

The Natural Environment May Be the Most Important Source of Antibiotic Resistance Genes

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I found the recent paper by Wichmann et al. (1) of great interest, and it illustrates an aspect of antibiotic resistance that has concerned me for a long time, namely, the origin of that resistance.

The authors approach the problem from the point of view of misuse of antibiotics in animal food production systems. For years, attempts have been made to make that connection, with a view to restricting antibiotic use in agriculture. Establishing a link has not been truly successful, yet we frequently hear about how antibiotic use should be restricted. The underlying assumption here is that the direct use of antibiotics leads to the development of antibiotic resistance in the animal, which can then be transferred to important human pathogens. On the face of it, the argument seems reasonable, but I suggest it could not be further from the truth.

It must be remembered where these antibiotics came from. The major groups of antibiotics Wichmann et al. studied are the beta-lactams, phenicol, aminoglycosides, and tetracyclines. All of these antibiotics are derived from various environmental microbial species: the beta-lactams from species of the fungus *Penicillium*, phenicol from species of the complex bacterium *Streptomyces venezuelae*, aminoglycosides from species of *Streptomyces* and *Micromonospora*, and tetracyclines from species of the *Actinobacteria* group. These organisms have surely been in existence for millions of years, and their production of these natural antibiotics would have been normal as they competed in the natural environment. A consequence of their activity would have been the development of resistance by other microbes in the environment so they could compete against the antibiotic producers. This would have led to the development of antibiotic-resistant bacteria and antibiotic resistance genes in the natural environment.

So I suggest that all along, the most important source of anti-

biotic resistance genes has been the natural environment. If this is the case, then it should change how we think about the origins of antibiotic resistance and how we should manage it.

I think the large number of resistance genes discovered by Wichmann et al. (1), i.e., 80, supports this idea. The large number of antibiotic resistance genes that are found in manure, and that can be found in the feces of many other animals, comes directly from their environment. Cows eat grass and during that feeding activity take in soil and other material as well, just as chickens do, and the material ingested over time would include antibiotic-resistant organisms and their genes. All of this food material containing these antibiotic-resistant bacteria could easily accumulate in the cow rumen, to be excreted in cow feces, and a similar situation would apply to chickens.

Ultimately, manure and feces may well be sources of resistance genes for human pathogens, but I suggest that how we manage antibiotic resistance must rely on the assumption that the genes come from the environment and are not generated in the food animals.

Reference

1. Wichmann F, Udikovic-Kolic N, Andrew S, Handelsman J. 2014. Diverse antibiotic resistance genes in dairy cow manure. *mBio* 5(2):e01017-13. <http://dx.doi.org/10.1128/mBio.01017-13>.

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Reply to “The Natural Environment May Be the Most Important Source of Antibiotic Resistance Genes”

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O’Toole is absolutely right that most antibiotic genes probably evolved in the environment long ago (1), but the letter ignores the principle of selection, which is an essential component of Darwinian evolution. Antibiotic use in agriculture has been shown repeatedly to contribute to antibiotic resistance among human pathogens and commensals. We do not expect that any microbiologist would argue that human uses of antibiotics “created” resistance genes from scratch. Rather, the large quantities of antibiotics used in agriculture and medicine have selected for resistant strains that were already in the environment, people, or animals; i.e., the frequency of these strains in the population has been increased. It is difficult to explain the sharp increase in antibiotic resistance among human pathogens in the last 2 decades based on environmental sources alone, without the influence of selection.

Copious evidence shows that antibiotic use in agriculture is a contributing factor in the antibiotic resistance problem in human health. In particular, strong evidence suggests that agricultural use affects the frequency and distribution of resistance genes in retail meat, people, and clinical settings. For example, one study presented a survey of *Escherichia coli* in 180 retail poultry meat samples in Wisconsin and Minnesota and in people in hospitals and the community. Phylogenetic and biological characterization showed that the drug-resistant isolates from farm and human samples were very similar, whereas the drug-susceptible isolates differed between the sources (2), suggesting a common source of the resistant isolates. In another study, methicillin-resistant *Staphylococcus aureus* (MRSA) was tracked in 1,036 patients at the time that they were admitted to an Iowa hospital. Patients who lived within 1 mile of a large swine facility were almost three times more likely to carry MRSA than the general U.S. population (3). In another, quite elegant study, complete genome sequencing was used to follow a clade of *Staphylococcus aureus* strains in 19 countries on four continents. The research showed with genomic features such as single nucleotide polymorphisms (SNPs), prophages, and resistance cassettes that the clade originated in humans as methicillin-susceptible strains, spread to livestock, acquired a methicillin resistance cassette, and then migrated back to humans (4). A second study using whole-genome sequencing to track the evolutionary origins of antibiotic-resistant bacteria in Scotland showed that the isolates from human beings were likely acquired from multiple sources, including livestock. Moreover, the results showed that some of the isolates in farm animals were

acquired from people (5), suggesting bidirectional exchange of bacteria between animals and humans. Other studies suggest that people acquire antibiotic-resistant bacteria from meat, and acquisition of resistant organisms corresponds temporally and spatially to antibiotic use in animal agriculture (6). Although agriculture is not the only source of antibiotic resistance genes and resistant bacteria, it is undoubtedly one of the sources of genes and a substantial source of antibiotics that select for resistant populations.

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