

INFECTIOUS DISEASE

From Pigs to People: The Emergence of a New Superbug

The discovery of a novel strain of MRSA able to jump from livestock to humans has sparked a multicountry effort to see how dangerous it might be

The first infection was puzzling, almost inexplicable. In July 2004, Andreas Voss of Radboud University Nijmegen Medical Center in the Netherlands admitted a 6-month-old girl for surgery to repair a congenital heart defect.

Because an infection with the common bacterium *Staphylococcus aureus* would pose a grave risk following heart surgery, Voss and his colleagues screened the baby girl for the microbe. They found not just *S. aureus* but also a menacing drug-resistant form known as methicillin-resistant *S. aureus* (MRSA). The physicians were flummoxed. Although MRSA has reached epidemic proportions in much of the developed world, MRSA infections are rare in the Netherlands, thanks to an aggressive “search and destroy” policy the country launched in the mid-1990s to screen for the superbug in health-care settings, where it most frequently spreads. In the Netherlands now, the biggest risk for MRSA infection is a stay in a germ-ridden foreign hospital.

But this baby girl had never left the country. “We couldn’t find a single source” of exposure, Voss recalls. But there was one clue: Her parents were pig farmers.

Within weeks, a second MRSA-colonized patient appeared at the hospital: another pig farmer. Then a third: the child of a veterinarian who worked only with pigs. “It was dumb luck I would say,” Voss recalls. “We had within a short time three unexpected cases that all had pig written on them.”

Pigs and other livestock commonly, and generally harmlessly, harbor *S. aureus*. But except for a single report buried in the scientific literature, no one had realized that pigs

or other livestock harbored MRSA, and no MRSA strain had ever been known to jump from livestock to humans. If the Dutch doctors’ fears were correct, a novel strain had just gained that ability, opening up a new route for a potentially dangerous superbug to spread among humans. “Initially, we were very much afraid that this would be a major problem that could spread to the entire population,” says Jan Kluytmans, a microbiologist at VU University Medical Center in Amsterdam whom Voss recruited early on to help investigate.

In recent months, the dangers of livestock-associated MRSA have been played up in controversial media reports, including a special series by *CBS Evening News*, as a consequence of the livestock industry’s indiscriminate use of medically important antibiotics to fatten livestock. Such uses can lead *S. aureus* and other bacteria to swap whole sets of resistance genes, potentially transferring resistance to antibiotics like methicillin that haven’t even been used in agriculture.

Such awareness has fueled a push to restrict this long-debated use of antibiotics; this summer, the U.S. Food and Drug Administration has proposed to phase it out. Industry is opposed, saying the risk is negligible. Both sides are using the emergence of this new superbug to bolster their cases.

So far, the worst fears about the strain have not been realized. It did jump from pigs to people, scientists determined through gumshoe detective work. And it has caused serious disease—although rarely—among farmers and veterinarians who work with pigs and other livestock, and their families, although most of them carry the microbe harmlessly in their noses. But it doesn’t appear to be readily transmissible between humans, so the chance of a broad community epidemic seems low.

However, MRSA readily mixes and matches genes with other bacteria that make it more virulent, more trans-



Index case. MRSA from pigs on Eric and Ine van den Heuvel’s farm was detected in their daughter, Eveline, when she was an infant.

missible, and harder to treat—and this newly emerged strain could take that route too. “Is it something to worry about? Absolutely,” says infectious-disease specialist Vance Fowler of Duke University Medical Center in Durham, North Carolina.

A growing menace

MRSA appeared first in hospitals, where medical procedures can ferry bugs into the unprotected interior of the body and patients are particularly vulnerable to infection. Until the 1990s, it posed only a mild threat, and the vast majority of *S. aureus* infections remained sensitive to methicillin. But since then, MRSA strains have increasingly displaced sensitive *S. aureus* strains and acquired resistance to other antibiotics, making hospital infections far more dangerous (*Science*, 18 July 2008, p. 356). Today, *S. aureus* accounts for about 20% of all hospital bloodstream infections in the United States, and 65% of the *S. aureus* infections in intensive-care units resist methicillin, among other antibiotics. MRSA killed approximately 18,650 Americans in 2005, researchers from the U.S. Centers for Disease Control and Prevention (CDC) reported in *The Journal of the American Medical Association* in 2007, a higher death toll than that of HIV/AIDS.

For years, the most dangerous strain of MRSA remained inside hospitals. Some strains began to circulate in the wider com-



At risk. Pigs in confinement barns can harbor MRSA. A few farm families have contracted dangerous infections.

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munity, mostly among people in tight spaces such as prisons, and those with a lot of skin contact, such as family members and participants in contact sports. They were largely considered a nuisance, far less dangerous than hospital-acquired infections, mostly because they infected healthy people whose skin and immune defenses kept them from infiltrating the body, and they were easier to stop with antibiotics.

Since the 1990s, however, community-acquired MRSA has grown more menacing, picking up genes that make it more virulent and resistant to an increasing variety of antibiotics. Most life-threatening infections still occur in hospitalized patients or those who have undergone outpatient treatments such as dialysis or surgery. But each year in the United States, community-acquired MRSA causes about 13,000 infections serious enough to require hospitalization and more than 1400 deaths, according to the 2007 CDC report. What's more, the lines between hospital-associated and community-associated strains are blurring, as strains formerly limited to the hospital have begun colonizing healthy people, and strains once limited to the community now sicken many patients in hospitals.

So when the livestock-associated strain showed up in people, public experts had no idea how risky it might be or become.

A peculiar strain

The three isolates from the Nijmegen hospital turned out to be from a single strain, which researchers now call ST398.

With permission from the young patient's father, Voss's team cultured bacteria from pigs on his farm and did a quick and dirty test on him and 25 of his pig-farming colleagues. Within 2 months of the girl's admission, they'd learned that one in four was asymptotically carrying MRSA, compared with just 0.03% of the general Dutch population. Although crude, the analysis provided pretty strong evidence that the bug had come from pigs.

To confirm that route of transmission, Kluytmans and Voss did a case-control study that examined years' worth of MRSA infection data housed at the Dutch national microbial reference center. In 2007, they reported in *Emerging Infectious Diseases* that those who carried ST398 were 12 times more likely to be pig farmers than nonfarmers and that almost all the MRSA from farmers belonged to strain ST398. Cattle farmers were also 20 times more likely to carry the strain. The strain has since turned up in chickens, horses, dogs, and cats, posing a potential but poorly understood threat to humans.

Soon scientists in two other European pig-

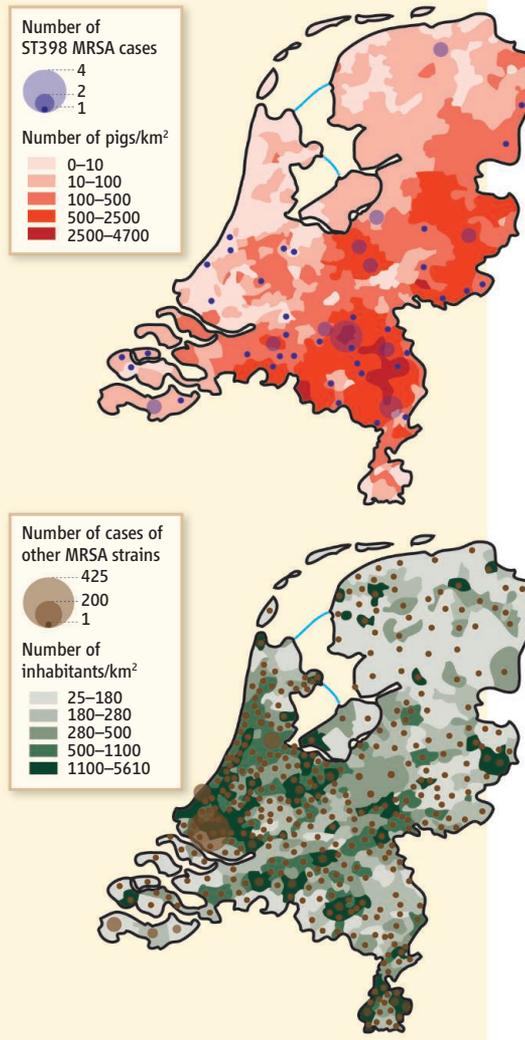
farming hot spots, Denmark and Germany, began finding the strain in their backyards. And in 2008, medical microbiologist Robert Skov of the Statens Serum Institut in Copenhagen reported a case-control study in *Emerging Infectious Diseases* that showed that the strain had spread in Denmark and was clearly linked to pig farming there as well.

No one knew then how virulent the strain was, but some of the data were and remain concerning. Case reports continue to appear of MRSA strain ST398 causing minor skin and soft tissue infections as well as mastitis, severe wound infections, pneumonia, and even some flesh-eating disease in countries throughout Europe. To date, Voss has seen about 10 cases of severe bloodstream infections of ST398 and two ST398 infections following hip-replacement surgery.

More recently, researchers have tested how readily ST398 can spread among humans and have learned, somewhat reassuringly, that it does not spread easily beyond farms. Medical microbiologist Wolfgang Witte's team at the Robert Koch Institute in Wernigerode, Germany, tested at a school in North-Rhine Westphalia, an area of Germany where pigs are farmed intensively, figuring that if the strain spread among healthy people, it would likely show up among schoolchildren who spend each day together. The team reported last year in *PLoS ONE* that while 250 of 462 students at the school were positive for some sort of *S. aureus*, only three carried ST398 MRSA in their noses, and all three lived on pig farms.

ST398 is also spreading on farms in North America, according to a handful of recent studies. For example, last year Tara Smith of Iowa State University in Ames and colleagues reported in *PLoS ONE* that nearly half the hogs and 45% of the workers on a Midwestern hog farm were colonized with ST398. But the strain seems less menacing in North America than it is in Europe. Only one farm worker in Smith's study became ill. And microbiologist Michael Mulvey's team from Canada's National Microbiology Laboratory in Winnipeg reported in *Emerging Infectious Diseases* in April that only 0.25% of the 3687 MRSA isolates from people infected in Manitoba and Saskatchewan were strain ST398. Researchers speculate that the transatlantic difference may simply be due to the fact that ST398 got a head start in Europe, or it may face more competition in the United States and Canada from other human-adapted MRSA strains.

For New MRSA Strain, a New Distribution



Follow the pork. In the Netherlands, rates of human infections with MRSA strain ST398 tracked with pig populations (*top*), while rates of other MRSA strains tracked with human populations (*bottom*).

Opinion is divided on whether ST398's behavior so far provides reassurance about its future conduct. Brandi Limbago of CDC, who tracks infection-causing MRSA strains in the United States, says that "for now I think it's a nonissue in this country." But others, such as Fowler of Duke, warn that it is too soon to sound the all clear. Half the swine herd in the Iowa study was carrying ST398, he points out. That's a lot of pig noses. And the strain could yet adapt and become more dangerous, just as community-acquired MRSA has done. That's why ST398 needs to be carefully monitored, says veterinary microbiologist Gail Hansen of the Pew Health Group in Washington, D.C. "Sometimes these things don't become a problem, but you don't want to take your eye off the ball."

—DAN FERBER