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How Mainstream Oral Antibiotics Cause Major Public Health Problems - And What Can be Done to Avoid Harm

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The discovery of antibiotics that have saved countless human lives was a landmark in human history. But now studies are linking the use of antibiotics in human medicine and food animal production to major public health threats. "Antibiotic resistance" occurs when bacteria adapt in ways that reduce the effectiveness of antibiotics that would otherwise cure or prevent infections. Such resistance currently causes 23,000 American deaths and $34 billion in financial losses annually. Similarly, antibiotic uses are also implicated in disruptions of healthy gut microbiota – disruptions that can cause a wide variety of diseases from diabetes to autoimmune diseases (like inflammatory bowel disease, celiac disease, and joint problems) and various neurological disorders. These diseases lead annually to hundreds of thousands of deaths, hundreds of millions of illnesses, and hundreds of billions of dollars in U.S. financial losses.

The primary strategy for combatting such problems calls for limiting the uses of antibiotics in human medicine and food and in animal production. However, in modern society, antibiotics are essential for human and animal health. Antibiotics cure pneumonia, for example, which still causes 450 million illnesses and four million deaths worldwide each year. Without prompt disease prevention and treatment, minor infections can turn into persistent and life-threatening disasters.

Given the apparent necessity of antibiotics, are the public health costs they cause also necessary, and thus, inevitable? Perhaps not, because recent scientific breakthroughs offer new hopes to address this challenge.

Gut Microbiomes and Antibiotic-resistant Genes

Research I have conducted along with my innovative team has discovered that the problems caused by antibiotic resistance and disruptions of healthy gut microbiota are not inevitable. The application of antibiotics, a necessity for maintaining a healthy society, is not the issue. Instead, the responsibility for harmful side-effects lies in the current mainstream practices for administering antibiotics. Since the 1970s, both humans and animals have primarily taken antibiotics *orally* – and this turns out to be a problem.

Why is that? Trillions of bacteria reside in the guts of humans and animals, exceeding the actual numbers of host cells. Collaboratively, these bacteria play critical roles in human and animal development and health. They help people and animals digest food and nutrients; and they produce small molecules and signals that impact the maturation and functioning of the host person's or animal's immune system and neurological communications. Antibiotics can kill useful bacteria and disrupt their important functions – but it makes a big difference how people and animals receive antibiotics. Our research team found that taking antibiotics by mouth *unnecessarily* exposes the huge populations of gut bacteria to a high concentration of drugs.

This happens because taking antibiotics orally causes a rapid surge in the corresponding antibiotic-resistant gene pool and the disruption of gut microbiota. For instance, in tests done with mice, the same dosage of the commonly used antibiotic *ampicillin* taken for five days by mouth – rather than by injection – led to 100,000 times more antibiotic resistant genes. In both test mice and poultry, moreover, drugs taken by mouth also caused much more damage to the gut microbiota than did the same amounts of drugs administered by injection.

Historical evidence also supports these laboratory findings. Penicillin has been broadly used worldwide since World War II. But the spreading resistance problem was not evident until after the 1970s in industrialized countries, and after the 1990s in China – in both cases after the mainstream method for administering penicillin switched from injection to oral dosages. Such timings make sense of the worrisome trends in

diseases summarized earlier. And this interpretation fits the picture for food animal production, where antibiotics are mostly given by mouth through water and feed, resulting in animal feces that contain antibiotic-resistant bacteria. Indeed, the antibiotic-resistant and microbes-rich feces that billions of animals and humans across the world release each day may be the most impactful factor in the changing global ecology and swelling the antibiotic-resistant gene pool.

Our team has further established – again, by experiments on test mice – that without oral exposure to antibiotic-resistant bacteria before applying antibiotics, the antibiotic-resistant gene pool is no longer detected in mice feces during the five-day treatment periods. This means that reducing antibiotic-resistant genes in food for human and feed for animals is essential. Moreover, the main risk from foodborne antibiotic-resistant microbes comes from ready-to-eat foods, not from the tiny number of pathogens in raw meat and poultry, which are mostly eliminated by further cooking.

Next Steps

These important new findings open the doors for effective and innovative strategies to solve many of the problems antibiotic use has recently caused for human health. Already, through collaboration and prompt actions by the food industry, effective mitigation of the largest foodborne antibiotic-resistant gene pool – in cheeses and yogurt, was already achieved by 2010, just five years after the original discovery.

Human medicine and the practices of producers of food animals are the next places where reforms based on these findings can make a big difference. Beneficial changes in policy and practices are inevitable – and not necessarily difficult to achieve. The good news is that the antibiotics vital to modern health and society's wellbeing are not, themselves, the direct cause of adverse side effects. Instead, the ways antibiotics have recently come to be administered – by mouth, rather than injections – are the culprits in causing antibiotic resistance and killing useful microbes. Those practices can change, allowing humans to continue to use antibiotics, in safer ways with fewer destructive side-effects. All it will take are new, well-targeted efforts to modify practices in patient care, food production, and agriculture in light of the new research findings discussed here.

Read more in Lu Zhang, Ying Huang, Yang Zhou, Timothy Buckley, and Hua Wang "Antibiotic Administration Routes Significantly Influence the Levels of Antibiotic Resistance in Gut Microbiota" *Antimicrobial Agents Chemotherapy* (online publication, 2013).