epidemiology of MRSA in humans. Increasingly frequent reports of MRSA in livestock and other animals have raised concerns about animals as reservoirs of MRSA.[3] The term "Livestock associated MRSA" (LA-MRSA) is applied to a lineage of closely related MRSA isolates first identified in three people in Holland with exposure to pigs.[4] These previously unrecognized strains belonged to a new MLST sequence type, ST398.[5] An industry survey found 39% of pigs slaughtered in Holland were positive for ST398 MRSA, including three spa types within the ST398 lineage. This led to considerable research into ST398 MRSA in animals and humans in Holland, and to surveys for MRSA in pigs and other livestock in many countries.[6]

It is now established that MRSA colonization of healthy pigs is prevalent in many countries including the USA and Canada, although prevalence in North America appears to be relatively low compared to many European countries.[7-9] ST398 MRSA are typically the predominant lineage detected in swine populations in Europe and North America, though different patterns have been reported in studies from Asia.[10-13] Apart from two reports of outbreaks of exudative epidermitis in pigs,[14,15] the organisms appear to be of negligible concern for swine health.[16] Where ST398 MRSA is prevalent in livestock, people with occupational exposure to live animals (especially farmers, veterinarians, abattoir workers and their families) are at elevated risk of MRSA *colonization*, and therefore possibly infection, compared to the general population.[4,17-21]

Community-based studies in swine-dense rural areas of both Germany and Holland found that exposure risk is largely limited to people having direct contact with pigs and their immediate families, and did not extend to the adjacent communities.[17,21] There has yet to be a community based outbreak of ST398 infection reported from any country, and two reports of hospital associated "outbreaks" were of small scale and predominantly involved asymptomatic carriage and contamination of superficial wounds. Evidence to date indicates the health risks associated with ST398 organisms *of livestock origin* are largely restricted to people with direct animal contact and their immediate families.

## What has been the public health burden of LA-MRSA?

With support from the National Pork Board, published studies of ST398 *S. aureus* were compiled in a Refworks database and reviewed, focusing on reports of human clinical disease. The review did not assess studies reporting colonization alone (i.e., culture positivity in the absence of disease), but attempted to identify all published information related to clinical infections with ST398 organisms [both MRSA and MSSA (i.e. susceptible to methicillin)]. Eighty three papers or reports were identified to contain information on ST398 associated clinical cases in humans, including several where most isolates were from screening samples rather than lesions. For each report, the following information when available was recorded: country; numbers of isolates that were from screening swabs; numbers of isolates that were from clinical infections; clinical presentations (e.g., bacteremia; pneumonia; skin or soft tissue infection;…); invasiveness (number of cases with invasive infections, i.e. not skin or soft tissue infections); history of animal contact; and number of fatalities. Cases were deemed invasive if reported as bacteremia or pneumonia, or if isolates were obtained from sites other than skin or soft tissue infections (e.g., urine, sputum isolates). This conservative interpretation is likely biased towards overstatement of counts of invasive disease. The studies reviewed reported 2,213 events of positive screening (isolates not linked to infection) and 495 isolates from

humans with clinical infections. Of these, 89 cases were deemed invasive, and 5 fatalities were documented. Clinical presentation was not described for 213 (43.7%) of the clinical infections mentioned in these studies. More than half of the specified presentations were skin or soft tissue infections, or infected wounds.

Some European studies have not distinguished clearly between events of colonization and clinical infection,[22] and thus there is a lack of quantitative information about the actual clinical risks associated with livestock exposures and colonization with ST398 MRSA. A small number of reports of severe or fatal systemic infections with ST398 *S. aureus* have spawned inferences that organisms of this lineage can be serious human pathogens.[23-26] However, analysis of two years of data for a laboratory serving an estimated population of 800,000 people in a pig dense area in Holland identified 30 'clinical' ST398 isolates, of which 6 were pneumonia or systemic infection (1 blood, 3 sputum, 2 urine). These data suggest an annual risk of approximately 2 clinical infections (and 0.38 invasive infections) per 100,000 people.[27]

Studies assessing the relative importance of ST398 infection in human *S. aureus* disease in Europe found significantly lower incidence of systemic infections with ST398 cases. A survey including 24 laboratories in 17 countries in Europe in 2007 found ST398 MRSA accounted for only a small proportion of MRSA isolates from humans in 2007, with most cases identified in the Netherlands, Belgium, Denmark, and Austria.[28] Furthermore, ST398 isolates were significantly less likely to be found in cases of systemic disease compared with other MRSA. A larger study of 357 laboratories serving 450 hospitals in 26 countries collected 2,890 MSSA and MRSA isolates from patients with invasive *S. aureus* infection.[29] This study found no cases invasive infections with ST 398 MRSA. However, MSSA isolates of the ST398 lineage were found in 12 invasive cases. The most recent DANMAP report (2010) from Denmark identified 11 (0.8%) of 2,418 *S. aureus* bacteremia cases were caused by ST398, but again all were MSSA and association with pig farming was unknown.[30] All these studies include countries where ST398 MRSA are known to be prevalent in swine, and indicate relatively low contribution of LA-MRSA to the burden of human disease. Also, patients with ST398 MRSA, versus all other MRSA, had significantly shorter length of stay in hospitals (7 days versus 13 days) and were less likely to be admitted to intensive care units.[31] Three studies assessing the transmissibility of ST398 among people at hospitals consistently found lower transmission risk for ST398 compared with common human MRSA isolates.[32-34] The conclusion from one study was that the transmission risk of ST398 may be too low to support an outbreak.[33] In terms of health related costs due to ST398 MRSA, the most significant impact has been in Dutch hospitals where the 'search and destroy' policy mandates isolation and treatment of patients found to be culture positive for MRSA. In the wake of the discovery of LA-MRSA in Holland, a policy of screening of livestock workers as "high risk" individuals (farmers) has taxed hospital infrastructure for managing patients who are colonized with MRSA.[32-35]

Some spa types (t571, t567) of ST398 appear to occur more commonly among human clinical isolates than livestock isolates[27, 36-38] raising the possibility that different ST398 sub-types may vary in their ability to colonize and/or cause disease in humans. Notably, spa type t571 ST398 MSSA was detected in residents of Manhattan, NY, who had no known contact with livestock.[39] Spa type t571 was also the predominant (11%, 17%) MSSA type in 2 Chinese studies at a Beijing hospital, again in the absence of apparent livestock exposure.[40,41] More recently, a study of t571 MSSA strains from cases of bloodstream infections in France determined that these isolates differed from 'pig-borne' strains and shared similarities with Chinese strains from humans and virulent USA300 strains.[42] There is growing evidence that ST398 strains of diverse genotype and geographic origin may also be epidemiologically distinct with respect to host adaptation and virulence.[43]

To date, there have been 5 reported fatalities associated with ST398 *S. aureus*. In 4 of these cases, the organisms were t571 MSSA with no known livestock contact. The other case was t011 MRSA and the patient had indirect contact with pigs. However, this elderly patient suffered from lung carcinoma and chronic obstructive pulmonary disease.[44] Other than infected bite wounds, reports of medically significant ST398 MRSA infections in healthy livestock workers are remarkably scarce and livestock contact is a notably inconsistent feature of invasive ST398 infections. Current information suggests serious *S. aureus* infections (invasive and/or fatal) have been more often associated with ST398 variants of MSSA that are not directly related to livestock exposure, than to MRSA strains prevalent in livestock.

Information on human disease associated with ST398 MRSA is sparse in North America than Europe. A retrospective assessment of 3,687 MRSA clinical isolates in Canada identified only 5 cases with ST398 MRSA, 4 of which presented with skin or soft tissue infections.[45] The CDC has examined over 12,000 U.S. isolates and is yet to identify ST398 among human clinical isolates (Dr. Brandi Limbago, personal communication). Similarly, in the hog dense state of Minnesota, the MN Department of Health has tested over 7,000 clinical isolates of MRSA with *sma*1 PFGE (inability to type isolates with *sma*1 is a characteristic of ST398 lineage) and is yet to identify an 'untypable' isolate (Dr. Kirk Smith, personal communication). Given

the known presence of ST398 in the North American swine industry, and the sporadic reports of clinical infections in swine workers in Europe, it is likely that some clinical infections may have occurred in occupationally exposed individuals in the U.S.A. The absence of reported cases until now in the U.S.A. is likely attributable to both a low incidence and low severity of ST398 infections.

## Are LA-MRSA relatively avirulent?

The modest burden of serious clinical infections thus far linked to ST398 MRSA (particularly in groups with frequent occupational exposure), together with apparently reduced risk of invasive disease, suggests that LA-MRSA may be less virulent than common HA-MRSA and CA-MRSA clones. This hypothesis is supported by several studies of known *S. aureus* virulence determinants in LA-MRSA. Full genome sequencing of a single ST398 isolate (spa type t011) from a non-fatal case of human endocarditis in a transplant patient found the isolate lacked several virulence factors (enterotoxins, and phage encoded toxins including Panton-Valentine Leucocidin toxin). The authors suggested that the absence of major virulence factors may explain the relative infrequency of serious clinical infections with ST398 MRSA.[46] A larger study of 100 ST398 isolates from various sources (healthy carrier and diseased pigs, dust from pig farms, milk, and meat) in Germany examined 37 virulence and 31 resistance determinants.[47] A high number of resistance determinants and a low number of virulence factors were identified and the authors speculated that the lack of virulence determinants could be attributable to limited interaction of livestock adapted strains to more pathogenic bacteria common in hospitals. A Belgian study comparing 18 ST398 isolates with CA-MRSA (21) and HA-MRSA isolates found the accessory genome content of ST398 strains lacked human-associated virulence and adhesion determinants. The authors also noted that the absence of enterotoxin genes among ST398 LA-MRSA strains pointed to their likely insignificance with respect to risk of foodborne enterotoxicosis.[48]

## Foodborne risks

Foodborne staphylococcal enterotoxicosis ("food poisoning") is an important disease caused by S. *aureus* toxins ingested in food. However, staphylococcal food poisoning is not an infectious process, antimicrobial treatment is not indicated for treatment, and therefore the antimicrobial resistance of foodborne *S. aureus* is of no clinical relevance in this disease. Risk of staphylococcal "food poisoning" is a function of the ability of staphylococci to produce enterotoxins. Current evidence indicates negligible foodborne risk due to ST398 *S. aureus* in meat because the rare occurrence of enterotoxin genes in ST398 isolates (although enterotoxin positive ST9 isolates were reported from Thailand). A Swiss study reported the complete absence of overlap of spa types causing staphylococcal food poisoning in people and spa types of isolates from pork carcasses or bovine mastitis, concluding that neither milk nor pork are common causes of enterotoxicosis.[49] Therefore the major concern with ST398 MRSA in the food supply relates to the potential risk of pork (or other animal products) as mechanical vehicles for transmission of MRSA to consumers handling the products.[50]

There are several reports of showing that ST398 MRSA can occur in meat products including pork,[51-53] with high prevalence (11% of pork; 35% of turkey meat) reported in one study in Holland.[54] In a Canadian study where a MRSA prevalence of 5.8% was reported in pork, the predominant spa types were common human MRSA strains and ST398 were not detected despite their predominance among Canadian swine isolates.[55] Other North American studies to date have similarly shown that ST398 *S. aureus* constitute a minority of *S. aureus* isolates in retail pork. The relative contribution of pigs, compared with other sources (particularly people) in the abattoir and meat processing chain, to contamination of retail pork with MRSA remains uncertain and may vary among countries.

Like swine farm workers, slaughter plant workers with live animal exposure are at elevated risk of colonization with ST398 MRSA.[20] MRSA was not detected in professional meat handlers despite their exposure to contaminated product.[19] A report from the European Food Safety Agency concluded that the risk from contact with contaminated food appears to be small, and certainly much reduced from that associated with contact with live animals or humans.[57] The DANMAP 2010 report inferred that "the relatively frequent occurrence of MRSA in meat combined with very few cases in urban areas makes it safe to conclude that there is very little if any risk for meat being a risk for contracting MRSA CC398".[30] Relative to the high rates of exposure to ST398 for people occupationally exposed to live animals, the theoretical (but likely non-zero) risk of exposure of consumers via the food chain is arguably trivial. As suggested by Weese *et al* (2010),[55] "standard recommendations for handling and cooking raw meat should greatly reduce if not eliminate the risk of transmission of MRSA, just as proper cooking and food handling should reduce or eliminate the risk of enterotoxin-associated gastroenteritis."

## Summary

The apparently recent emergence of ST398 MRSA in livestock populations in many countries is a valid cause of consternation, and the public health implications need to be better understood. However, in approximately seven years since being first recognized, the burden on human

health has been minor, and the risk of exposure to these organisms is overwhelmingly concentrated in people with occupational exposure to livestock. Available data indicate that ST398 MRSA are less transmissible among people, and also may be less virulent. Risks to people without direct livestock contact appears to be minimal, even in pig dense communities, and foodborne disease risk also appears to be negligible. The observation that some ST398 variants may circulate in humans independent of livestock reservoirs (particularly t571 MSSA) requires further investigation. Quantifying the occupational health risks in livestock workers, and education of these groups about proper management and treatment of wounds should be the main priorities for the immediate future.

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