Misuse of Antibiotics Leads to Antibiotic Resistant Bacteria

Tyler Lewy

Writer's Comment: *Immunology has been an interest of mine since high school. I had known about antibiotic resistant pathogens for some time, but never really knew all the details behind the phenomenon. When the scientific review was assigned in my UWP104E (Writing in Science) class, I saw an opportunity to learn more about the subject. The articles I found opened my eyes to new mechanisms of resistance evolution such as agricultural antibiotic use. This article also taught me how to critically analyze scientific papers, a skill with which I had little previous experience. The growing dilemma of antibiotic resistant bacteria is largely overlooked, and I hope this paper will motivate others to educate themselves about the issue.*

Instructor's Comment: *Students in UWP 104E, writing in the sciences, are among the most focused that I encounter. Most are finishing advanced coursework in their specialized disciplines, and many are simultaneously working in the field or in labs on campus. They are steeped in the technical discourse and intricate details of science when they come into my class, and I often have to hustle to keep up with them. One of the primary course goals of a course like 104E is to address the importance of audience, and to practice strategies for conveying highly specialized information clearly and professionally—students sometimes ask if I'm telling them to "dumb it down" when I talk about this kind of balance. Thus the course focuses on how to write clearly while maintaining the integrity of the scientific information being presented. In truth, during the short ten week quarter, many students never fully achieve this. Yet Tyler Lewy was a notable exception to this, as his writing throughout the course was stellar, and consistently exhibited the balance of technical rigor and clarity. His literature review published here, "Misuse of Antibiotics Leads to Antibiotic Resistant Bacteria," synthesizes current research and findings on the topic and presents an overview of the issue in an engaging essay. Though Tyler is likely headed for a career as a scientist, as essays like this attest, he could just as easily find success as a writer.*

—Katie Rodger, University Writing Program

Antibiotics are often considered the greatest medical achievement of the modern age. Since the discovery of penicillin in 1928 by Scottish scientist Alexander Fleming, antibiotics have reduced mortality rates drastically and allowed pioneering of advanced surgeries, chemotherapy, and organ transplantation. However, this miracle of modern medicine is slowly fading away. Bacteria around the world are evolving to overcome the lethal properties of antibiotics using a variety of mechanisms, and today's rampant misuse of antibiotics is accelerating this phenomenon. Antibiotics prescribed for viral infections as well as subpar regiments can promote antibiotic resistant bacteria proliferation in the patient. Large quantities of antibiotics added to livestock feed every day encourage growth of resistant bacteria colonies. Because antibiotic resistance often comes with little cost to the bacterium itself, it can take years for the resistant phenotype to leave a population. Only through better clinical and agricultural practices can this new wave of antibiotic resistance emergence be slowed.

Mechanisms for Acquiring and Losing Resistance

Antibiotic resistance is a naturally occurring phenomenon in bacteria. A bacterium can acquire a resistance gene through several different mechanisms. The original resistance gene arises through chance as a mutation. Resistance genes have been found in bacteria isolated from the rest of the world for over 4 million years (Bhullar et al., 2012). This evidence suggests that the majority of resistance genes already exist and are shared with other cells. Bacteria have the ability to share genes residing on plasmids with other cells through horizontal gene transfer. Because of this, they are often able to acquire new traits and assimilate them into everyday functions quite easily. Although there are many methods of horizontal gene transfer, the most common route for exchanging plasmids coding for antibiotic resistance is bacterial conjugation (Jacob & Hobbs, 1974). This cell to cell interaction occurs when a bacterium with an F plasmid attaches to a bacterium without an F plasmid using a structure called a pilus. The F plasmid, which may contain an antibiotic resistance gene, is copied and shared with the other cell. Upon separation, both bacteria have a copy of the F plasmid and are able to give it to others. What is perhaps most fascinating about this process is that interspecies conjugation is not only possible but common. The pathogenic bacteria *H. influenzae* can freely share antibiotic resistance with the commensal species *H. parainfluenzae* (Chung et al., 2007). Resistant bacteria are generally much more successful under pressures of antibiotics and quickly gain dominance over other species due to natural selection pressures.

While bacterial resistance can evolve in a population relatively quickly, it often takes much longer for a bacterial population to lose a resistance gene (Goossens et al., 2005; Chung et al., 2007; Megraud et al., 2012). The resistance mechanism often comes with minimal cost to the organism, whereas not having it risks death. Low costs of operation also allow bacteria to accumulate resistance genes to multiple antibiotic agents (Zhu et al. 2013).

Current Contributors: Poor Clinical Prescription of Antibiotics

A clear correlation can be seen between clinical antibiotic use and antibiotic resistance. In a cross-national study of several European countries, it was shown that the rates of antibiotic resistance were much higher in southern and eastern Europe compared to northern Europe. This correlated with the average amount of antibiotic drugs prescribed in each area. France had both the highest prescription rate, 32DDD (defined daily dose, a measurement unit started by the World Health Organization) per 1000 people, and the highest incidence of penicillin resistant S. pneumoniae, nearly 50% of cases. This contrasts sharply with the data collected from the Netherlands, which had a prescription rate of 10DDD per 1000 people and only 1% resistance rate in S. pneumonia (Goossens et al., 2005). Often doctors incorrectly or apathetically prescribe antibiotics for upper respiratory tract infections (URTIs) likely caused by viral pathogens, which are unaffected by the drugs. Different countries are more likely to prescribe antibiotics according to cultural practices regarding URTIs, especially during seasonal flu epidemics. Dutch doctors diagnose most URTIs as common cold or influenza, whereas Flemish doctors diagnose most as bacterial bronchitis and prescribe more antibiotics (Goossens et al., 2005). The administration of antibiotics when no infection is present selects for antibiotic resistance in commensal bacteria, which can prove detrimental if a commensal bacterium shares a copy of its resistance genes to a later pathogenic invader (Chung et al. 2007).

Even when antibiotics are correctly prescribed, poor practices regarding the type of regiment used can contribute to antibiotic resistance. Duration of treatment plays a pivotal role in the acquisition of antibiotic resistance (Moller et al., 1977; Nasrin et al., 2002). It has been demonstrated that the likelihood of finding ß-lactam (a common antibiotic family including penicillin and amoxicillin) resistant bacteria in children with pneumococcal infections increases over time. Children prescribed 90 mg of amoxicillin per day for five days produced significantly less resistant bacteria than those prescribed 40 mg of amoxicillin for ten days (Nasrin et al., 2002). Bacteria that are resistant to an antibiotic require higher doses to treat; therefore, the small doses can prove inadequate, only killing off competitors of the resistant bacteria (Goossens et al., 2005; Nasrin et al., 2002). Repeated use of the same agent can also fortify resistant strains present in an individual (Moller et al., 1977; Chung et al., 2007). Resistance genes were found in children up to 12 weeks after discontinuing amoxicillin treatment, reducing the efficacy of ß-lactam antibiotics (Chung et al., 2007).

Current Contributors: Overuse of Agricultural Antibiotics

While the misuse of antibiotics in a clinical setting is widely recognized in the scientific community as a contributing factor to bacterial resistance, the use of agricultural antibiotics is a more hotly debated topic. Antibiotics are currently fed to livestock in the United States for at least one of the following reasons: therapeutic use for diseased animals, control use on herds with high disease mortality, prevention-prophylaxis use to prevent infection of herds, and growth promotion where antibiotics are administered to enhance the physiological performance of the animals (Peak et al., 2006). Antibiotic-mediated growth promotion is the practice most commonly associated with resistant bacteria emergence. In 2004, the World Health Organization called for the ban of growth promoting antibiotics that are also used in humans for pharmaceutical purposes. So far, only the European Union has acknowledged this, banning the use of growth promoting antibiotics entirely in 2006 (Peak et al., 2006; Zhu et al., 2013). China is the world's largest producer and consumer of antibiotics, using an estimated 96 million kilograms of antibiotic for livestock alone. Studies performed in three Chinese swine farms have identified 149 unique resistance genes spanning all major types of antibiotics in manure. In addition, the relative concentrations of resistant bacteria were up to 28,000 times that of average soil samples (Zhu et al. 2013). Similar studies have shown the same general trend on US cattle farms that are designated as high antibiotic-use feedlots (Peak et al., 2006).

Solutions: Better Protocols for Prescribing Antibiotics

To prevent future strains of antibiotic resistant bacteria, stricter prescription guidelines need to be adhered to. The global amount of antibiotics consumed in clinical practices is far too high. Financial incentives such as reduced co-payments for less common agents may convince doctors to prescribe widely used antibiotics such as tetracycline and fluoroquinolones less, reducing the rate resistance is accrued. Denmark, a country with low rates of antibiotic use and bacterial resistance, has removed subsidizations from more common drugs, resulting in lower consumption rates (Goossens et al., 2005).

More rigorous testing could be implemented to confirm URTIs are truly the result of a bacterial pathogen before antibiotics are prescribed (Chung et al., 2007; Nasrin et al., 2002). This may result in longer periods of infection in individuals with bacterial infections; however, it will reduce the amount of antibiotics consumed. Many viral infections such as the common cold are self-limiting and will only infect an individual for a few weeks, regardless of antibiotic usage.

When antibiotics are absolutely required, better practices can be followed. Shorter duration and larger doses can increase the likelihood of eradicating a pathogen, even if it is slightly resistant (Nasrin et al., 2002). In cases where an individual must receive multiple doses over a 12-week period, agents targeting different parts of the bacterium should be utilized. For example, if an individual was given amoxicillin two months prior, it is ill advised to prescribe another ß-lactam (Chung et al., 2007).

Solutions: Better Protocols for Agricultural Antibiotic Use

Combatting agricultural antibiotic use needs to start with eliminating the practice of adding antibiotics to feed for growth promotion. The World Health Organization advised against it in 2004, and, so far, only the European Union has outlawed it. Significantly decreased amounts of resistant bacteria have been isolated on European farms since implementing the ban (Zhu et al., 2013). Small volume use of antibiotics in livestock, for therapeutic and control use, is necessary for the health of the livestock industry. There are techniques to reduce the impact of these farms on the community, however. Mandatory implementation of feedlot lagoons, areas where manure runoff can be collected and processed, can limit the possibility of waterborne resistant pathogens from entering public water supplies. Feedlots should also consider monitoring lagoons closely, making sure to not irrigate crops with contaminated water (Peak et al., 2006). This is especially important in rural settings with limited water treatment systems already in place.

Conclusion

Antibiotic resistant bacteria threaten to render the benefits of modern medicine obsolete. With emergence of resistant *M. tuberculosis*, methicillin-resistant *S. aureus* (MRSA), and *E. coli*, among other pathogens, it is clear the problem is growing. The question asked should no longer be if antibiotic resistance is worth worrying about, but rather what can the world do as a whole to curb this increasing problem. Stricter guidelines and regulation should be implemented in prescription practices to minimize chances of resistant bacteria formation. Growth promoting antibiotics in livestock feed used in human pharmaceuticals should be banned and overall usage on farms should be decreased to prevent selection for resistant strains. Cleaner waste management systems should also be considered to limit the chance of contaminating human food and water supplies with resistant bacteria. Close monitoring and scrutiny of antibiotic use in clinical and agricultural applications is the key to maintaining the health standards that antibiotics have afforded us.

References

Bhullar, K., Waglechner, N., Pawlowski, A., Koteva, K., Banks, E. D., . . . Wright, G. D. (2012). Antibiotic Resistance Is Prevalent in an Isolated Cave Microbiome. *PLoS ONE, 7*(4). e34953. doi: 10.1371/journal.pone.0034953.

Chung, A., Perera, R., Brueggemann, A. B., Elamin, A. E., Harnden, A., . . . Mant, D. (2007). Effect of antibiotic prescribing on antibiotic resistance in individual children in primary care: prospective cohort study. *BMJ, 335,* 429-429.

Goossens, H., Ferech, M., der Stichele, R. V., & Elseviers, M. (2005). Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *The Lancet, 365,* 579-587.

Jacob, A. E., & Hobbs, S. J. (1974). Conjugal Transfer of Plasmid-Borne Multiple Antibiotic Resistance in Streptococcus faecalis var. zymogenes. *Journal of Bacteriology, 117*(2), 360-372.

Megraud, F., Coenen, S., Versporten, A., Kist, M., Lopez-Brea, M., . . . Glupczynski, Y. (2012). Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut, 62*(1), 34-42.

Moller, J., Bak, A. L., Stenderup, A., Zachariae, H., & Afzelius, H. (1977). Changing Patterns of Plasmid-Mediated Drug Resistance During Tetracycline Therapy. *Antimicrobial Agents And Chemotherapy, 11*(3), 388-391.

Nasrin, D., Collignon, P. J., Roberts, L., Wilson, E. J., Pilotto, L. S., & Douglas, R. M. (2002). Effect of beta lactam antibiotic use in children on pneumococcal resistance to penicillin: prospective cohort study. *BMJ, 324,* 28-28.

Peak, N., Knapp, C. W., Yang, R. K., Hanfelt, M. M., Smith, M. S., Aga, D. S., Graham, D. W. (2006). Abundance Of Six Tetracycline Resistance Genes In Wastewater Lagoons At Cattle Feedlots With Different Antibiotic Use Strategies. *Environmental Microbiology, 9*(1), 143-151.

Zhu, Y., Johnson, T. A., Su, J., Qiao, M., Guo, G., . . . Tiedje, J. M. (2013). Diverse and abundant antibiotic resistance genes in Chinese swine farms. *Proceedings of the National Academy of Sciences, 110*(9), 3435-3440.