Disturbing new findings have provided a key link in the chain of evidence connecting antibiotics used on livestock to outbreaks of disease caused by antibiotic-resistant human pathogens

Superbugs on the Hoof?

When the severe diarrhea didn't stop after nine awful days, the 62-year-old Danish woman dragged herself to the emergency room at Bispebjerg Hospital in Copenhagen. The diagnosis was a cinch: food poisoning from *Salmonella*. Doctors rolled out their big gun, an antibiotic called ciprofloxacin that can vanquish the nastiest *Salmonella* strains in a few days. But as the hours passed, the infection worsened—becoming so bad that the *Salmonella* punched a hole in her colon, allowing it and other bacteria to invade the rest of her body. As the situation grew desperate, doctors blasted her with heavy doses of two more antibiotics and stitched up her damaged colon. The drugs knocked off the *Salmonella*, but other escapees from the gut sent her into septic shock; one by one, her organs failed. Four days after doctors realized the *Salmonella* was impervious to ciprofloxacin, she was dead.

The Danish woman was not the first person to succumb to a superbug resistant to antibiotics. But she and another *Salmonella* victim in the summer of 1998 put a human face on an alarming trend: pathogens rapidly acquiring resistance to drugs that are similar to antibiotics used for years to treat livestock. In a nice piece of detective work, a team led by microbiologist Henrik Wegener of the Danish Veterinary Laboratory in Copenhagen traced the drug-resistant strain of *Salmonella* to infected swine. To fight *Salmonella* outbreaks, some farmers had been dosing herds with enrofloxacin. It turns out that this drug and ciprofloxacin belong to a class of compounds called quinolones that gum up bacterial machinery for replicating DNA. The researchers traced the deadly strain to contaminated pork products from a single Danish herd. The findings, reported last November in *The New England Journal of Medicine (NEJM)*, are the strongest indictment yet implicating livestock antibiotics in human deaths. Says microbiologist Abigail Salyers of the University of Illinois, Urbana-Champaign: "It's the closest that anybody has come to a smoking gun." And just last week, researchers reported evidence linking a case involving a resistant *Salmonella* strain in the United States to the use of animal antibiotics.

For decades farmers have mostly had free rein in dosing livestock with antibiotics to treat illnesses, prevent infections, and fatten animals on less feed. With evidence mounting that this unfettered practice can spawn new superbugs, agencies worldwide are beginning to clamp down on antibiotic use in agriculture. The European Union has issued new rules limiting the use of several livestock antibiotics, while the U.S. Food and Drug Administration (FDA) has proposed similar regulations.

The moves have riled industry officials, who argue that antibiotics are essential to keeping animals healthy and the food supply safe. They contend that regulators and public health activists are blowing the problem out of proportion. The most serious threat, they point out, comes from indiscriminate use of antibiotics in people, not livestock. "We're not saying there isn't any concern," says Richard Carnevale of the Animal Health Institute, which represents U.S. animal-drug producers. "But in the whole scheme of things, we believe that it's relatively minor."

A growing number of scientists, however, are taking the threat quite seriously, as is the British Royal Society of Medicine, which brought experts together in Washington, D.C., this week to brainstorm on the issue and to educate the public. Although drug use on the farm may have little to do with drug-resistant tuberculosis or other pathogens transmitted from person to person, it "has everything to do with bacteria acquired through the food supply," says medical epidemiologist David Bell of the U.S. Centers for Disease Control and Prevention (CDC).

Wallowing in bacteria. After a vicious strain of drug-resistant *Salmonella* killed two people in Denmark in 1998, scientists traced the bug to a single herd of Danish pigs. The strain, they found, was resistant to a livestock antibiotic similar to the human drug that failed to cure the victims.

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Gut reaction

The case against antibiotic use in livestock rests largely on drug resistance observed in food-borne pathogens such as *Salmonella* or *Campylobacter*, which often infect animals without causing symptoms. First, microbial sleuths must link a livestock antibiotic to a drug-resistant strain. Next, they must show that the strain can survive the slaughterhouse. Finally, to cement the connection to human illness, they must prove that eating tainted meat leads to an infection that defies antibiotic treatment. The last link is the hardest to verify. "That's where the chain of evidence starts to get frayed," Salyers says.

Luckily for the Danish team, the deadly bug did not take them by surprise. It's a variant of *Salmonella typhimurium* DT104, a strain that resists five common antibiotics and had flared up in many European countries—but rarely in Denmark. Hoping to keep it at bay, Danish officials set up in 1997 what Wegener calls the world's most aggressive surveillance system for resistant *Salmonella*. They test for drug resistance in every Danish patient who sees a doctor for a *Salmonella* infection, about 3200 people a year; in roughly 1 million samples of meat shipped each year to grocery stores; and in nearly every flock of chickens and herd of pigs—the usual sources of *Salmonella* that infect people—raised for the market.

When word came on 18 June 1998 that a quinolone-resistant strain had shown up in a hog slaughterhouse on the island of Zealand, Kåre Mølbak of Copenhagen's Statens Serum Institute leaped to action. By coincidence, earlier that day his team had identified samples of a vicious DT104 strain in five Danish patients. This strain, and the one in the slaughterhouse, beat back the same

Pigs were treated with antibiotic similar to cipro

The strain that killed the patient was the same as the one isolated from pigs treated with cipro. The two strains had the same "signature" or "fingerprint".