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Methicillin resistant *Staphylococcus aureus* in pigs and people – a story unfolding

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Introduction

Staphylococcus aureus is a ubiquitous commensal organism found on the skin and mucous membranes of homeothermic species. It is also an opportunist pathogen causing superficial or invasive infections in many species. Approximately 20% of people are persistently colonized; 60% are intermittently colonized; and another 20% are rarely colonized.^{1,2} Recent national estimates reported prevalences of 31.6% and 0.84% of colonization with *S. aureus* and methicillin resistant *S. aureus* (MRSA) respectively, suggesting that around 3 million Americans are colonized with the resistant organism.³ Methicillin resistance in *S. aureus* is encoded by the *mecA* gene, which is located on a mobile genetic element called the Staphylococcal Cassette Chromosome *mec* (SCC*mec*). This gene encodes a penicillin binding protein (PBP2a) that has a low affinity for beta lactams and confers resistance to all beta lactam antibiotics (e.g. penicillins, cephalosporins). MRSA infections are a major clinical problem in hospitals and in recent years infections acquired outside hospitals (i.e. ‘community acquired’) have increased in importance worldwide. While media reports tend to portray infection with MRSA and other ‘superbugs’ as a virtual death sentence, the magnitude of the increased risk to patients is not often clearly reported, and infections with methicillin susceptible *S. aureus* (MSSA) can be fatal. Two meta-analysis studies found that the risk of mortality due to invasive MRSA infections was approximately twofold that seen with invasive MSSA infections.^{4,5}

Until recently, accepted medical wisdom held that the epidemiology of transmission and antimicrobial resistance of MRSA were essentially confined to the human arena, and that animal reservoirs (and associated antimicrobial use) were of negligible importance. However, the increasing rate of reports of MRSA in animals and of animal-to-human transmission have undermined this view.^{6,7} Recognition that domestic animals can act as reservoirs of MRSA has occurred concurrently with a rise in incidence of community acquired MRSA infections, prompting concerns about the importance of non-human species in the changing epidemiology of MRSA in people. Since the initial implication of pigs in MRSA cases in Holland, studies from several countries have shown the MRSA occur commonly found in the nasal cavities of pigs and people who are occupationally exposed to pigs.

In Holland it is estimated that swine farm workers are 760 times more likely to be colonized by MRSA than members of the general public (although comparison of infection risks are thus far not reported). Furthermore other livestock, particularly horses and cattle, are also implicated in the epidemiology of MRSA. Predictably, alarmist reactions have ensued in media articles on both sides of the Atlantic. However, some scientific publications raising concerns about a coming epidemic of livestock associated MRSA,⁸ and there is an urgent need for better understanding of the epidemiology of MRSA in livestock and of its implications for human health, particularly with respect to occupationally exposed people.

The state of play

As of July, 2008, all published investigations of MRSA in pigs, pork producers, or veterinarians have reported MRSA to be present, and the prevalences observed have been consistently high enough to raise concerns.⁸⁻¹⁵ The majority of reports are from Europe, where remarkably only one strain of MRSA (MLST type 398; PFGE untypable) has been found in pigs (and occupationally exposed people). The sole peer reviewed study of pigs and pork producers in North America,¹⁴ yielded prevalence data (45% in pigs; 20% in farm workers) similar to those seen in Holland and more recently in Germany,^{13,15} but a broader range of MRSA subtypes were found. Studies of veterinarians have consistently reported prevalences of MRSA that are higher than those reported in the general population. This has been observed in equine, swine and companion animal veterinarians.¹⁶⁻¹⁹ Furthermore, MRSA has also been demonstrated on pork products,²⁰ attracting attention from consumer advocates about the potential for foodborne transmission.

The key observations to this point are:

- Prevalence of MRSA in pigs may be of the order of 40% (Holland, Canada) but was lower in a small study in Germany
- Prevalence of MRSA in pig farm workers has been consistently of the order of 20% or more, considerably higher than in the general population.
- Prevalence of MRSA in veterinarians of the order of 10%

- In Europe, only the ST 398 clone has been associated with livestock (cattle and pigs). In Canada, although this clone predominated (75%) among swine isolates, several other subtypes were identified.
- Clinical cases, including a small number of severe infections, have been reported with the livestock ST398 clone in Europe. As yet there are no reports of fatal cases linked to this organism.
- Contamination of pork with MRSA has been shown. The Dutch authorities have concluded that foodborne risk is negligible and the major public health concern relates to occupational exposure.

As yet, there are no published peer reviewed studies from the USA, but a number of studies are underway. Dr. Tara Smith of the University of Iowa has reported preliminary data demonstrating that MRSA closely related to ST 398 were prevalent in pigs and in farm workers in Iowa. We are conducting a study of MRSA prevalence in slaughtered pigs, swine veterinarians and retail pork samples. The survey of swine veterinarians has been completed and 8 (7.1%) positive culture results were obtained from 113 swine veterinarians attending AASV in 2008. Six (7%) positive results were obtained from 87 US swine veterinarians, and 2 from 26 veterinarians from other countries. Based on spa typing, 5 of the 8 isolates were closely related to the ST 398 'livestock associated' MRSA clone that appears to be widespread in the Dutch and Canadian swine industries. Three of these were isolated from US veterinarians (n = 87) from 3 different states, and the other 2 from Canadian veterinarians (n = 23). Together with a Dr. Smith's report of this organism in Iowa, these findings indicate that the main livestock associated subtype of MRSA found in Europe and Canada is present in the US industry. Data from our ongoing swine and retail pork studies will be presented at the conference. Dr. Scott Weese at Ontario Veterinary College is studying retail pork in Canada and has found a prevalence of contamination of the order of 10%. These collective findings have spawned some media interest and brought calls for government efforts to test meat samples for MRSA.²¹

How concerned should we be?

The 'superbug' status of MRSA, and the paucity of knowledge of its epidemiology in food animal populations, create conditions apt to generate considerable public concern which may or may not prove to be warranted. The ST 398 strain appears to be adapted to pigs but can also colonize and cause infections in humans, dogs, and horses.¹² Although ST 398 is widespread in pigs in Holland, it is important to recognize that Holland has one of the lowest rates of MRSA in the world, and that the public health risk associated with this particular clone remains to be quantified. However, it seems unequivocal that pig exposure increases the risk of colonization of people

with selected strains and that these strains are capable of causing clinically significant disease. The role of antibiotic use remains uncertain. Although these isolates have been almost uniformly resistant to tetracyclines, a study of 65 'pig associated' MRSA in Holland found all isolates were sensitive to vancomycin, teicoplanin, nitrofurantoin, rifampicin, linezolid, and quinupristin-dalfopristin, with variable sensitivity to erythromycin (40%), clindamycin (48%), cotrimoxazole (48%), aminoglycosides (92%), and quinolones (94%).²²

Although MRSA has been found in retail pork products, the Dutch authorities have assessed that foodborne transmission is of negligible importance. However, this has not deterred calls in the United Kingdom for 'quarantining' or testing imported meat, and similar suggestions were floated in the US media.^{22,21} Concerns about foodborne risk have been reinforced by the first report of a 'life threatening' infection with the 'pig' ST 398 MRSA-strain in a 63-year-old Dutch woman who was not exposed to pigs, suggesting indirect (possibly foodborne) routes of transmission.²³ Similarly, 3 ST398 cases in Scotland in people without pig contact have been proffered as cases of foodborne infection with no direct evidence and ignoring the real possibility of alternate sources of exposure.²¹ It should be noted that staphylococcal food poisoning is one of the most common foodborne diseases throughout the world, but is a toxin mediated illness in which antibiotic treatment is not used (therefore MRSA and MSSA may be considered of equivalent medical concern in foodborne exposures). Cooking will destroy *S. aureus*, and the principal risk related to products is likely to be handling of raw product in the kitchen.

Much remains to be learned about MRSA in pigs, its consequences for human health and the extent to which antimicrobial use in livestock has contributed to the current situation. Some of the key questions are:

- Is this truly an emerging phenomenon (as believed in Holland), or discovery of a situation that has been established for some time?
- What is the relative importance of animal reservoirs and animal to human transmission of MRSA to the changing epidemiology of human MRSA (particularly the increase in community acquired disease)?
- What is the role of antibiotic use in food animals and companion animals in the epidemiology of MRSA in animal reservoirs?
- Can altered patterns of use lead to a meaningful reduction in MRSA exposure in farm workers?
- What is the risk of farm-to-table foodborne transmission of MRSA via meat?

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