RESEARCH REPORT

PUBLIC HEALTH/WORKER SAFETY

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Title: Quantitative Risk Assessment of Human MRSA Caused by Antibiotic Use in Swine - **NPB #09-161**

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INDUSTRY SUMMARY

Recent news stories, and many web sites and blogs, have suggested that routine use of antibiotics on pig farms may be threatening public and worker health. A widely expressed fear is that tetracycline and other antibiotics may create selection pressures that favor the spread of antibiotic-resistant "superbugs," such as methicillin-resistant *Staphylococcus aureus* (MRSA). The scariest stories discuss the rapid increase in antibiotic-resistant illnesses in recent years, and the large death toll – as many as 70,000 deaths per year in the United States – that resistant infections are causing. The implication is clear: farming practices that threaten human lives must be changed, perhaps through Congressional action.

Conspicuously absent from these stories has been a quantitative discussion of *how many* excess deaths, treatment failures, or days of illness each year are caused in the United States by MRSA arising from use of antibiotics in pig production. In other words, *how big is the risk?* It is impossible to make wise policy decisions without first understanding how large the human health risks are now, and how much they would be changed by proposed interventions. The objectives of this report are, therefore, to quantify risks to the public and to pig farm workers, by using available facts and data to estimate the annual number of pig-associated MRSA deaths and illnesses in the United States, and the fraction that might be prevented by halting antibiotic use.

We examined two major exposure pathways by which the specific type of MRSA that is associated with pigs (Clonal Complex 398, CC398 MRSA) might reach and infect humans: via the food chain, and via direct

contact on farms. (Other occupational risks, e.g., in slaughter houses, are much smaller, and would not greatly change the total risk estimate.) A review of health statistics and scientific literature on CC398 MRSA in the United States, Canada, and Europe showed that pig-associated MRSA risks are minimal. In contrast to the large risks (e.g., 70,000 excess deaths per year) mentioned in some news stories, the actual number of deaths that have ever been found to have been caused by pig-associated (CC398) MRSA in the United States is zero. In fact *no human deaths and no serious infections have been found to have been caused by pig-associated MRSA.* (The large numbers of excess deaths per year referred to in some stories about public health risks from antibiotic use and MRSA on pig farms are actually caused by something else: hospital-associated MRSA and other resistant bacteria, arising from hospital antibiotic use and inadequate hand washing and infection control in hospitals, and mainly affecting patients with severely compromised immune systems. Attributing these risks to antibiotic use on pig farms is simply incorrect.)

That the risk to human health from pig-associated MRSA in the United States has so far been undetectably small does not mean that it is necessarily zero.   We therefore quantitatively estimated colonization rates among pig farmers, and infection rates per colonized individual. From these, we calculated that the true risk of serious MRSA infection or deaths in the United States due to pig-associated (CC398) MRSA from pig farms, while uncertain, is probably *less than 1 excess infection case per year in the entire United States population.* The true risk could be much smaller (possibly zero), but more years of data showing no adverse consequences among colonized people are needed to reduce the plausible upper bound on quantitative risk much below 1 case per year. Modeling the dynamics of MRSA in hospitals shows that CC398 MRSA risks are unlikely to increase dramatically in future, e.g., via rapid spread through hospitals, as the CC398 type has a relatively low potential for spread (basic reproductive rate).

Finally, even if the risk to humans from CC398 MRSA, although vanishingly small, eventually proves to be greater than zero, it is unlikely that ceasing use of antibiotics in pig production would affect the risk significantly. Indeed, current knowledge suggests that the main selection pressure favoring MRSA on pig farms may not come from antibiotics at all, but from zinc compounds fed to recently weaned pigs. Thus, although MRSA from pigs poses minimal health risks to humans, efforts to reduce the *perceived* risk (which can be much larger than the real risk) by banning animal antibiotic use is unlikely to create any human health benefit.

KEY WORDS: Antimicrobial risk assessment, quantitative risk assessment (QRA), MRSA, risk analysis, animal antibiotics, pigs, tetracycline, risk perception, risk communication

SCIENTIFIC ABSTRACT

Recent news stories have suggested that routine use of antibiotics on pig farms may threaten human health by selecting for resistant "superbugs," such as methicillin-resistant *Staphylococcus aureus* (MRSA), that contaminate meat and/or farm workers. Conspicuously absent from these stories has been quantification of *how many* excess deaths, treatment failures, or days of illness each year are caused by MRSA arising from use of antibiotics in pig production. In other words, *How big is the risk?* We address this question by using available data to develop a conservative (plausible upper bound) estimate of risks to the public and to pig farm workers from pig-associated (Clonal Complex 398) MRSA deaths and illnesses in the United States. In contrast to the large risk numbers (e.g., 70,000 excess deaths per year) mentioned in some news stories, empirical data show that zero deaths or serious infections have been found to have been caused by pig-associated (CC398) MRSA in the United States. (The large numbers of excess deaths sometimes referred to is for hospital-associated MRSA and nosocomial infections, arising mainly from hospital antibiotic use and inadequate hand washing and infection control.) Since zero recorded cases does not necessarily imply zero risk, we use estimated colonization rates among pig farmers, and infection rates per colonized individual, to calculate how large the true risk might be of serious MRSA infection or deaths due to pig-associated (CC398) MRSA from pig farms. The answer is that less than 1 (and possibly as low as zero) excess infections per year are expected in the entire United States population from CC398 MRSA; moreover, this number is unlikely to increase sharply in future, if present conditions are maintained. Even if the risk to humans from CC398 MRSA eventually proves to be greater than zero, it is unlikely that ceasing use of antibiotics in pig production would affect the risk significantly. Indeed, current knowledge suggests that the main selection pressure favoring MRSA on pig farms may not come from antibiotics at all, but from zinc compounds fed to pigs, especially the recently weaned, to augment or substitute for antibiotics. Thus, although MRSA from pigs poses minimal health risks to humans at present, efforts to reduce the *perceived* risk (which can be much larger than the real risk, thanks in part to social amplification of perceived risk and irresponsible journalism) by banning animal antibiotic use is unlikely to create any detectable human health benefit. Ironically, a shift away from antibiotics and toward zinc products (as on some organic farms) might increase the prevalence of CC398 MRSA.

INTRODUCTION

Risk communication is one of the most effective and widely used means for raising concerns and shaping public perceptions and preferences for policies (Gardner, 2009). Scaring people works: it grabs attention, raises concern and outrage, and stimulates reactions. Various interest groups routinely release dramatic stories about real or conjectured health and safety risks to mass media outlets – who too often seize upon well-packaged sensationalism and omit or minimize critical or skeptical analysis an caveats – to manipulate public sentiments and nudge political funding or action priorities in directions favorable to the interest groups. This practice may be almost as old as politics, but it has gained in sophistication, reach, and visual and visceral impact as television and other media have learned to bypass "head" (cognitive, analytic risk assessment) and appeal directly to "gut" (emotion and instinct) in presenting risk stories (*ibid*).

1. Motivating Example: A News Story About Emerging MRSA Risks Due to Antibiotic Use on Farms

Box 1 presents a recent example, excerpted from a CBS news report on possible public health risks from methicillin-resistant *Staphylococcus aureus* (MRSA), a "super-bug" that is resistant to multiple antibiotics. The report suggests that antibiotics in food animals are contributing to a dramatic rise in multi-drug resistant superbug infections that may threaten us all, as resistant bacteria "go from the farm to the meat counter, to having an adverse effect on humans." The nature of that effect is dramatically described: "Drug resistant infections have sky-rocketed over the past two decades, killing an estimated 70,000 Americans last year alone."

Box 1: Example of a CBS Report on Animal Antibiotics and MRSA

"**(CBS)** "It's scary, I mean, you just can't describe it really," said Bill Reeves.

Two years ago, 46-year-old Bill Reeves, who worked at a poultry processing plant in Batesville, Arkansas, developed a lump under his right eye.

"It went from about the size of a mosquito bite to about the size of a grapefruit," he said.

CBS Evening News anchor Katie Couric reports doctors tried several drugs that usually work on this potentially deadly infection: methicillin resistant staph or MRSA - before one saved his life. …
Health officials are concerned if workers who handle animals are getting sick - what about the rest of us? Drug resistant infections have sky-rocketed over the past two decades, killing an estimated 70,000 Americans last year alone. It's an emerging health crisis that scientists say is caused not only by the overuse of antibiotics in humans, but in livestock as well. Antibiotics fed to healthy animals to promote growth and prevent disease.

"My fear is that one of these days we are going to have an organism that's resistant to everything that we know, and we'll be left powerless," said Thomas Cummins, Batesville's chief medical officer.

"There are a lot of concerns about antibiotics being added to animal feeds that may be contributing to MRSA as well as other antibiotic resistance," Cummins said. "Certainly the more bacteria are exposed to antibiotics in any shape or form, the more tendency there is for resistance."…

Evidence of MRSA has been found in the nation's meat supply. But it's unclear how widespread it may be, because only a small fraction is tested for MRSA.

Shelley Hearne has studied the health effects of factory farming for 25 years.

"How does this go from the farm to the meat counter, to having an adverse effect on humans," Couric asked.

"If the bacteria becomes resistant to antibiotics, it can actually spread in many ways," Hearne said. "It could be in the food supply, but it also can be in waters that runoff in a farm. It could be in the air. It can happen very quickly in many different ways. It's why it's a practice that has to stop on the farms."

Source: (CBS, 2010)

Before going further, it may be useful to briefly consider the following kinds of critical thinking

questions, which a risk analyst might ask about this report.

- *Hazard identification.* Has the story identified a hazardous agent or practice that threatens or harms human

    health, perhaps contributing to the reported sky-rocketing increase in resistant infections? If so, what is it?

    (Some possible suggested answers, if this were a multiple choice test, might be: (a) MRSA transmitted to

people from farm animals via meat; (b) the practice of using antibiotics in "factory farming"; (c) meat from farms that use antibiotics in raising food animals; (d) all of the above; or (e) None of the above.)

- *Prospective exposure assessment.* Has the report compared the potential extent of exposures to MRSA via meats from different sources, such as conventional vs. antibiotic-free chicken or pork?

- *Retrospective exposure assessment:* Conversely, has it compared exposures between patients with and without MRSA?

- *Dose-response or exposure-response modeling.* Does the report inform its audience about differences in risks of MRSA infections among people with different exposures (e.g., among consumers of conventional vs. organic chicken or pork, or consumers of meats with and without MRSA contamination – or, for that matter, for meat consumers vs. vegetarians?)

- *Risk characterization.* Is the audience informed about how large is the risk from MRSA-contaminated meat (*absolute risk*), how much this risk is increased by use of antibiotics on farms that raise food animals (*incremental risk*), or how many times greater is the average probability of a MRSA infection in a year for a consumer of MRSA-contaminated meat compared to a consumer unexposed to MRSA-contaminated meat (*relative risk*)?

- *Uncertainty characterization.* Does the report provide a balanced, responsible discussion of any remaining uncertainties about how the risk of MRSA infections varies with use of animal antibiotics, MRSA found on meats, and/or consumption of meat from different sources?

The answer to each of these questions is, No. (The correct answer to the suggested multiple choice questions about hazard identification is also (e), none of the above.) Although a quick glance at the story might suggest that MRSA-contaminated meat has been identified as an emerging hazard to public health, this is an illusion, created in part by the technique of juxtaposing alarming statistics about one thing – an increase in *detected and reported hospital-acquired infections* (the "Drug resistant infections [which] have sky-rocketed

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over the past two decades, killing an estimated 70,000 Americans last year alone") – with concerns about something else: imagined public health risks from *farm animal-derived MRSA* transmitted to consumers via the food chain. But hospital-acquired MRSA and farm-animal acquired MRSA are very different (typically, different strains – clonal complex 398 for food animals, vs. USA100, 300, and 400 commonly found in human infections in North America) (Cox & Popken, 2010). There is no evidence that farm-animal derived MRSA has played any role in the escalation of hospital-acquired infections. The report has not identified any causal connection between them, nor provided any hazard, exposure, or risk information about MRSA.

What the report *has* done, very well, is to outline a gripping narrative about an easily imagined danger to public health, made even more vivid by the personal account of a MRSA-infected worker and by expressions of concerns from a plant medical officer and by an environmental health scientist (identified only as someone who "has studied the health effects of factory farming for 25 years," with no mention that this "study" consisted of work at the National Resources Defense Council and the Pew Charitable Trusts, both of which actively advocate Congressional bans on the use of all antibiotics as growth promoters and to protect the health of farm animals).

Even in the absence of any quantitative, factual information about frequencies of exposures and adverse outcomes – or, perhaps, especially in their absence – such accounts are compelling to our gut feelings. They scare Gut, even if not Head, in the terminology of Gardner (2009). They trigger an emotional reaction that something of potentially vital concern is being discussed, even if a more careful cognitive and analytic review finds that no factual claims about hazards, exposures, or resulting risks are actually made. The technical content of the concerns – that MRSA or other resistant bacteria from farm animals will flow "very quickly" through air, food, and water to threaten human health, or that continued exposure to antibiotics necessarily renders bacteria resistant, rather than dead or inactive – might quickly be dismissed by a microbiologist as being unsupported by (and, indeed, inconsistent with) empirical data (Cox & Popken, 2010). But such details are lost on Gut, which

responds at the level of "clean = good, contaminated = bad," and which is powerful in shaping risk perceptions and policy preferences.

The narrative in Box 1 strongly suggests, without quite saying, that MRSA in meat from animals raised with antibiotics endangers public health, and that continued use of antibiotics may lead to irreversible and uncontrollable escalations in multidrug-resistant strains of food-borne bacteria. The one piece of quantitative data cited, "Drug resistant infections have sky-rocketed over the past two decades, killing an estimated 70,000 Americans last year alone" is certainly striking. Juxtaposing it with the rest of the story suggests, again without actually asserting, that the increase is known or suspected to have something to do with MRSA or other resistant superbugs that "go from the farm to the meat counter, to having an adverse effect on humans." But such juxtaposition of worrying statistics is no substitute for hazard identification, which addresses the *causes* of adverse effects. The main cause of the dramatic increase in drug-resistant infections, and, specifically, of MRSA infections, is well known, although not mentioned in the story: it is not consumption of contaminated meats, but *failure of infection controls in hospitals*. This is typically due to a combination of inadequate hand washing by care providers (Pope *et al.*, 2009) and to the extreme vulnerability of hospitalized patients with suppressed immune systems (AIDS, leukemia, other cancer, and transplant patients), recent surgery, or open wounds and sores (e.g., http://en.wikipedia.org/wiki/Methicillin-resistant_Staphylococcus_aureus). By presenting two different sets of facts together, the story invites its audience to draw a terrifying, though unwarranted conclusion – good for ratings, but bad for understanding of public health issues.

While such gaps in the logic of the story may be obvious to trained microbiologists and risk analysts, they are invisible to many members of the audience, as evidenced by responses to the story on many blogs. To many listeners, the story conveys the impression that its policy-relevant risk management conclusion, that "It's why it's a practice that has to stop on the farms" (presumably referring to use of antibiotics in general on farms, since farm animals are not exposed to methicillin in particular) somehow follows from the facts and data presented (MRSA infections are a growing problem).

We have selected the news story in Box 1 as an example, not because it is especially bad, but because it is in many ways typical of how risks – or, more accurately, concerns about hypothesized risks – are too often communicated to the public via news sources(Gardner, 2009). The story begins with an account of a highly unusual case, which Gut will probably misinterpret and recall as typical. It follows with some large, scary numbers (70,000 deaths per year, rapidly escalating), without noting that these are not actually caused by the subject of the story. It skips any discussion of causation, exposures, dose-response, risk, or uncertainty – perhaps the chief interests of Head, but certainly not of Gut – yet nonetheless delivers a strong risk management recommendation, that farm practices must change to address the concerns that have been raised. This recommendation is based on imaginary scenarios that speak directly to Gut, undisturbed by formal risk analysis or critical thinking.

2. A More Factual (But Less Terrifying) Narrative

Here is a very different alternative narrative about MRSA risks from eating meat, more solidly rooted in empirical data.

- MRSA is a common commensal bacterium, routinely carried by people (especially in the nose) and other mammals. It is normally harmless, although MRSA infections (and other opportunistic infections by normally harmless bacteria) can become life-threatening to AIDS patients, cancer and leukemia patients, transplant patients, or patients with open sores or wounds. (Similarly, the 70,000 deaths per year that the story in Box 1 attributes to drug-resistant bacteria occur disproportionately among high-risk, hospitalized patients with compromised immune systems, many of whom have sadly short life expectancies even in the absence of infections. Attributing such deaths to drug-resistant infections, rather than to the underlying serious illnesses, illustrates the elasticity of the concept of causation, as used in reports that assign deaths to specific individual causes.)
- The average number of deaths per year in the United States traced to eating meat contaminated with MRSA, originating from food animals reared with antibiotics, is: zero. No such case has ever been recorded. The

scenario in which MRSA "go from the farm to the meat counter, to having an adverse effect on humans" (Box 1) is entirely hypothetical.

- Over the past half century, the cumulative number of MRSA infections (not just deaths) ever identified in the United States as being due to transmission of MRSA through the food chain, from farm to fork, is also zero. Although a livestock-associated strain, CC398, also called ST398, has indeed been identified, there is no evidence that it spreads through the food chain to infect consumers of meat (EFSA, 2009).

- Although MRSA strains were first identified as an infection problem in hospitals in the 1960s, and community-acquired MRSA cases were identified in the 1990s, there is still no empirical support for the fear that MRSA transmitted via the food chain, from farm to fork, creates any detectable human health risk – let alone an "emerging health crisis." For example, no difference in MRSA infection rates has been reported between consumers of chicken or pork from conventional *vs.* antibiotic-free farms. Significant differences in carriage rates of some other drug-resistant commensal bacteria have been reported for vegetarians vs. chicken eaters, but the difference is in the opposite direction from what might be expected based on Box 1: vegetarians have somewhat higher rates of resistant bacteria (Cox & Popken, 2008).

- For MRSA, it is simply untrue that drug-resistant infections constitute "[a]n emerging health crisis that scientists say is caused not only by the overuse of antibiotics in humans, but in livestock as well." For example, EFSA (2009) concludes that "Food may be contaminated by MRSA (including [the typically farm livestock-acquired strain] CC398): eating and handling contaminated food is a potential vehicle for transmission. There is currently *no evidence for increased risk of human colonisation or infection following contact or consumption of food contaminated by CC398 both in the community and in hospital*" (emphasis added.) Thus, food borne transmission of MRSA from livestock to humans is *not* an "emerging health crisis" and is *not* detectably "caused by the overuse of antibiotics… in livestock as well." The entire premise for the gripping story in Box 1 is mistaken.

- What is true, and perhaps equally exciting, is that MRSA infections have indeed risen dramatically in recent decades. Most or all of the explanation for the increase in, apart from improved detection and reporting, appears to be use of antibiotics *in hospital environments*, coupled with failure to adequately wash hands and control the spread of hospital-acquired infections (Pope *et al.*, 2009; Cox & Popken, 2010). MRSA typically spreads from hospitals into the surrounding community, rather than the other way around, and the fluctuations of MRSA in hospital environments and surrounding communities can be predicted from use of antibiotics in human patients(Cox & Popken, 2010).

This account of the human health risk from livestock-associated MRSA is obviously much less exciting than the one in Box 1. Instead of an emerging health crisis, we have no detectable risk. If public risk management policies and Congressional actions are to be guided by compelling narratives, rather than by quantitative risk analysis, then whoever tells the most stirring story or expresses the most convincing concerns may end up shaping public policy and commandeering the allocation of limited public concern and resources. The story in Box 1 may then trump the alternative story that there is little or nothing to worry about, even if the former amounts to speculative fiction and the latter is factual.

Fortunately, quantitative risk analysis (QRA) provides an alternative to story-telling as a way to figure out what concerns are worth responding to, e.g., with resource commitments and policy changes. Although the "No worries" narrative may be less intrinsically less appealing to the amygdala (or Gut) than the "Emerging health crisis!" narrative in Box 1, it is possible, and desirable, to let Head adjudicate dispassionately between them, by emphasizing numbers rather than concerns, and a more comprehensive understanding of causation, rather than juxtaposition of factoids.

The remainder of this report re-examines the threat to human health from CC398 (livestock-associated) MRSA, using QRA principles. The main objective is to place a data-driven upper bound on the risk (number of CC398 MRSA-related treatment failures per year, or cases of compromised treatment), in the United States, that might be caused by use of antibiotics in swine on farms. We focus on swine, as they have been identified as a reservoir of principle concern for CC398 (Smith et al., 2009). The results can then be used to better inform risk management policy debates that now rest on qualitative speculations (such as the "Emerging health crisis!" frame in Box 1, or the "No worries!" frame discussed above) by providing well-supported quantitative estimates (e.g., "At most one excess treatment failure per billion person-years.")

OBJECTIVES

The main objective is to place a data-driven upper bound on the risk (number of MRSA-related treatment failures per year, or cases of compromised treatment), in the United States, caused by use of antibiotics in swine. The result can then be used to inform policy debates that now rest on qualitative speculations ("This could be a crisis!") by providing well-supported quantitative estimates (e.g., "At most one excess treatment failure per hundred million person-years.")

Secondarily, we wish to assess the relative contributions to MRSA-related treatment failures of different swine-to-human MRSA transmission pathways, including handling or eating meat products, environmental runoff, and direct contact.

As indicated by the, "no worries" scenario above, we expect that quantitative risk assessment (QRA) will show that *human antibiotic use in hospitals* accounts for almost all MRSA risks in humans, and that animal sources contribute at most an undetectably small fraction of human MRSA cases. This is quite different from some current popular and policy-maker perceptions.

MATERIALS AND METHODS

Hazard Identification for MRSA Risks from Swine

Quantitative risk assessment (QRA) typically begins with *hazard identification*. This step takes inventory of what is known about the adverse health outcomes that might be caused by exposure to a particular source of risk (i.e., hazard) – here, CC398 from pigs. To be most useful for QRA, it is helpful to include data on the numbers and types of adverse health consequences per year that might be attributable to CC398 MRSA.

CC398 Hazards to Consumers of Retail Pork

The most alarming concerns about CC398 MRSA have arisen with respect to the risk of contamination from retail pork products, either through consumption or handling of raw meat. Recent studies of retail meat samples in the U.S. showed MRSA prevalence rates of 0% (Chan *et al.*, 2008) in beef, chicken, and pork (organic and conventional) in the northeastern United States, and 5% (Pu *et al.*, 2009) in retail pork and beef in Louisiana. DNA strain testing in the latter study showed that that none of the isolates was of type ST398.

A large-scale study by Davies (Davies, 2009) collected 143 retail pork samples from 15 states of the U.S. and tested them for the presence of *Staphylococcus aureus*. The study also examined the prevalence and types of MRSA in market hogs at slaughter. While 80% of retail pork samples were positive for *S. aureus*, among spa types common in market hogs, only 3 isolates of spa type 539 (Ridom t034 – a type of CC398) MRSA and 4 of spa type 2 were detected in retail pork (4.9% overall, 2.1% for CC398). The report states: "For almost all samples, very few suspect colonies were present, despite the multiple enrichment steps, suggesting a likely low level of contamination."

MRSA in U.S. meats appears to occur infrequently, and at low levels when it does occur. The situation in other countries is less favorable, however. In Canada, Weese *et al*. (2009) sampled retail pork in 4 different provinces. MRSA was isolated from 7.7% of pork chops, 7.4% of ground pork, and 8.3% of pork shoulders. CC398 accounted for 30% of the isolates. In the Netherlands, de Boer *et al*. (2009) tested samples of retail meats for the presence of MRSA. Strains were isolated from 264 (11.9%) of 2217 samples analyzed. Isolation percentages for the meat species were: beef (10.6%), veal (15.2%), lamb and mutton (6.2%), pork (10.7%), chicken (16.0%), turkey (35.3%), fowl (3.4%) and game (2.2%). The majority (85%) of the isolated strains belonged to spa-types of pulsed-field gel electrophoresis (PFGE) non-typable (NT)-MRSA, corresponding to the multilocus sequence type CC398. An earlier study in the Netherlands (van Loo, I. H. *et al.*, 2007) found MRSA in two of 25 pork samples, one of which was CC398. However, the authors of the first study concluded

that: "At present, the high prevalence of MRSA in meat has not been shown to contribute significantly to the dissemination of MRSA to humans and the possible health hazard for consumers of the presence of MRSA in foods should be further elucidated."

These data points in Europe indicate the potential for CC398 to become much more prevalent in retail meats than it is at present in the U.S. However exposure does not automatically constitute a health threat – often a difficult lesson for Gut to believe, since the "Contamination = bad" heuristic is powerfully ingrained in us (Gardner, 2009), but one that Head can nevertheless see to be true based on sufficient quantitative data. For example governmental authorities in Europe have not found any link between CC398 in food and human health. After extensive study they concluded, as previously mentioned, that:

"Food may be contaminated by MRSA (including CC398): eating and handling contaminated food is a potential vehicle for transmission. There is currently no evidence for increased risk of human colonisation or infection following contact or consumption of food contaminated by CC398 both in the community and in hospital." (EFSA, 2009)

"MRSA commonly carry enterotoxin genes but there has been only one report of food intoxication due to MRSA. At present, CC398 has not been associated with staphylococcal foodborne intoxication." (EFSA, 2009)

Given that the amount of MRSA in retail meat in Europe is several times that of the US, there appears to be no detectable risk to U.S. consumers from this source, consistent with the "No worries" narrative above.

Other researchers investigating CC398 risks in the United States (Davies, 2010) have likewise concluded that, "The 'pig associated' clone is very distinct from the major clones causing human MRSA infections in the USA and Canada. The CDC has determined that these clones are not implicated in the increase

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in community acquired MRSA in the US over recent years. …[In addition, based on Dutch data], we are not likely facing any imminent crisis for occupational health in the industry." However, it remains to consider other, perhaps more dangerous, pathways by which CC398 might reach and infect occupational subpopulations, especially on farms, where colonization of workers with CC398 MRSA has been found.

Potential CC398 Hazards to Pig Farmers

Even if MRSA in pigs does not cause any detectable risk to public health via the food chain, it may still present an occupational hazard to workers, as suggested in the first part of Box 1. Research in Denmark (Lewis *et al.*, 2008) identified the specific strain of MRSA, CC398, most associated with pigs. Since then, CC398 MRSA has increasingly been looked for, and found, in humans on farms. Cases of CC398 MRSA colonization and infection occur mostly to individuals having direct contact with livestock, especially pigs. Cuny *et al.* (2009) compared rates of CC398 MRSA colonization among individuals in Germany in direct contact with pigs, their family members, and students attending school in a high-density pig farming area, with rates of 86% (97/113), 4.3% (5/116), and 0.6% (3/462) respectively. (The colonized students all lived on pig farms). Nasal colonization was also found among 45% (22/49) of veterinarians attending pig farms, and in 9% (4/44) of their family members.

Among Dutch hospital patients with non-typable MRSA (assumed to be CC398), attributable causes were determined to be: 4% - stay in a foreign hospital, 87% - exposure to pigs and calves, and 9% - unknown (van Rijen *et al.*, 2008),. In this study, the non-typable MRSA carriage rate among patients exposed to pigs was 36% (14/39), which was estimated to be 1000 times higher than in the general population. Another Dutch study (Voss *et al.*, 2005) found the MRSA carriage rate to be 760 times greater among pig farmers than in patients admitted to Dutch hospitals. In Canada, Khanna *et al.* (2008) found that 20% (5/25) of pig farmers tested were colonized with MRSA strains, and the strains were identical to those carried by pigs on their farms (3 consistent

with CC398, one new, and on USA100).   No human cases were found on MRSA negative farms. In Belgium,

Denis *et al.* (2009) found a MRSA (all types) colonization rate of 50% (47/94) on MRSA positive farms and 3%

(1/33) on MRSA negative farms. Finally, in the U.S., Smith *et al.* (2009) found a CC398 MRSA colonization

rate of 64% (9/14) on farms where pigs were colonized, and 0% (0/6) on farms where they were not. A follow-

up study (Harper & Smith, 2010) reported a human colonization rate of 50% (27/54) on CC398 MRSA positive

farms, compared to 0% (0/30) on MRSA CC398 negative farms. Taken together, these data show a clear,

strong association between CC398 colonization in pigs and in people who work with them.

Estimating the Number of U.S. Pig Workers

To estimate the number of individuals in the U.S. in close contact with pigs it is useful to consider the

number of pig farms by herd size, because the average number of workers per pig decreases with herd size.

Due to such economies of scale, herd sizes have shifted over the past two decades toward larger operations, so

that most pigs live within larger herds (Figure 1). However, the total number of hogs has increased only slowly

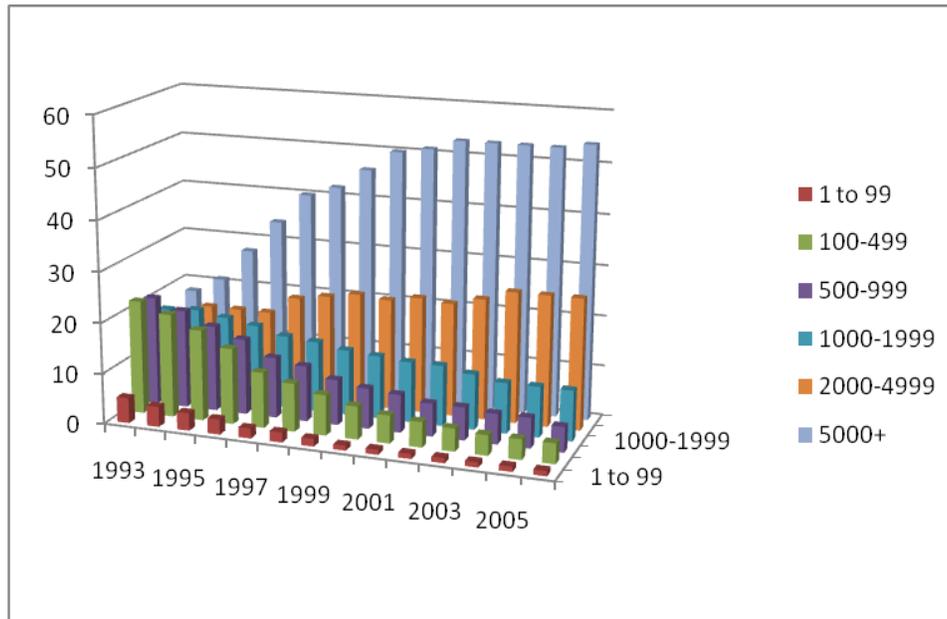over the same period, to 62,490,000 pigs located at 65,940 sites in 2006 (USDA, 2008).

Figure 1. Percent of Hogs by Herd Size 1993-2006

Otto *et al*. (1998) performed an economic analysis of Iowa hog production that estimated direct workers required (for farrow-to-finish operations) as a function of herd size as follows: 150 pigs/1.4 workers, 300 pigs/3 workers, 1200 pigs/10 workers, and 3400 pig/21 workers. Interpolating these estimates to the midpoints of the USDA herd size breakouts used in Figure 1 yields the values in column 2 of Table 1. Subsequent calculations shown in the table determine the estimate for total workers on pig farms in the U.S.

Herd Size	Workers/Herd[1]	Percent of Herds[2]	Number of Herds[3]	Total Workers[4]
1-99	1.4	60.5	39621	55,470
100-499	3	14.6	9561	28,685
500-999	6.5	6.8	4453	28,947
1000-1999	11.5	6.4	4191	48,201
2000-4999	19	8.0	5239	99,5445
5000+	31	3.7	2423	75,117
Total		100	65490	335,964

Table 1. Computation of Total Pig Farm Workers in the US

This "bottom up" estimate of 335,964 workers is roughly consistent with the latest available "top down" estimates. The USDA Economic Research Service estimates that in 2002 (the last year for which such statistics are available) that total U.S. farm employment, including both workers *and* proprietors, was 3,074,946 (USDA-ERS, 2005). In a recent report from the USDA National Agricultural Statistics Service (USDA-NASS, 2009), the portion of field and livestock workers (only) employed within "Livestock, Dairy, and Poultry" (versus crop related) constituted 31% of the total in Oct. 2009, from which one might estimate the total number employed in

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[1] For example, the computation for the number of workers in 500-999 herd sizes is 3 + (10-3) x (750-300)/(1200-300). The smallest herd size category (1-99) simply assumes the same number of workers (1.4) as the first estimated category (150). The largest herd size category (5000+) assumes the same ratio of pigs to workers as the last estimated category (3400).

[2] USDA (2008). Swine 2006 - Part IV: Changes in the U.S. Pork Industry, 1990-2006. USDA - #N520.1108, Available at http://www.aphis.usda.gov/vs/ceah/ncahs/nahms/swine/swine2006/Swine2006_PartIV.pdf Last accessed on 12/16/2009.

[3] Rounded, 65,490 herds multiplied by the given Percent of Herds value for each herd size.

[4] Workers/Herd x Number of Herds

this category would be somewhat under 1 million. Our estimated number of 335,964 for pig farm workers

specifically would be a little more than 1/3 of this total.

To model uncertainty, we will tentatively assume that this estimate of the risk population may be off by as much

as 20% (67,193) in either direction. This subjective uncertainty is expressed as a **uniform probability**

distribution ranging from 268,771 to 403,157. This range is admittedly subjective – other ranges could be

considered –but it suffices to explore the sensitivity of results to uncertainty in the size of the heavily exposed

worker population.

Estimating the Proportion of Farms with MRSA

The European Food Safety Commission sponsored an extensive survey of the prevalence of MRSA on

pig farms throughout the EU during 2008 (EFSA, 2009). Figure 2 shows the estimated prevalence in each

country.

The overall MRSA prevalence among all countries surveyed was 26.9% (25.5% for CC398 MRSA only).

Eleven of 26 participating countries (3,309 farms) reported no CC398 MRSA. The CC398 prevalence levels

were highest in Spain (50.2%) and Germany (37.4%).

No similar survey has been performed in the US.   While Davies *et al.* (2009) performed a nationwide

study of CC398 among pigs at slaughter, farm prevalence cannot be determined from these data. However,

Table 2 summarizes several recent relevant data points for the U.S. and Canada.

Location	# Farms CC398 Positive	# Farms Tested	Reference
Ontario, Canada	9	20	(Khanna *et al.*, 2008)
Five Canadian Provinces[5]	2	28	(Weese, J. S. *et al.*, 2009)
Iowa and Illinois	4	8	(Smith, 2009)
Iowa and Illinois[6]	1	2	(Smith *et al.*, 2009)
Total	16	58	

Table 2. ST398 MRSA Positive Farms in the U.S. and Canada

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[5] Interestingly, the two ST398 positive farms were in Saskatchewan, with 0 out of 5 positive in Ontario. Note that Khanna et al (2008) had found 9/20 in an earlier study.

[6] Production systems rather than individual farms

The overall proportion of farms in the U.S. and Canada positive for CC398 MRSA is 16/58 = 27.6%, very close to the overall prevalence in Europe. To approximate uncertainty regarding the true proportion, we assume a standard Uniform[0, 1] (non-informative) prior for the probability of a pig farm being colonized with CC398 MRSA. Bayesian updating of this prior in a Bayesian binomial sampling framework implies a Beta($s+1$, n - s +1) posterior distribution, where n is the number of observations ($n = 58$) and s is the number of positive observations ($s =16$). The posterior probability distribution for the fraction of MRSA-posutive farms is thus a **Beta(17, 43)** distribution, with a mean of $(s+1)/(n+2) = 17/60 \approx$ **0.28.**

Estimating the Probability of Colonization with MRSA for Exposed Workers

Many, but not all, farm workers having direct contact with CC398 MRSA positive swine herds become colonized themselves. Table 3 below summarizes the available worldwide data (described above) on this proportion.

Location	# Positive	# Farm Workers Tested	Reference
Ontario, Canada	5	9	(Khanna *et al.*, 2008)
Germany	97	113	(Cuny *et al.*, 2009)
Belgium	47	94	(Denis *et al.*, 2009)
Iowa and Illinois	9	14	(Smith *et al.*, 2009)
Iowa and Illinois	27	54	(Harper & Smith, 2010)
Total	185	284	

Table 3. CC398 MRSA Colonization Among Those Exposed to CC398 MRSA Pigs

Combining all of the samples above for workers on MRSA positive farms yields an empirical ratio of 185/284. To approximate uncertainty regarding the true proportion, we note that a (non-informative) unit uniform prior distribution for the probability that a pig farm worker in direct contact with pigs is colonized with MRSA, leads to a Beta($s + 1$, $n - s + 1$) = **Beta(186, 100)** posterior distribution, with a mean of $(s+1)/(n+2) = 186/286 = $ **0.65** and a standard deviation of **0.028**. This mean and standard deviation make a normal approximation useful, as the endpoints (0 and 1) are many standard deviations away from the mean.

Estimating the Annual Probability of MRSA Infection for Colonized Workers

Colonization of the human nasal passages with *Staphylococcus aureus* is common. Gorwitz et al. (2008) estimated a 28.6% prevalence in the U.S. in 2004. A fraction of these are methicillin-resistant, approximately 1.5% of the U.S. population. Approximately 19.7% of these could be classified as community-associated MRSA (as opposed to hospital-associated).

Only a small fraction of those colonized with MRSA develop active MRSA infections. Although the relationship between colonization and infection is not fully understood, in one instance researchers have shown that more than 80% of bloodstream infections caused by *S. aureus* in hospitalized adults were preceded by colonization of the anterior nares with the same strain (Graham *et al.*, 2006). For initial approximation purposes, we assumed that the relationship of infected to colonized can be expressed as a fraction, that is, the number of infected/year is a given fraction of those colonized. Klevens *et al*. (2007) determined an annual incidence rate for community-associated invasive MRSA infections in 2004 of 4.6/100,000. This would imply a *ratio of annual invasive infections to colonized* of approximately (4.6/100000) / (0.015 MRSA colonization fraction in U.S. x 0.197 community-associated fraction of MRSA cases in U.S.) = 0.0156.

However, the CC398 strain appears to less virulent and less transmissible than both community and hospital associated strains (EFSA, 2009). Recent research has shown that CC398 lacks virulence genes found

in other MRSA strains. In Belgium (Hallin *et al.*, 2009), CC398 strains were shown to lack genes encoding enterotoxins, proteases (spl operon, sak), haemolysins (hlgB, hlY) or adhesion factors (embbp, ebpS, hlgB, mapW). Similarly, research in Germany (Argudin *et al.*, 2009) found that CC398 strains were negative for leukotoxins, exfoliatins and superantigen toxins. "The ST398 isolates from swine, milk, carcasses and meat lack several clinically important *S. aureus* associated virulence factors, including PVL ["flesh-eating"]. Generally, only some haemolysin encoding genes and the agr type I were present. Other virulence mechanisms related to the adhesion or production of biofilms may play an important role in the wide spread of ST398 isolates." An Austrian study (Krziwanek *et al.*, 2009) found that all CC398 isolates examined were negative for PVL. However, the risk of invasive infections from CC398 MRSA is not zero. In some cases (although none so far in the U.S.), CC398 MRSA has been associated with serious infections such as endocarditis (Ekkelenkamp *et al.*, 2006), ventilator-associated pneumonia (Witte *et al.*, 2007), or severe soft-tissue infection (van Loo, I. *et al.*, 2007; Wulf *et al.*, 2007; Declercq *et al.*, 2008).

To date, no deaths have been reported for CC398 MRSA. Still, even simple infections with CC398 are uncommon enough in Europe that their detection is noteworthy (Potel *et al.*, 2009; Aspiroz *et al.*, 2010). In a Belgian study of pig farm workers, 1 out of 48 farm personnel carrying CC398 MRSA had a concurrent infection (skin lesion) with CC398 MRSA (Denis *et al.*, 2009).   In the Netherlands, Van Rijen et al. (2008) found the odds ratio for the frequency of infection in typable MRSA versus non-typable MRSA in hospitalized patients (i.e. CC 398) to be 4.83 (95% CI of 1.34 to 17.09), corresponding to a relative risk of 5.83 [7]. Therefore, we adjust the ratio of estimated annual invasive CC398 MRSA infections to colonized downward from the

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[7] Note that: [Invasive CC398 cases + Invasive non-CC398 cases]/colonized cases = .0156

[Invasive CC398 cases + 4.83 x Invasive CC398 cases]/colonized cases = .0156

5.83 x Invasive CC398 cases/colonized cases = .0156

→Invasive CC398 cases/colonized cases = 0.0156/5.83 = 0.0027

above initial estimate (0.0156 of colonized people per year) to approximately $0.0156/5.83 = 0.0027$ of colonized people per year.

However, even this reduced estimate probably vastly overestimates the risk in the U.S., based on the observed scarcity of cases. In a comprehensive study of 1166 MRSA isolate submissions in Iowa (invasive cases only) from 1999-2006, *no* CC398 strains were found (Van De Griend *et al.*, 2009). We note that 343 of these isolates were from the latest year, 2006. In addition, Smith *et al.* (2009) state, in apparent reference to the same study group, that "we have not identified this strain among the hundreds of human MRSA isolates examined in several ongoing studies of MRSA (including invasive infections) in Iowa". A member of the Van De Griend *et al.* study group reported that typing had been performed on all 2007 isolates and some of the 2008 isolates (Diekema & Herwaldt, 2010). Yet no reports of CC398 MRSA have publicly appeared from this ongoing analysis. Thus, while CC398 appears likely to be not uncommon among Iowa swine, there are no reported cases of invasive or even soft-tissue infection cases of CC 398 in Iowa through the time of the most recent studies, despite the fact that Iowa accounts for 28% of U.S. pork production (USDA, 2008).

No correlation between total MRSA prevalence and pork production has been found on a state-by-state basis. Figure 3 shows the results of combining 2006 state-by-state data from the USDA (USDA, 2008), U.S. Census Estimates, and MRSA prevalence among inpatients at health care facilities (Jarvis *et al.*, 2007). While Iowa has by far the most hogs per capita (5800 hogs/1000 people), its overall MRSA rate of 41/1000 among inpatients was less than the average of 44.5/1000 over all 50 states. The correlation between MRSA/1000 and hogs/1000 for the 50 state data points is -0.12. Moreover, rates for MRSA (all strains) bloodstream and surgical site infections in Iowa both decreased significantly from 2008 to 2009 (first 6 months), by 23% and 55% respectively (IHC, 2009).
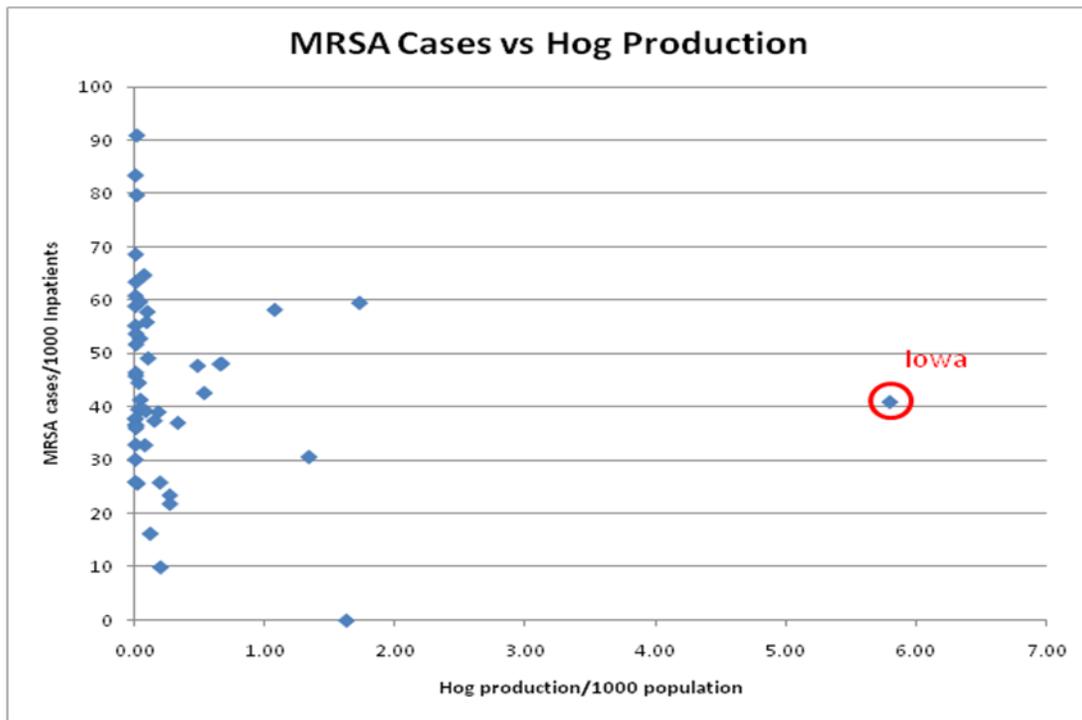
Figure 3. MRSA Cases/1000 Inpatients versus Hog Production/1000 Population in States of the US

In summary, for a period of one year, and likely longer, there were no detected invasive CC398 MRSA cases in Iowa, even though pigs likely had significant colonization rates. To put an upper bound on the probable human health risk that is consistent with these observations, we first estimate the mean number of human colonizations of CC398 MRSA in Iowa as:

0.28 of U.S. pigs in Iowa x 335,964 U.S. pig farmers x 0.28 herd prevalence x 0.65 colonization rate $\approx$ 17,121 colonized pig farmers in Iowa.

If an estimated 17,121 CC398 MRSA colonizations in Iowa during a given year produced 0 invasive cases, then, using a Bayesian analysis similar to that described earlier, we can estimate the annual posterior probability of infection given colonization as belonging to a beta distribution with mean: $1/17,123 = 5.84\ e^{-5}$. Because the prior distribution for the mean posterior annual infection probability is Uniform[0,1] with mean

0.50, however – four orders of magnitude greater than the final estimate – this should be considered an extremely conservative (high) upper bound. To allow for uncertainty in the underlying colonization rate, we assume that our estimated number of colonizations follows a normal distribution with mean 17,121. To obtain the standard deviation, we simulated 100,000 trials of the estimate, using the probability distributions described earlier for the components, and multiplying the results. The resulting variates had a standard deviation of 4140.4. Therefore, 1/(*infection rate*) has approximately a **N(17123, 4140)** probability distribution.

Estimating Secondary Cases

While transmission of MRSA between hospital patients is a significant health concern worldwide, the secondary case rate for CC398 MRSA appears to be much lower than that for other types of MRSA. For instance, recall that Cuny *et al.* (2009) compared rates of CC398 MRSA colonization among individuals in Germany in direct contact with pigs, their family members, and students attending school in a high-density pig farming area, with rates of 86% (97/113), 4.3% (5/116), and 0.6% (3/462) respectively (the colonized student were all found to have lived on pig farms). Nasal colonization was also found among 45% (22/49) of veterinarians attending pig farms and in 9% (4/44) of their family members.   In a study by van Cleef *et al.*(2009) , veterinary sample takers gathering MRSA samples from pigs were themselves tested before and after the sampling. CC398 MRSA was acquired by 48% of the sample takers immediately after exposure. However, in 11 of the 13 cases the strain was not found the next day. Wulf *et al.* reported an instance of an apparent outbreak of CC398 MRSA in a Dutch hospital (Wulf *et al.*, 2007). This and other anecdotal instances reported in Europe indicate that secondary infections are possible.

Van Rijen et. al (van Rijen *et al.*, 2008) compared the secondary transmission rates for typable MRSA versus non-typable MRSA (presumably CC398) in a Dutch hospital. They reported that "Sixteen patients who carried typable MRSA stayed in the hospital without precautions, for a total of 138 days. Twenty-two of 2139

persons exposed to these 16 patients were shown to be colonized with the index strain. For nontypable MRSA, during 37 exposure days for 8 patients, 0 of the 408 exposed patients and health care workers were colonized….. Only recently, in 2007, 1 health care worker was colonized with nontypable MRSA, acquired from a patient who had not been treated in isolation."

Based on these data, a conservative upper bound on the secondary case rate, using Bayesian analysis again, would be that the transmission rate of CC398 MRSA within the hospital is approximately $(1/410)/(22/2139) = 0.238$ that of typable strains. Further, it appears that the average length of stay for nontypable MRSA was $(37/8) = 4.625$ days versus $(138/16) = 8.625$ days for typable MRSA, a reduction by a factor of $4.625/8.625 = 0.536$. As discussed in the previous section, the Van Rijen results also imply a rate of conversion from colonization to infection in nontypable strains that is approximately $(1/4.83) = 0.207$ that of typable strains.

We can utilize this information by employing the framework of Webb et al. (2009), who developed a set of deterministic differential equations describing the epidemiological dynamics of MRSA in hospitals. Their motivation was to determine the conditions under which community acquired MRSA (CA-MRSA) would displace hospital acquired MRSA (HA-MRSA) as the dominant infection. They derived a basic reproduction number, R_0, which corresponds to the steady state number of secondary infections per initial infection. Using baseline empirical parameter values, they computed an R_0 for community associated MRSA (R_0^C) of approximately 0.66, and 0.69 for hospital associated MRSA (R_0^H). We modified their baseline model by multiplying each transmission parameter, β, by 0.238, each infection rate parameter, φ, by 0.207, and each length of stay parameter, γ, by 0.536, in accordance with the Van Rijen *et al.* results discussed above. Using the same equations, with all other parameters held at baseline values, we obtained an R_0^C value of approximately 0.04, and an R_0^H value of approximately 0.05. Therefore, if cases of invasive CC398 MRSA are ever detected in U.S. hospital, it is likely that their ability to spread would be at least 16 times less than that of existing MRSA strains.

In our QRA model, we will use a midpoint value of 0.045 to capture the secondary hospital case rate. We will not attempt to estimate the uncertainty, since the value has an insignificant effect upon the total.

RESULTS

Objective 1: Data-Driven Upper Bound on CC398 MRSA Risks to Humans

Combining the preceding estimates allows a quantitative estimate of the annual burden of CC398 MRSA infections from pigs in the United States. A conservative *point estimate* for the mean annual number of CC398 MRSA cases is:

Annual U.S. Cases < (Number of US Pig Farmers) x (fraction of CC398 MRSA-positive farms) x (fraction of colonized workers on MRSA-positive farms) x (Annual rate of Infection per person-year | colonization) x (1 + secondary case rate) = (335,964 U.S. pig farmers) x (0.28 MRSA-positive herd prevalence) x (0.65 colonization fraction) x (5.84 e^{-5} infections per year per colonized worker) x (1 + 0.045 spread factor) = **3.73 year**.

Using the uncertainty distributions for inputs developed above (and 100,000 iterations of random sampling of inputs) yields the uncertainty distribution for annual CC398 cases in Figure 4.
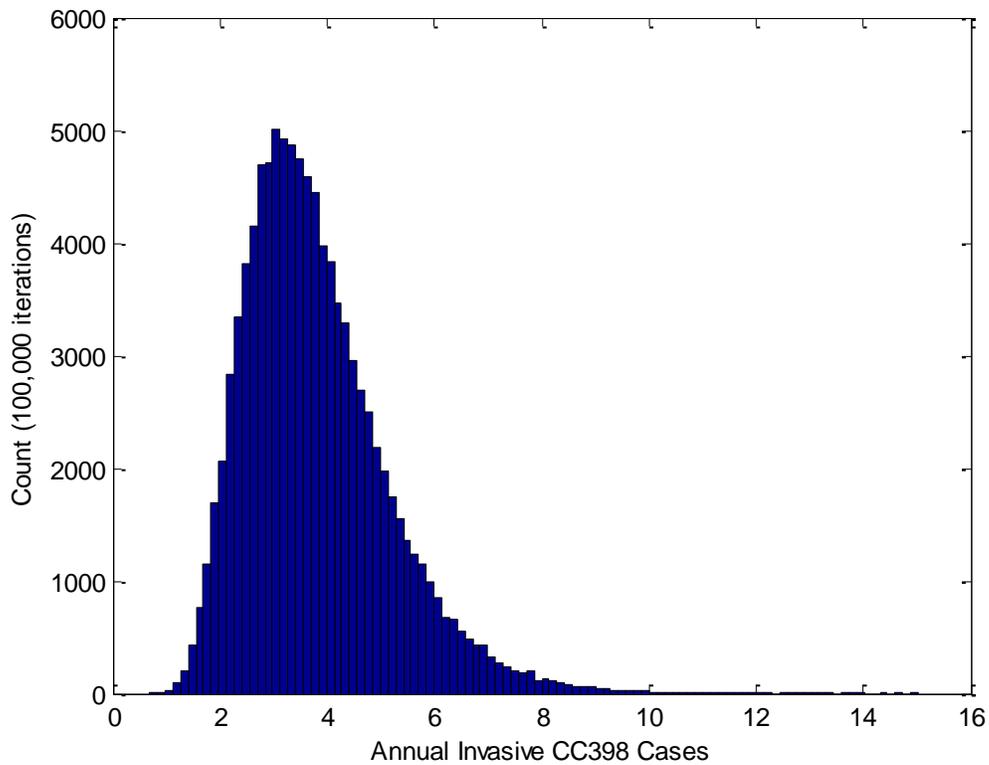
Figure 4. Distribution of (Conservative) Estimate for Annual Invasive CC398 MRSA Cases in the U.S.

Attributable to Pigs

This distribution has a mean of 3.79 and a standard deviation of 1.34. Both the point estimate and the uncertainty distribution are based on the assumption that CC398 MRSA was not detected in Iowa for a one year period. In the longer term we could say that the point estimate is approximately **3.79/N**, where N is the number of years since 2006 during which no invasive CC398 cases are detected. For example, if no cases are detected through the end of 2010, then the conservative (plausible upper bound) point estimate for the total number of such CC398 infections per year would be 3.79/5 = 0.76.

A fraction of invasive MRSA cases lead to death. Klevens, et al. (2007) estimated that approximately 20% of invasive MRSA cases will be fatal. However, *there have been no fatalities associated with CC398 MRSA strains in the U.S. or Europe.* Therefore the mortality rate for CC398 in the U.S. is likely to be much less than 0.20 x 0.76 invasive cases/yr = 0.15/yr and may even be zero.

Objective 2: Comparison of Risks From Different Pathways

As discussed above (Hazard Identification), the contribution to any CC398 MRSA-related treatment failures that might arise, stemming from handling or eating meat from pigs with MRSA, is negligible (EFSA, 2009). The risk analysis is dominated by the direct contact pathway.

DISCUSSION

Does Tetracycline or Zinc Cause CC398 MRSA in Pigs?

To what extent can any CC398 cases occurring in humans and transmitted from pigs be attributed to the use of antibiotics in those pigs? There has been some recent speculation that the development of CC398 MRSA among pigs has been due to the relatively heavy use of AGPs in modern swine feeding operations in general, and to the use of tetracycline-based feeds in particular. The main pieces of (circumstantial) evidence motivating this speculation are that CC398 is the most common type of MRSA found among swine (Khanna *et al.*, 2008; Hasman *et al.*, 2009; Smith *et al.*, 2009), and that all CC398 MRSA in swine seem to be tetracycline-resistant (de Neeling *et al.*, 2007; van Duijkeren *et al.*, 2008; Smith *et al.*, 2009). In addition, preliminary results of a study by Smith et al. (2009) compared MRSA prevalence at confinement versus "organic/antibiotic-free" pig farms in Illinois and Iowa. They found no MRSA on the antibiotic-free farms, but significant amounts, 24% overall prevalence, on the confinement farms which use conventional feed and medication regimens.

However, recent research indicates a much more likely cause for the selection of CC398 MRSA: zinc compounds often used in the feed of newly weaned pigs. In contrast to the above findings by Smith *et al.* , a recent Canadian study (Weese, J. S. *et al.*, 2009) selected an *antimicrobial free* farm for a longitudinal study of MRSA prevalence in piglets. CC398 MRSA was decidedly present, with prevalence peaking at 65% among 42

day old piglets.   Therefore, use of antibiotics on pigs is not necessary for developing CC398 MRSA. It is also

the case that pig farms subscribing to organic practices have numerous management and husbandry techniques,

besides non-use of antibiotics, that differ from confinement operations.   For example, measures particularly

recommended for organic pig farms such as bio-security, closed herd, all-in-all-out, separation by age, and more

conscientious health management could account for observed differences.   These measures would help reduce

the spread of MRSA between farms, which was shown to be the primary transmission route in Dutch pigs (van

Duijkeren *et al.*, 2008) and could account for the results seen by Smith *et al*.

In some countries, including the US, zinc is routinely fed at pharmacological doses – 1500 to 3000

mg/kg – to newly weaned pigs for treatment or prevention of diarrhea (Poulsen, 1995) and for growth

promotion (Mavromichalis *et al.*, 2000; Baker *et al.*, 2001). The ban (in the EU) or discouragement (in the U.S.

and other countries) of the use of antibiotics for similar purposes has increased the motivation to use alternative

feed additives such as zinc compounds (Simpson, 2009).   Use of zinc oxide is recommended on organic pig

farms (PFI-ISUE, 2007) as an alternative to antibiotics. Lack of pharmacological levels of zinc in newly

weaned pigs has been shown to have a negative economic impact (Tokach *et al.*, 2000), so there are strong

motivations for using it.

Aarestrup *et al*. (2010) compared MRSA and MSSA from various swine farms in Denmark. No

difference in susceptibility to tetracycline was observed between methicillin-resistant and susceptible isolates of

CC398 MRSA, consistent with previous research. Similarly, a recent study of *Staphylococcus aureus* carried

by swine and swine farm personnel in Belgium (Denis *et al.*, 2009) similarly found that 83% of MRSA isolates

were resistant to tetracycline while *all* MSSA isolates were resistant to tetracycline.   In the Aarestrup *et al*.

study, *most (74%) of the CC398 MRSA isolates had reduced susceptibility to zinc chloride whereas all MSSA*

ST398 isolates showed very little resistance to zinc chloride. The authors conclude that this is the first

biological evidence that *zinc compounds, rather than tetracycline, can be implicated in the emergence of MRSA*

among swine in Denmark. While the routine use of zinc feed additives in Denmark is limited by EU

regulations, the authors note that the prescribed use of zinc in pigs in Denmark is very high. They also note that farmers can buy zinc compounds themselves without a prescription, concluding that it is likely that virtually all piglets in Denmark receive zinc compounds.

There is other evidence to support the conclusion that use of zinc in the feed of newly weaned pigs (pigs are typically weaned at ages 3-6 weeks) may be partially responsible for the development of CC398 MRSA in pigs. Smith *et al*. (2009) reported that MRSA prevalence in pigs from MRSA-positive farms in Iowa generally decreased as a function of age, with values of 100% in 9-week old pigs (the youngest age group tested) and 36% among adult pigs. Research in Canada has shown that MRSA prevalence is highest shortly after weaning . In Weese *et al*. (2009) pigs on an antimicrobial free farm were tested for MRSA at various ages ranging between 1 and 70 days. MRSA prevalence started at 0 on the day 1 tests, peaked sharply at 65% on the day 42CC MRSA.

Another possible clue to the biology of MRSA comes from research by Conrady *et al* (2008), who found that zinc is required for MRSA to form biofilms - bacterial communities that adhere to both biological and abiotic substrates. These biofilms are difficult to eradicate and enable the spread of bacteria over periods of time.   While there is no direct evidence that zinc compounds in the feed of piglets have similar growth-enabling or disease-spreading effect, the implied zinc/MRSA causal link may warrant further investigation.

Conclusions

The specter of a surge in life-threatening MRSA infections in the United States is daunting. That such a surge could be caused by selection pressures for MRSA on pig farms that use antibiotics (specifically, tetracycline), with MRSA-contaminated meat then spreading to the public through the food supply chain, has raised great concerns and been a topic of national news (Box 1). Missing from the discussion, however, has

been any careful discussion of the quantitative magnitude of the health risks being discussed. The preceding calculations help to fill that gap.

The pork industry in the United States is under great political and activist pressure to change beneficial production practices, including prudent use of animal antibiotics to prevent disease and improve productivity, because such practices are being blamed for a significant role in causing emerging multi-drug-resistant "superbugs," such as MRSA. However, QRA calculations indicate that, quantitatively, the contribution of the pork industry to human health risks from MRSA is negligible. *Human antibiotic use in hospitals* accounts for almost all MRSA risks in humans, and animal sources (CC398) have so far contributed no known MRSA mortalities or severe infections. As in Europe (EFSA, 2009), so in the United States, there appears to be no detectable risk to the public from MRSA transmitted via the food chain. News stories to the contrary (Box 1) are essentially propagating a scientific urban legend, and should not be used to shape risk perceptions or policy; they are merely irresponsible journalism.

The numbers (negligible risk via the food chain, perhaps 1 excess infection per year for all farm workers) provide a strong contrast to *perceived* (but, typically, not quantified) risks, which can be large (Box 1). This contrast illustrates why QRA information is essential to inform current policy debates, e.g., on the Preservation of Antibiotics for Medical Treatment Act (PAMTA), and to provide scientific support for saner policy decisions

We have sought to place empirically justified upper bounds on risk (number of MRSA-related treatment failures per year, or cases of compromised treatment), in the United States, caused by use of antibiotics in swine. To date, no such cases have been documented. We estimate that the true case rate is unlikely to exceed about 1 excess case per year, and could be as small as zero. We have also sought to realistically assess the relative contributions to MRSA-related treatment failures of different swine-to-human MRSA transmission pathways, including handling or eating meat products, environmental runoff, and direct contact. The direct contact pathway dominates the calculation. There is a real potential for pig farmers to acquire MRSA infections

from pigs. We estimate that the case rate could be as high as 1 excess case per year of MRSA infection (specifically, CC398 MRSA infection) in the entire United States, although this estimate may decrease as more years pass with no observed cases of pig-associated (CC398) infections. However, it is not at all clear that such infections are increased by the use of animal antibiotics, including tetracycline, as there appears to be no causal relation between their use and MRSA prevalence. To the contrary, the zinc products used on antibiotic-free farms (as well as on conventional farms) provide a biologically plausible source of selection pressure for MRSA. Since the human health risk due to farm-associated MRSA appears to be minimal, changing current farm practices to use less zinc (or fewer antibiotics) would not be expected to make any detectable change in MRSA risks.

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