

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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