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ANTIBIOTIC RESISTANCE

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Antibiotic resistance poses serious challenges to health and national security, and policy changes will be required to mitigate the consequences of antibiotic resistance. Resistance can arise in disease-causing bacteria naturally, or it can be deliberately introduced to a biological weapon. In either case, life-saving drugs are rendered ineffective. Resistant bacterial infections are difficult to treat, and there are few new antibiotics in the drug development pipeline. This article describes how antibiotic resistance affects health and national security, how bacteria become antibiotic resistant, and what should be done now so antibiotics will be available to save lives in the future.

ANTIBIOTIC RESISTANCE: A PROBLEM FOR HEALTH AND NATIONAL SECURITY

FOR DECADES, ANTIBIOTICS have been cheap, effective drugs that kill disease-causing bacteria. A diagnosis of plague or tuberculosis used to be a virtual death sentence; at the least, these diseases required long convalescences. With the advent of antibiotic therapy in the 1940s, however, they became survivable illnesses. Those days are rapidly ending.

Many common disease-causing bacteria have become antibiotic resistant, so antibiotics have little or no effect. Patients may take the drugs, but the bacteria continue to divide and proliferate, with life-threatening consequences. For example, in 1999, fatalities in New York City were found to be 2.5 times higher for methicillin-resistant *Staphylococcus aureus* (MRSA) than for regular (methicillin susceptible) *Staphylococcus aureus*.[1] Even when patients survive the infections, there are increased costs because of the expensive treatments and longer hospital stays that are required.[2]

Few New Antibiotics in the Pipeline

A clear medical need for more treatment options has not, unfortunately, spurred the development of new antibiotics. The profit margin for antibiotics can be 10 times less than for drugs to treat chronic diseases: antibiotics are typically taken for a week or 2, but treatments for chronic diseases may be taken every day for the rest of a person's life.[3,4] Antibiotics are near the cutoff for what pharmaceutical companies calculate to be the minimum profit of a drug, which is used to determine whether or not to develop a product.[5] The problem of antibiotic resistance makes that slim profit margin even more uncertain. The process of developing an antibiotic and getting FDA approval costs approximately $500 to $800 million; few pharmaceutical companies would invest those millions on drugs that can quickly become useless.[6]

As a result, fewer antibiotics are being developed than ever before. Between 1940 and 1970, 10 classes of antibiotics were identified. A "class" of antibiotics is defined by

Science for Policymakers is a journal column aimed at informing key decision makers about scientific advancements that affect biosecurity and biodefense. The articles describe a novel type of research that is currently underway or recently developed, or an issue in the field of biosecurity, and engage readers in thinking about what impact the research has on biosecurity. Kunal J. Rambhia is an Analyst and Gigi Kwik Gronvall, PhD, is a Senior Associate, both at the Center for Biosecurity of the University of Pittsburgh Medical Center, Baltimore, Maryland.

how it works or the type of bacteria it kills. In the years that followed and up until the late 1990s, only derivatives of those 10 classes were developed, and no new classes were identified.[7] Between 1998 and 2004, only 2 antibiotics with a novel mechanism were approved by the FDA.[8] Many large pharmaceutical companies have left the business of making antibiotics altogether. As recently as 2004, only 1.6% of drugs in development at the 15 largest pharmaceutical companies in the world were antibiotics, and none of them were new classes of antibiotics.[5]

How Bacteria Become Resistant to Antibiotics

Antibiotics generally work in 2 ways. Some antibiotics prevent bacteria from reproducing and growing—these are called *bacteriostatic*. This interruption in bacterial growth gives a person's immune system time to target and fight the bacteria, without being overwhelmed.[9] Other types of antibiotics kill bacteria directly by interrupting a function that is critical to their survival. Regardless of how they work, some antibiotics are effective against only certain types of bacteria, while others target a wide range; these are said to be "broad spectrum" antibiotics.

Resistance to Antibiotics Occurs through Several Pathways

- **Mutation:** Bacteria are single-cell asexual organisms, and they reproduce by creating exact copies of themselves. However, this copying process is not perfect, and mutations occur. Small pieces of bacterial DNA may be added, deleted, repeated, or shifted. These changes are often lethal to the bacteria, or produce no effect at all, but a small number of these mutations may confer antibiotic resistance to the bacteria.
- **Genetic transfer of resistance from one bacterium to another:** Bacteria frequently exchange DNA. For example, 80% of the DNA of some *Enterococcus* species, a common food contaminant, is variable, meaning it is constantly changing and acquiring new genes from other bacteria. Some bacteria are naturally resistant to a number of antibiotics, while others may have previously acquired resistance by random mutation. In a process called gene transfer (see Figure 1), one type of bacterium can acquire small pieces of DNA from bacteria of another type. Similar to mutation, most of the time these gene transfers are lethal to bacteria or produce no effect. However, this is the most common way that bacteria acquire antibiotic resistance.

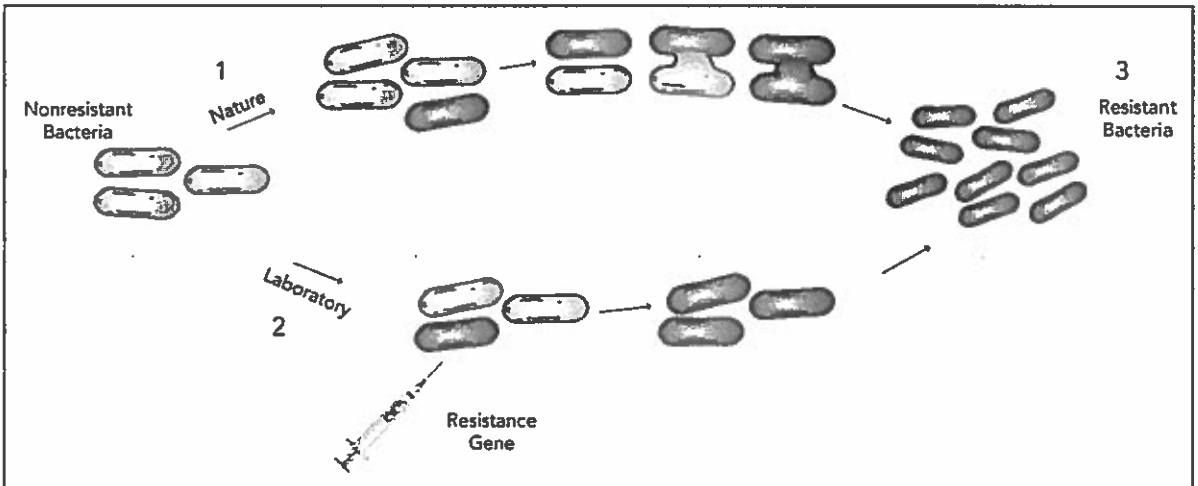

Figure 1. Gene Transfer

1. Gene transfer is a main route for acquiring resistance for bacteria in nature. In nature, there are several different ways that bacteria can share DNA. Some bacteria are naturally resistant to antibiotics or have previously acquired a resistant gene. These bacteria can share their resistant traits. In the upper half of this figure, a gene that causes antibiotic resistance is copied directly from one bacterial cell to another.
2. Many of the genes that cause resistance are known. Some are stored in the laboratory. Scientists often use these genes to create resistant bacteria to aid laboratory experiments. As shown in the lower half of this figure, a scientist in a lab can introduce a gene known to cause resistance to bacteria. Any bacteria that obtain this gene can withstand antibiotic treatment and will reproduce and grow.
3. The final product of both processes is bacteria that are resistant to antibiotic treatment. In the laboratory, resistant bacteria are commonly used for legitimate scientific research. However, these same techniques can be used to create biological weapons that are resistant to the antibiotics we have to counter them.

effectiveness of medically important antibiotics used in the treatment of human and animal diseases by reviewing the safety of certain antibiotics for nontherapeutic purposes in food-producing animals."[33] This bill, titled the Preservation of Antibiotics for Medical Treatment Act of 2009, was also introduced in the Senate (S. 619). This legislation could be an important first step in preserving the remaining useful antibiotics.

Following a July 13, 2009, hearing in the U.S. House of Representatives Committee on Rules on H.R. 1549, Representative Slaughter wrote a letter to the U.S. Government Accountability Office (GAO) requesting a review of federal efforts to track and monitor antibiotic resistance and calling for an assessment of progress to mitigate the human health impact of antibiotic resistance.[34] On October 7, Representative Slaughter addressed the House of Representatives to urge support of this legislation, and on October 8, she wrote a letter to the President encouraging him to support the ban on nontherapeutic antibiotics in livestock production.[35,36]

Dr. Joshua Sharfstein, Principal Deputy Commissioner of Food and Drugs at the FDA, supported the elimination of nontherapeutic use of antibiotics in agriculture in his testimony before the House Committee on Rules. He also indicated that the U.S. Interagency Task Force on Antimicrobial Resistance would be releasing a revised Public Health Action Plan to Combat Antimicrobial Resistance in late 2009. This revised Action Plan will replace a 2001 Action Plan, which established 4 areas of focus for combating antimicrobial resistance: surveillance, prevention and control, research, and product development. Federal partners in this plan include the FDA, the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), the Agency for Health Research and Quality (AHRQ), the Centers for Medicare and Medicaid Services (CMS), the Health Resources and Services Agency (HRSA), the U.S. Department of Agriculture (USDA), the Department of Defense (DoD), the Department of Veterans Affairs (VA), the Environmental Protection Agency (EPA), and the U.S. Agency for International Development (USAID).[37]

Conclusion: More Antibiotics Need to Be Developed

Unfortunately, although reducing the use of antibiotics can delay resistance, it cannot prevent it. Once resistance has taken hold, stopping the use of an antibiotic does not necessarily cause the bacteria to revert to a treatable form.[27] Stopping the use of antibiotics is also difficult in practice: while many bacterial infections may resolve themselves without treatment, it is unlikely that physicians will not prescribe them if they think it would cure their patients.[6]

This makes the development of new antibiotics critical to being able to continue to fight infections.[6] The long-term strategy should be to develop new classes of antibiotics that are effective against a wide range of bacteria—so-called broad spectrum antibiotics—as well as antibiotics that are less susceptible to resistance. As part of this effort, it will be important to learn more about how antibiotic resistance develops. Studies have shown that bacteria develop resistance to some drugs faster than others.[10] Understanding why this occurs may lead to the development of new antibiotics that are less prone to resistance.

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Further Reading

- Miller HI. Bad bugs, few drugs. *Washington Times* October 23, 2007. http://washingtontimes.com/news/2007/oct/23/bad-bugs-few-drugs/. Accessed November 4, 2009.
- Trends in antimicrobial drug development: implications for the future. *Clin Infect Dis* 2004;38:1279-1286.
- Harrell E. The desperate need for new antibiotics. *Time* October 1, 2009. http://www.time.com/time/health/article/0,8599,1926853,00.html. November 4, 2009.
- Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis* 2009;48(1):1-12.

References

1. Rubin RJ, Harrington CA, Poon A, Dietrich K, Greene JA, Moiduddin A. The economic impact of *Staphylococcus aureus* infection in New York City hospitals. *Emerg Infect Dis* 1999;5(1):9-17.
2. Elixhauser A, Steiner C. Infections with methicillin-resistant *Staphylococcus aureus* (MRSA) in U.S. hospitals, 1993-2005. Statistical Brief #35. Rockville, MD: Agency for Healthcare Research and Quality [AHRQ]; July 2007.
3. Projan SJ. Why is big pharma getting out of antibacterial drug discovery? *Curr Opin Microbiol* Oct 2003;6(5):427-430.
4. Power E. Impact of antibiotic restrictions: the pharmaceutical perspective. *Clin Microbiol Infect* Aug 2006;12 Suppl 5:25-34.

5. Mossialos E, Morel C, Edwards S, Berenson J, Gemmill-Toyama M, Brogan D. *Policies and Incentives for Promoting Innovation in Antibiotic Research.* London: London School of Economics and Political Science; 2009. http://www2.lse.ac.uk/LSEHealthAndSocialCare/LSEHealth/News/Policies%20and%20incentives%20report.pdf. Accessed October 23, 2009.
6. Livermore DM. Minimising antibiotic resistance. *Lancet Infect Dis* Jul 2005;5(7):450-459.
7. Federation of American Scientists. *Antibiotic Resistance: Case Study.* http://www.fas.org/biosecurity/education/dualuse/FAS_Levy/index.html. Accessed July 21, 2009.
8. Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE Jr. Trends in antimicrobial drug development: implications for the future. *Clin Infect Dis* 2004;38(9):1279-1286.
9. Alliance for the Prudent Use of Antibiotics. About bacteria & antibiotics. http://www.tufts.edu/med/apua/Q&A/Q&A_bact.html. Accessed March 31, 2009.
10. Roberts JA, Kruger P, Paterson DL, Lipman J. Antibiotic resistance—what's dosing got to do with it? *Crit Care Med* Aug 2008;36(8):2433-2440.
11. Jernigan DB, Raghunathan PL, Bell BP, et al. Investigation of bioterrorism-related anthrax, United States, 2001: epidemiologic findings. *Emerg Infect Dis* Oct 2002;8(10):1019-1028.
12. Trust for America's Health. *Ready or Not?* December 2008. http://healthyamericans.org/assets/files/bioterror-report-2008.pdf. Accessed July 21, 2009.
13. U.S. Centers for Disease Control and Prevention. Anthrax Q & A: Treatment. Updated March 25, 2005. http://www.bt.cdc.gov/agent/anthrax/faq/treatment.asp. Accessed August 5, 2009.
14. Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon, 2002: updated recommendations for management. *JAMA* 2002;287(17):2236-2252.
15. Price LB, Vogler A, Pearson T, Busch JD, Schupp JM, Keim P. In vitro selection and characterization of *Bacillus anthracis* mutants with high-level resistance to ciprofloxacin. *Antimicrob Agents Chemother* Jul 2003;47(7):2362-2365.
16. Brook I, Elliott TB, Pryor HI 2d, et al. In vitro resistance of *Bacillus anthracis* Sterne to doxycycline, macrolides and quinolones. *Int J Antimicrob Agents* 2001;18(6):559-562.
17. Welch TJ, Fricke WF, McDermott PF, et al. Multiple antimicrobial resistance in plague: an emerging public health risk. *PLoS One* 2007;2(3):e309.
18. Athamna A, Athamna M, Abu-Rashed N, Medlej B, Bast DJ, Rubinstein E. Selection of *Bacillus anthracis* isolates resistant to antibiotics. *J Antimicrob Chemother* Aug 2004;54(2):424-428.
19. Alibek K. Behind the mask: biological warfare. *Perspective* September-October 1998;IX(1). http://www.bu.edu/iscip/vol9/Alibek.html. Accessed November 5, 2009.
20. World Health Organization. Antimicrobial resistance. http://www.who.int/mediacentre/factsheets/fs194/en/. Accessed March 31, 2009.
21. Kardas P, Pechere JC, Hughes DA, Cornaglia G. A global survey of antibiotic leftovers in the outpatient setting. *Int J Antimicrob Agents* Dec 2007;30(6):530-536.
22. Gever J. Antibiotic reactions send thousands to emergency rooms. *MedPage Today* August 13, 2008. http://www.medpagetoday.com/ProductAlert/Prescriptions/10549. Accessed October 23, 2009.
23. Union of Concerned Scientists. European Union bans antibiotics for growth promotion. Last revised February 14, 2006. http://www.ucsusa.org/food_and_agriculture/solutions/wise_antibiotics/european-union-bans.html. Accessed July 21, 2009.
24. Silbergeld EK, Davis M, Leibler JH, Peterson AE. One reservoir: redefining the community origins of antimicrobial-resistant infections. *Med Clin North Am* Nov 2008;92(6):1391-1407, xi.
25. Chapin A, Rule A, Gibson K, Buckley T, Schwab K. Airborne multidrug-resistant bacteria isolated from a concentrated swine feeding operation. *Environ Health Perspect* Feb 2005;113(2):137-142.
26. Keep Antibiotics Working. Linking antibiotic use in livestock & poultry to increasing resistance in humans. July 2005. http://www.keepantibioticsworking.com/new/resources_library.cfm?RefID=36444. Accessed July 21, 2009.
27. Silbergeld EK, Graham J, Price LB. Industrial food animal production, antimicrobial resistance, and human health. *Annu Rev Public Health* 2008;29:151-169.
28. Shea KM. Nontherapeutic use of antimicrobial agents in animal agriculture: implications for pediatrics. *Pediatrics* Sep 2004;114(3):862-868.
29. Cimitile M. Worried about antibiotics in your beef? Vegetables may be no better. *Sci Am* January 6, 2009. http://www.scientificamerican.com/article.cfm?id=vegetables-contain-antibiotics. Accessed November 5, 2009.
30. The Pew Campaign on Human Health and Industrial Farming. Important human medicines used on industrial animal farms. http://www.saveantibiotics.org/resources/Important_Human_Medicines.pdf. Accessed July 21, 2009.
31. Keep Antibiotics Working. Fluoroquinolones: A (slow) success story. http://www.keepantibioticsworking.com/new/indepth_fluoro.cfm. Accessed July 23, 2009.
32. Unicomb LE, Ferguson J, Stafford RJ, et al. Low-level fluoroquinolone resistance among Campylobacter jejuni isolates in Australia. *Clin Infect Dis* 2006;42(10):1368-1374.
33. To amend the Federal Food, Drug, and Cosmetic Act to preserve the effectiveness of medically important antibiotics used in the treatment of human and animal diseases. Slaughter L, trans. 111th Congress 1st Session ed; 2009.
34. Congresswoman Louise Slaughter. Slaughter asks GAO for additional data on antibiotic use in animals. September 21, 2009. http://www.louise.house.gov/index.php?option=com_content&view=article&id=1306:slaughter-asks-gao-for-additional-data-on-antibiotic-use-in-animals&catid=41:press-releases&Itemid=109. Accessed October 20, 2009.
35. Congresswoman Louise Slaughter. Slaughter asks House to support antibiotics legislation, warns of continuing food safety issues. October 7, 2009. http://www.louise.house.gov/index.php?option=com_content&view=article&id=1365:slaughter-asks-house-to-support-antibiotics-legislation-warns-of-continuing-food-safety-issues&catid=41:press-releases&Itemid=109. Accessed October 20, 2009.
36. Congresswoman Louise Slaughter. Slaughter asks White House to ban excessive use of antibiotics in farm animals. October 8, 2009. http://www.louise.house.gov/index.php?