

Methicillin Resistant *Staphylococcus aureus* (MRSA)

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■ What is MRSA?

“MRSA” is a short form for Methicillin Resistant *Staphylococcus aureus*. In the media, MRSA is often described as a “superbug”. It is definitely a serious human health issue that is evolving from a problem confined to hospitals to a much more general concern and certainly deserves attention. A recent study estimated that there were over 94,000 invasive MRSA infections in the United States in 2005, with over 18,000 deaths (Klevens et al, 2007).

Staphylococcus aureus is found almost everywhere, particularly on the skin and mucous membranes of animals, including humans. It is estimated that about 60% of the human population are colonized by *S. aureus* from time to time and as high as 20% of humans are persistent carriers. The nose is a favorite site for the bacteria to survive but it can live on skin and in the environment for relatively long periods of time. Whether *S. aureus* is susceptible to methicillin (an antibiotic) or resistant to methicillin and other antibiotics, it can cause superficial skin infections and on occasion can cause invasive and serious disease. As is the case with most of the common bacterial pathogens, animals or people with compromised immune systems are much more susceptible to the serious invasive form of infection.

Another common health concern associated with *S. aureus* is foodborne illness related to improper handling and storage of food and the production of heat stable enterotoxins by certain strains of *S. aureus*. These health issues, both the vomiting and diarrhea from Staphylococcal toxins in food and the wound infections, have long been recognized. Likewise, the problem of *S. aureus* being resistant to antibiotics (MRSA) has also long been recognized and has been considered in human medicine to be primarily a problem of hospitals, until recently. The problem of antibiotic resistance associated with *S. aureus* and how resistant strains of the bacteria are spreading outside the

hospital setting is a new concern of public health workers and it is this aspect that has caused some focus to be placed on pigs.

■ Antimicrobial Resistance

In the 1950s it was recognized that many strains of *S. aureus* produced penicillinases, making them resistant to penicillin. Methicillin was developed partly to solve this problem of bacteria being resistant to penicillin. Methicillin became available in the late 1950s and almost immediately it became the antibiotic of choice to treat penicillin-resistant staphylococcal infections. By 1961 reports of methicillin resistance began to appear (Barber, 1961) and during the 1970s MRSA emerged as a serious problem in some hospitals in the USA and by the 1990s MRSA in hospitals was a worldwide problem. Resistance is commonly mediated by the *mecA* gene which encodes for a protein binding protein (PBP2a). The whole family of antibiotics referred to as beta-lactams including penicillin, methicillin, and even cephalosporins are rendered ineffective if the bacterium possesses the *mecA* gene. The traditional risk factors associated with acquiring MRSA infection have been: prolonged hospitalization, prolonged antimicrobial therapy, surgery, close proximity to other patients with MRSA. Recently, MRSA colonization has been identified in people who have had no known association with hospitals or the other risk factors. These cases of MRSA have been identified as community-acquired (CA) MRSA, as opposed to hospital-acquired (HA) MRSA.

■ Animals as a Source of Human MRSA

Animals have been identified as one source of CA-MRSA. The first isolation of MRSA in animals was from a cow with mastitis (Devriese et al, 1972). It is now recognized in Europe that people who work with cattle are many times more likely to be colonized with MRSA than the general population. Pets have long been known to be a source of MRSA (Scott et al, 1988, Smith et al, 1989, Cefai et al, 1994) and it appears that owners can infect their pets and then the pets infect other people or re-infect their owners. More recently, horses have been recognized as a source of MRSA (Sequin et al, 1999). The most common type of MRSA isolated from horses appears to be distinct from the usual CA-MRSA of people and it is thought that there is a horse-specific MRSA strain that spreads amongst horses but does occasionally infect people who handle the infected horses. In addition, as in the case of dogs and cats, humans can pass on CA-MRSA to horses.

MRSA colonization in pigs was first reported in the Netherlands where pigs were implicated as a source of human MRSA infections (Voss et al, 2005). In all likelihood the reason that the Dutch were the first to identify MRSA in pigs

was because of their very diligent efforts to eradicate MRSA from their hospitals through extensive screening programs. Investigation of 'unexpected' CA-MRSA infections in pig farmers and veterinarians, and their families, led to investigation of MRSA colonization of pigs and their human contacts. One pig was identified as carrying an MRSA strain indistinguishable from the one that caused an infection in a pig farmer's family, and it was subsequently reported that a high percentage (23%) of pig farmers in the region were carrying MRSA in their nasal cavities. This 23% rate was astounding for a country where CA-MRSA colonization rates are extremely low (<0.1%).

Interestingly, a distinctive characteristic of MRSA strains recovered from pigs is that they are not typable by pulsed field gel electrophoresis (PFGE), a common typing technique (Bens et al, 2006). For that reason, *spa* typing, which involves sequencing of the X region of the protein A gene, is commonly used. A variety of *spa* types have been isolated from pigs and their human contacts, however the majority of those *spa* types are classified as sequence type (ST) 398 by multilocus sequence typing (MLST), suggesting that ST398 strains are somehow more adept at colonizing pigs and can be transmitted between pigs and their human contacts. It is now thought that ST398 *S. aureus* is truly a pig (or food animal) origin strain.

Subsequently, ST398 MRSA has been identified in pigs in France, Denmark, Singapore, Canada and the United States. Prevalence data are variable but tend to indicate high colonization rates. A study of pigs from various types of farms in the Netherlands reported colonization of 11% of pigs (van Duijkeren et al, 2008). Slaughterhouse sampling identified colonization of 39% of pigs in another study in the same country (de Neeling et al, 2007). Eight of ten pigs associated with a cluster of human infection or colonization in the Netherlands were colonized. In those studies, all isolates were ST398 (Huijsdens et al, 2006).

We performed a study in Ontario to determine whether MRSA could be found in pigs and pig farmers (Khanna et al, 2008). In our study, MRSA was isolated from pigs on 45% of farms, with an overall pig prevalence of 25%, and ST398 was the most common strain. However, other strains were also found, including a common human strain, suggesting that MRSA can move in both directions between pigs and humans. Preliminary results from a US study reported MRSA carriage by 70% of pigs on 7 farms that were part of the same production system (Smith et al, 2008). All isolates were non-typable by PFGE, suggesting that they were ST398.

■ MRSA in Pork

While having contact with pigs (or cattle) is a significant risk factor for ST398 infection or carriage, infections can occur in people without animal contact (van Loo et al, 2007a). The spread of ST398 in humans and high prevalence of carriage in pigs has led to concerns about MRSA in food, and contamination of retail meat has been reported. A study of retail meat in the Netherlands reported isolation of MRSA from 3% of pork and 0% of beef samples, with ST398 accounting for 1 of the 2 pork isolates (van Loo et al 2007b). An Italian study reported 6 MRSA isolates from pork, however, the sampling methodology was unclear and no information regarding prevalence was presented (Simeoni et al, 2008).

A pilot study of retail pork from Canada identified MRSA in approximately 4% of samples (JS Weese, unpublished data). Interestingly, the most common strains found in pork in the Canadian study were not those that have been predominantly found in pigs, at least in the preliminary Ontario and US studies, raising questions about whether MRSA contamination of pork is actually from pigs or is from human sources during processing. Broader studies of pigs in more regions of North America are ongoing to determine whether there is more diversity in strains found in pigs and help identify possible sources of contamination. A weakness of preliminary studies of retail meat is the use of unvalidated and potentially very sensitive enrichment methods that could detect very low levels of MRSA. Methods to determine the actual numbers of MRSA in contaminated pork are needed, and these studies are ongoing.

There are two main concerns about food contamination. One is regarding development of enterotoxin-associated food poisoning, which is independent of whether the *S. aureus* is resistant to antibiotics. MRSA food poisoning has been reported (Jones et al, 2002) but is rare and should be no different with enterotoxin-producing strains of MRSA versus methicillin-susceptible *S. aureus*. Perhaps a greater concern is the potential for food as a source of MRSA colonization, whereby people contaminate their hands when handling food or improperly disinfected surfaces and inoculate themselves with MRSA. An additional potential concern is a risk of infection through contact of contaminated meat with open sores or following cuts during meat preparation.

The real risk of food as a source of MRSA is unknown. Proper evaluation of this requires more information on the prevalence of MRSA in pigs in North America, the types of MRSA in pigs in North America, the prevalence of MRSA in retail pork, the types of MRSA in retail pork and the degree of contamination of positive samples. It is possible, if not likely, that MRSA contamination of pork is often human-in-origin and occurs during processing. It is also possible that the amount of MRSA contamination is low, which would

decrease the relevance of simply finding MRSA. In contrast, if the prevalence of meat contamination is high and/or evidence is discovered implicating food as a source of human infection, it is critical that a better understanding of MRSA contamination be obtained to elucidate the source and develop control measures.

■ **Clinical Diseases Associated with MRSA**

One positive note about MRSA in pigs is that there is currently little evidence that MRSA has any effect on pig health or production. There is only one report of disease caused by MRSA in pigs, and that resembled “greasy pig disease” (van Duijkeren et al, 2007). Considering the apparent high prevalence of MRSA in pigs internationally and the limited evidence of virulence in pigs, it is unlikely that MRSA is a significant cause of disease in pigs. Like the methicillin sensitive strains of *S. aureus*, MRSA likely acts as an opportunist and can cause skin infections and possibly arthritis in neonatal pigs. Because MRSA does not appear to be an economically important pathogen of pigs there is no financial incentive for producers to actively try to control this problem.

■ **Control of MRSA on Pig Farms**

It is becoming increasingly clear that MRSA is widely distributed in the pig population internationally. Currently, there is no information about whether MRSA eradication is possible (or necessary) on farms. Eradication of this pathogen is unlikely because of the high rates and subclinical carriage; however, evaluation of transmission and infection control methods may lead to measures to reduce transmission on farms. We have recently completed a longitudinal study of pigs on a farm with a high prevalence of MRSA (incidentally a farm that does not use antibiotics). Piglets born to negative sows were less likely to become colonized with MRSA by the time they were weaned than piglets born to positive sows. However, transmission to negative litters did occur prior to weaning and prevalence greatly increased in all piglets shortly after weaning (Zwambag et al, 2009).

A common response to the finding that MRSA is present in the pig population has been to blame the use of antibiotics and call for the ban of growth promotants. MRSA is one of a growing example of cases illustrating that not all antimicrobial resistance problems can be solved by eliminating antibiotic use in livestock. MRSA thrives quite well on farms that don't use antibiotics so apparently the genes associated with resistance also provide some other competitive advantage that allows MRSA to displace other *S. aureus*. It's unlikely this is a new situation because a similar strain is found everywhere people have looked. In all likelihood, a common method of introduction onto

farms is via the purchase of MRSA-carrying replacement breeding-stock. However MRSA ST398 is so widespread that human carriers have likely been involved. It might be time for the swine industry to look at public health issues like MRSA when developing biosecurity and monitoring protocols. Once MRSA is present in a herd it is likely very difficult to eliminate it. To date, little is known about the on-farm risk factors such as housing or management that may reduce the prevalence in a herd.

■ Concern for Public Health

There is a significant concern among pig producers and veterinarians (and their families), because of the high rates of MRSA colonization and evidence that MRSA may be an occupational infection in these groups. All people with pig contact should be aware of their potential for increased risk of MRSA colonization and infection, and ensure that their physician is aware they are in a high-risk group. The possibility of MRSA should be considered, especially in skin and soft tissue infections, and concerns communicated with physicians to ensure that proper testing and treatment are provided. Clinical cases of human infection with the pig strain ST378 have been reported in Europe, although currently no fatal cases associated with this organism have been identified. The isolates so far identified do not carry the virulence factors related to the most dangerous strains of MRSA.

The possibility that MRSA may be a foodborne pathogen is of concern for the pork industry, largely because of concerns about consumer confidence given the high profile nature of this pathogen. Studies are ongoing to determine sources of pork contamination and determine the relevance of contamination. Realistically, safe meat handling practices that are already recommended should be adequate for MRSA, and education of consumers may be the main need.

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