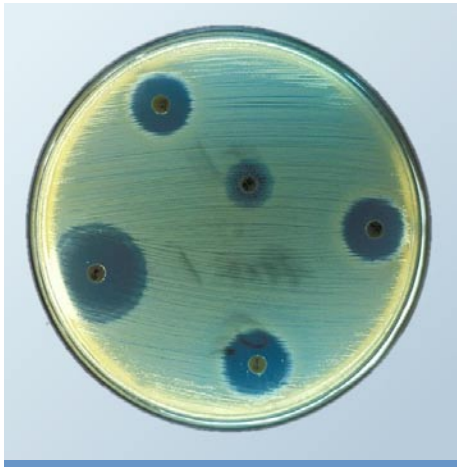
Farming out Antibiotics: The fast track to the post-antibiotic era

Author: Dr. Kristen Kerksiek | March 22, 2010

Its depths are teeming with life, an ancient and complex ecosystem that we don't fully know or understand. Over thousands of years, this community has evolved to ward off pathogenic microorganisms, participate in digestion, synthesize essential nutrients and train the immune system. However, it seems that a fragile balance has been damaged, and it's probably affecting our health. The depths in question are in our own bodies, and the life is the microbiota – resident microorganisms - that colonize our mucosal and cutaneous surfaces. Although it has long been appreciated that these microorganisms (primarily bacteria) are beneficial, recent research indicates that they may also be crucial for the development and regulation of the immune system; by altering the composition of this community, the stage may have been set for many health problems that have emerged in the modern world.

Pigs are often colonized but rarely infected with the livestock-borne MRSA strain CC398.
© Simone van den Berg / Fotolia.com

Antibiotics are, of course, used to treat sick animals. However, disease treatment does not account for the majority of antibiotics used in agriculture: there is widespread use of antibiotics to prevent disease or disease spread (prophylaxis/metaphylaxis). And low-dose antibiotic treatment has been used to promote growth of food animals since the 1950s, with studies showing improved production efficiency when antibiotics were given to poultry and swine. Although the mechanisms of this phenomenon have not been clearly defined, it seems that microflora vie with the host for nutrients; if the overall number/species of commensal „competitors" is reduced, more food energy goes to the host.



Once antibiotic resistance has been established, it's often difficult to get rid of *(here testing the sensitivity of Staphylococcus aureus)*. © CDC / Don Stalons

Reports of antibiotic resistance in treated poultry were already published in the 1950s, and antibiotic use in livestock – especially for growth promotion- has faced waves of criticism since the 1970s. In 2006 the European Union followed the examples of Sweden (1986), Denmark (1999) and Switzerland (2000) in banning the use of all antibiotics for growth promotion, even those not used in human medicine. As the United States considers a ban of medically important antibiotics for growth promotion, a bitter debate has again resurfaced. What is the cost of antibiotic use in agriculture?

Many roads lead to resistance

Under the pressure of antibiotic treatment, resistant bacteria can arise in a number of different ways. Researchers are actively investigating resistance mechanisms in the hope that the findings can be used to stem the tide of (multi-)resistant bacteria:

Kohanski MA, DePristo MA, Collins JJ. Sublethal antibiotic treatment leads to multidrug resistance via radical-induced mutagenesis.
Mol. Cell 2010 37(3): 311-320. http://dx.doi.org/10.1016/j.molcel.2010.01.003

Trindade S, Sousa A, Xavier KB, Dionisio F, Ferreira MG, Gordo I. Positive epistasis drives the acquisition of multidrug resistance.
PLoS Genet. 5(7): e1000578 http://dx.doi.org/10.1371/journal.pgen.1000578

Biohazard: Pig Farm

Pig farms are notorious for their "aroma", but the smell won't kill. Another lurking danger, however, just might: a new strain of methicillin-resistant *Staphylococcus aureus*, referred to as species type (st)398 or clonal complex (CC)398, was first identified in Dutch patients in 2003 and was later found to colonize a high percentage of pigs. CC398 has since been identified in pigs (as well as other livestock) – and people - in other Western European countries, North America, China and Singapore.

One of the most "pig-rich" areas in Germany is the Münsterland, which borders the equally pig-rich Twente region of The Netherlands. Dr. Alexander Friedrich from the University Hospital in Münster has been following the infection rate of CC398 in both pigs and humans. "Our latest study with veterinarians showed that up to 85% of farms have MRSA-positive animals, on both the Dutch and the German side of the border. And more than 20% of all incoming hospital patients in the region are colonized with livestock-associated MRSA." With a steady upward trend.

Although antibiotics can no longer be used for growth promotion of animals in Germany, far more antibiotics are used in veterinary medicine than in human medicine (approximately 784 tons vs. 250-300 tons, respectively in 2005; GERMAP 2008). For Friedrich, there is a clear link between the emergence of CC398 and the use of antibiotics in humans and animals. "CC398 here is 100% resistant to tetracyclines, which account for more than 50% of the antibiotics used in livestock; they often need to feed them to pigs as metaphylaxis. And tetracyclines are also the most-prescribed antibiotics by general practitioners on both sides of the border. We have a collective soup of tetracycline in pigs and humans. Inter-species transfer is made easy then."

Infection with CC398 is usually mild but has occasionally been associated with deep-seated infections of skin and soft tissue, pneumonia and septicemia.
© CDC / Bruno Coignard, M.D.; Jeff Hageman, M.H.S.

In a study published last year in the European Journal of Clinical Microbiology & Infectious Diseases, Friedrich and his colleagues found that carriers of CC398 don't have any of the classical risk factors for MRSA; the two strongest risk factors for CC398 colonization were youth (age 3-18 years) and contact with pigs. The vitality of the carriers might explain why CC398 only infrequently causes disease: approximately 1 in 250 individuals colonized with CC398 develops disease, while the disease rate for other MRSA strains is about 1 in 4. However, there is another possibility: "It could be that CC398 is not yet adapted to humans," says Friedrich.

Not yet. From the bacteria's point of view, there's still room for improvement. And plenty of space to work in. MRSA is typically a nosocomial infection, so the exposed population is relatively limited, an estimated 10 million per year in Germany. For CC398 the numbers look completely different: "46 million pigs, millions of other livestock animals… and many people exposed to livestock and raw meat, for which the risk of transmission is considered to be very low but is not entirely clear. It's a huge reservoir for the bacteria to play in, "says Friedrich. And play they do. The CC398 bacteria analyzed today are different from those discovered by chance in 2003.

Along with pigs, broilers (hens) and veal calves are primary reservoirs of CC398 in affected areas.
© Karam Miri / Fotolia.com

The threat of hospital-acquired MRSA can be reduced by strict infection control measures and reduced use of antibiotics: In the Netherlands, tightly restricted application of antibiotics and a "Search and Destroy" policy – identification of carriers and elimination of colonization – has succeeded in essentially wiping out MRSA in health care institutions. Dealing with CC398, however, will be more difficult because so little is understood about the critical points for bacterial transmission. "Agricultural conditions will have to change to control animal movement and reduce infection," says Friedrich. "However, 5 to 10 years of intense investigation of transmission in human and veterinary medicine will be required before effective intervention can be started." Hopefully CC398 will give us the time.

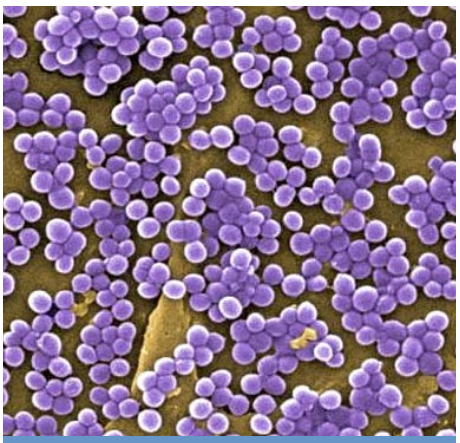
Resistant pathogens linked to antibiotic use in food animals:

- multidrug-resistant *Salmonella*
- multidrug (particularly beta-lactam antibiotic)-resistant *Escherichia coli*
- Fluoroquinolone-resistant *Campylobacter jejuni* (causes gastroenteritis); antibiotic withdrawn for use in poultry in the USA in 2005, but resistant strains still prevalent
- vancomycin-resistant *Enterococcus*; a perennial threat in hospital ICUs, linked to human vancomycin use but use of related avoparcin in animals may have contributed
- amantadine-resistant influenza; the antiretroviral drug, which was fed to poultry in China to prevent bird flu infection, is now largely ineffective against human influenza

Burden of proof

To many it may seem like a no-brainer: just like in human medicine, the misuse/overuse of antibiotics in food animals – especially prolonged low-dose treatments for growth promotion - leads to dangerous antibiotic-resistant bacteria. The generally high levels of antibiotic-resistant bacteria in the guts of pigs, chickens & Co. are certainly associated with antibiotic treatment, but it's not easy to unequivocally prove that these bacteria are hazardous to human health.

The gravest danger may not be presented by the transfer of resistant bacteria – either zoonotic or shared – themselves. Bacteria don't at all mind sharing their most intimate genetic secrets with their prokaryotic colleagues, and there is great concern that food animals may serve as a deep reservoir for plasmids and other elements with resistance-encoding genes that can be transferred to other strains or species that are already pathogenic for humans. It seems highly probably that such transfer of bacterial trade secrets already occurs, but documentation of the act is no easy task.



CC398 isolates encoding the cytotoxin Panton-Valentine leukocidin (PVL) are rare but have been sporadically identified in China and Europe.
© CDC / Janice Carr; Jeff Hageman

Opponents of antibiotic use in livestock contend that livestock can be raised both safely and economically without antibiotics; the "experiment" in Denmark and other European nations is deemed a success. Proponents counter – and are supported by the statistics – that following the ban on antibiotics for growth promotion, the use of some antibiotics of human importance (tetracyclines, β-lactames) has increased. Furthermore, they contend that antibiotics protect consumers by keeping sick animals (and potentially infected meat) from going to market and by enabling lower meat prices. However, neither camp is playing with open cards.

Antibiotic-resistant bacteria are ubiquitous; they can be found worldwide in organisms, soil and water. And there is evidence that once resistant strains are established, they're difficult to get rid of. It's therefore crucial to act early and prevent resistance where it is still possible; we can't afford to just hold onto the status quo until we have indisputable evidence. If we want to get off the fast track to a post-antibiotic era, it's time for renewal of a candid discussion.

References and additional reading:

- Köck R, Harlizius J, Bressan N, Laerberg R, Wieler LH, Witte W, Deurenberg RH, Voss A, Becker K and Friedrich AW. Prevalence and molecular characteristics of methicillin-resistant *Staphylococcus aureus* (MRSA) among pigs on German farms and import of livestock-related MRSA into hospitals. *Eur. J. Clin. Microbiol. Infect. Dis.* (2009) 28: 1375-1382. http://dx.doi.org/10.1007/s10096-009-0795-4

- GERMAP 2008: a report about the use of antibiotics and extent of antibiotic resistance from the German Federal Office of Consumer Protection and Food Safety (BVL, Bundesamt für Verbraucherschutz und Lebensmittelsicherheit) http://www.bvl.bund.de/cln_007/DE/08__PresseInfothek/00__doks__downloads/Germap__2008.html

- Lipsitch M, Singer RS and Levin BR. Antibiotics in agriculture: When is it time to close the barn door? *PNAS* (2002) 99: 5752-5754. http://dx.doi.org/10.1073/pnas.092142499

- Smith DL, Harris AD, Johnson JA, Silbergeld EK and Morris JG Jr. Animal antibiotic use has an early but important impact on the emergence of antibiotic resistance in human commensal bacteria. *PNAS* (2002) 99: 6434-6439. http://dx.doi.org/10.1073/pnas.082188899

- Dibner JJ and Richards JD. Antibiotic growth promoters in agriculture: history and mode of action. *Poult. Sci.* (2005) 84: 634-643.

- Collignon P, Powers JH, Chiller TM, Aidara-Kane A and Aarestrup FM. World Health Organization ranking of antimicrobials according to their importance in human medicine: A critical step for developing risk management strategies for the use of antimicrobials in food production animals. Clin. Infect. Dis. (2009) 49: 132-141. http://dx.doi.org/10.1086/599374

  Correspondence: Critically Important Antimicrobial—or Not? http://dx.doi.org/10.1086/648502

  Reply: http://dx.doi.org/10.1086/648503