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Formatting

Tina Smith Graphics
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CD-ROM

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Logo Design

Ruth Cronje, and Jan Swanson;
based on the original design by Dr. Robert Dunlop

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Pathogens in the twilight zone: Update on emerging disease issues with implications for the pork industry

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Introduction

For an industry under increasing public scrutiny, the emergence or discovery of apparently novel pathogens or diseases can rock public perceptions and markets to an extent which greatly exceeds the actual risks that the pathogens may pose to animal and/or human health. As recently shown during the 2009 H1N1 influenza pandemic, the conventional media are primed to shoot first and ask questions later. More troubling is that much of the blogosphere prefers just to shoot, ask no questions at all, and ignore any answers that don't fit the story! The initial uncertainty surrounding any emerging disease issue gives free reign to speculation, and the most pessimistic scenarios tend to be regurgitated throughout the media. Notable examples are BSE (mad cow disease) and H5N1 avian influenza.

- For BSE, one early (and widely disseminated) modeling prediction was 50,000 human deaths from variant CJD – the global tally after 15 years is around 200.

- For H5N1 “bird flu,” guesstimates up to 150 million can be found, but the reported tally of laboratory confirmed cases as of April 2011 is 562, with 329 fatalities.¹

Collectively, over 15 years, these two health scares linked to livestock have been responsible for a death toll equivalent to about one week of road fatalities in the USA. Without wanting to trivialize the reality that sooner or later an emerging disease may well meet or exceed the scale of history's worst plagues, until now actual outcomes have consistently fallen orders of magnitude below the doomsday scenarios promulgated in the media.

The swine industry has confronted several emerging disease issues over the last 20 years (Table 1). For most of these issues, the passage of time without significant or ongoing human health impact eventually has diluted most of the initial concerns and doomsday predictions for zoonotic impact. However, the human health implications of livestock reservoirs of MRSA and *C difficile* remain

Table 1: Emerging disease issues in swine over the last 20 years – relative impact on swine health, human health, and media coverage

What	Where	When*	Swine health*	Human health*	Media hype*
<i>Clostridium difficile</i> (pigs)	Global	1986	+/-	++(?)	++
PRRS	Global	1987	+++++	-	-
<i>Salmonella typhimurium</i> DT104	Global	1993	+/-	++	++++
PCV2	Global	1996	+++++	-	-
Hepatitis E infection	USA/global	1995	-	+/-	+/-
Menangle virus	Australia	1997	+	+/-	-
Nipah virus	Malaysia	1998	++	++	++
Bungowannah virus	Australia	2003	+	-	-
MRSA ST398	EU/global	2004	-	+/-	+++++
virulent <i>Streptococcus suis</i> type 2	China	2005	?	++	++
H1N1 pandemic influenza	Global	2009	+	++++(?)	+++++

* Subjective author rankings from “-” (negligible impact) to “+++++” (large impact)

? Indicates that role of zoonotic transmission is small or uncertain

more uncertain. The purpose of this paper is to provide an update on some recent information related to the zoonotic risks associated with these organisms. The two organisms share several epidemiologic features:

- Both *S aureus* and *C difficile* are common commensals found in healthy people and animals, and are opportunistic pathogens whose incidence and clinical severity in humans have increased.
- Both were recognized as human pathogens long before animal reservoirs were considered to have any epidemiological significance.
- Both are important nosocomial agents, and hospital infections have historically been the principal concern
- Community acquired infections have increased in importance for both agents in recent years. The recognition of animal colonization has raised the question of the role of livestock as sources of community acquired infections.
- Both organisms have been isolated from pork and foodborne transmission has been postulated. However, it has not yet been demonstrated to be important for either organism.

“Livestock associated” MRSA (LA-MRSA) – key points

Background

- The term ‘Livestock associated’ MRSA is used to describe a particular lineage of MRSA first linked to 3 hospitalized patients in Holland who were colonized (but not infected) with atypical isolates of MRSA.² All 3 patients were linked to pigs. The organisms represented a previously unrecognized lineage of MRSA.

- Several laboratory methods are used to subtype *S aureus* isolates. The typical features of livestock associated MRSA are shown in Table 2. The term livestock associated has become synonymous with organisms of the ST398 lineage. However, it is now recognized that other strains of MRSA can occur in livestock, and that livestock are not the only source of ST398 MRSA.
- Subsequent studies in Holland found 39% of slaughter pigs were culture positive for LA-MRSA, and all isolates were ST398.³ A high prevalence of nasal colonization of pig farmers was also reported.
- Subsequent studies in many countries have shown these organisms are present in many commercial swine populations, including in North America.⁴⁻⁶
- ST398 MRSA has also been isolated from numerous other animal species including cattle, dogs, and horses. Therefore it is suggested that this lineage of organisms lacks the degree of host specificity found in other *S aureus* lineages.
- Studies in Asia reported that other lineages (ST 9) were more common in pigs than ST398.^{7,8} Other sequence types have also been documented in pigs,^{9,10} indicating that the initial suggestion that MRSA in pigs may be limited to ST398 was an oversimplification. As further research occurs, it is likely that a wider range of MRSA organisms will be identified in livestock reservoirs.
- Studies of people with occupational exposure to livestock, including farmers and veterinarians, have consistently shown that these groups have a relatively high prevalence of nasal colonization with MRSA. However, they have not yet shown to be at elevated risk for clinical infections.

Table 2: Common typing methods for *S aureus*, with characteristics of livestock associated MRSA

Typing method	Outcome	Livestock associated MRSA
Pulsed Field Gel Electrophoresis (sma1)*	Gel patterns	Untypable
Multilocus sequence typing	Sequence types (ST) based on 7 conserved genes	ST398
Staphylococcal Cassette Chromosome (SCCmec typing)	Types I – VIII	Types III, IV, or V
Spa typing (two systems)	Repeat patterns in Protein A gene	
Ridom	e.g., t034	Over 30 spa types
egenomics	e.g., 539	within ST398 lineage

* sma1 is the standard restriction enzyme used internationally for PFGE typing of *S aureus*. ST398 isolates can be typed by PFGE using other restriction enzymes

Implications for human health

- Initial concerns for human health risk associated with LA-MRSA included occupational risks, foodborne risks, and risks to the general public.
- Recent European studies in hog dense areas have indicated that risk of exposure to LA-MRSA in communities surrounding areas of dense hog production is minimal, while occupational exposure was highly prevalent.^{11,12}
- Dutch authorities have conducted a risk assessment and concluded that meatborne exposure is not of importance. Although staphylococcal enterotoxigenesis is an important foodborne illness (and outbreaks have been linked to pork products), LA-MRSA isolates to date have lacked the genes coding for enterotoxins. Furthermore, methicillin resistance itself is not important for staphylococcal food poisoning, as treatment does not involve antimicrobials. There is no evidence that LA-MRSA have caused foodborne illness.
- Recent evidence suggests that LA-MRSA have relatively low transmissibility among people^{13,14} and low virulence^{15,16} relative to common human epidemic strains.
- In the 7 years since LA-MRSA were recognized, the cumulative burden of disease appears to be minimal. However, as many reports do not differentiate colonization from clinical disease, the actual burden of clinical disease is difficult to assess.
- Most cases of LA-MRSA infection appear to be skin and soft tissue infections. Large studies of invasive *S aureus* infections across European countries (including those with a high prevalence of LA-MRSA on pig farms) have indicated that these organisms are relatively unimportant causes of human infections,^{17,18} and are significantly less likely to cause invasive infections
- A small number of severe infections with ST398 have been reported, and a considerable proportion of these cases have no known livestock exposure. The sole documented fatal case of ST398 infection (necrotizing pneumonia) involved a methicillin sensitive isolate, and the subject had no known exposure to livestock.¹⁹ The tendency to immediately attribute ST398 cases to livestock reservoirs is likely misguided, as there is evidence that some variants of ST398 may be maintained in human populations independent of livestock.²⁰

Public health implications of *C difficile* (CD) in pigs – key points

- *C difficile* is considered a normal commensal and occasional pathogen of young pigs. Two closely related

large (toxins A and B) appear to account for the clinical manifestations in people.

- Like *S aureus*, CD exhibits enormous genetic diversity, and multiple approaches for sub-typing have been applied to study the organisms. PCR ribotyping is commonly used in outbreak investigations and MLST for longer term epidemiological studies.
- A hypervirulent strain (PCR ribotype 027) has been associated with an increasing incidence and severity of human infection in many countries.
- CD has a broad host range and is recognized as a pathogen of many animal species. In both animals and humans, prevalence of colonization is higher in the young, and in pigs prevalence highest is suckling pigs and much less common in older stock.²¹
- The predominant ribotype in pigs (078, toxinotype V) has also been isolated from human cases, and the isolates from pigs and people appear closely related.²²
- CD has been isolated from a broad range of foods, including retail meat product. Prevalence and ribotypes have been variable, and the importance of food as a source of human infection remains uncertain.²³

Summary

Understanding of the relationships between closely related commensal organisms that occur commonly in food animals and humans is challenging. For both LA-MRSA and CD, considerable uncertainties remain about the zoonotic risks they pose. Current evidence suggests that exposure risk to LA-MRSA is largely confined to those working directly with animals. To date, there is negligible information indicating significant occupational disease. Both further research and the passage of time will be important for understanding the mechanisms and magnitudes of zoonotic risk from these organisms.

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