The End of the Golden Age of Antibiotics?

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The discovery of penicillin heralded a revolution in medicine, and mankind believed that it had beaten bacterial infections. But now, looking back, it seems arrogant to have assumed victory. The emergence and spread of antibiotic resistance has rendered current treatments less and less effective over the last 100 years. With a crisis in medicine now looming, we have finally begun to address the issue of antibiotic resistance head-on.

Antibiotic resistance occurs when bacteria are no longer killed by a drug that used to kill them. We have known about it since antibiotics were first discovered: Alexander Fleming himself gave a "note of warning" about the development of resistance in his Nobel Prize acceptance speech.[1] He was proven to be right, with resistance to penicillin becoming widespread in the 20 years following its introduction into mainstream medicine.[2] The emergence of antibiotic resistance is simply evolution in action: bacteria that survive a course of antibiotic treatment are more likely to reproduce and so their progeny gradually become less sensitive to future antibiotic treatments. The use of antibiotics has been widespread in modern medicine, but even more so in agriculture, where they are used prophylactically at high levels to prevent disease and promote faster animal growth. This has accelerated bacterial evolution, resulting in resistance spreading across the globe at an alarming rate.

As traditional antibiotics are becoming less and less effective, we are relying on our 'last resort' antibiotics more and more. True to form, bacteria have begun to develop resistance to them. A class of bacteria called gram-negative bacteria (which includes common clinical strains such as Neisseria gonorrhoeae, the causative agent behind gonorrhoea) have become particularly difficult to treat, with carbapenems and colistin being the only two antibiotic classes remaining widely effective against infections caused by these bacteria. However, in 2008, a new gene (termed NDM-1), which confers resistance to carbapenems, was found in India[4] and in January this year a new resistance gene against colistin (termed MCR-1) was discovered in China.[5] We have no other treatment options for bacteria resistant to these last-line antibiotics, and so the discovery that these genes have already spread across the globe[6,7] is a major cause for concern.

Resistance to antibiotics is nothing new: there have been clinical cases of infections with bacteria resistant to almost every well-established antibiotic. The difference now is that for once we don't have an ace up our sleeves. Between 1940 and 1962, 20 new classes of antibiotics were brought to market (in part as a reaction to the emergence of resistance), allowing us to comfortably deal with resistant infections: over the following 50 years only two new classes have been commercialized.[8] This is largely due to the economic pressures of pharmaceutical research: the lifetime profits on the sale of novel antibiotics—which have small treatment groups and whose sale is highly restricted to limit the emergence of resistance—are small relative to those on drugs that manage chronic conditions (such as high blood pressure) which are common in western societies and require years of continual treatment. This has led most large pharmaceutical companies to retreat from the increasingly complex field of antibiotic research due to limited financial incentives.[9]

This lack of effective antibiotics is already having a real impact on society. Gonorrhoea has historically been easily treated with a single course of antibiotics, but strains found in Leeds in 2012 were classified as 'untreatable', meaning they cannot be cured by any available antibiotic therapies.[10] Meanwhile, the scare of 'extensively drug resistant TB' has been overshadowed by the discovery of 'totally drug resistant TB' - which is resistant to every licensed tuberculosis treatment - in Italy in 2007,[11] and Iran and India in 2009.[12,13] Should current trends continue, resistant infections will not only directly cause more deaths, but will have a knock-

on effect on the entire medical field. Almost all medical procedures carry a risk of bacterial infection, including surgery (which breaches the skin) and cancer chemotherapy (which causes suppression of the immune system), which is managed by prophylactic antibiotic treatment. If doctors do not have access to any antibiotic treatments that work, the risks of acquiring a lethal and untreatable infection will outweigh the benefits of many medical procedures, preventing doctors from providing care that is currently taken for granted.[3]

However, developing new drugs alone is not enough. If novel antibiotics are used carelessly, bacteria will simply evolve resistance to them. As elegantly put by Dr Dennis Maki, a member of the Infectious Disease Society of America, "The development of new antibiotics without having mechanisms to insure their appropriate use is much like supplying your alcoholic patients with a finer brandy".[16] Since antibiotics become less effective the more they are used, in the long term the most important measure to prevent disaster is not just the discovery of new drugs, but to use antibiotics more sparingly and more responsibly to reduce the spread of resistance. The emergence of NDM-1 in India was attributed to the widespread use of carbapenems in the Indian healthcare system to treat resistant infections,[6] while the emergence of MCR-1 in Japan was associated with high levels of colistin use on pig farms to increase profits,[7] indicating that controlling antibiotic use in both medicine and agriculture is essential for preventing the spread of resistance.

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A bleak future is a serious risk, but progress is starting to be made towards combating the spread of resistance. New drugs that render resistant bacteria susceptible to certain antibiotics again (called antibiotic resistance breakers) could allow us to reutilize old drugs; for example, the drug co-amoxiclav contains amoxicillin in combination with clavulanic acid, which breaks bacterial resistance to amoxicillin.[14] Scientists have also begun to explore more exotic treatment options beyond antibiotics—for example, creating a genetically engineered version of E.coli that hunts down and kills harmful bacteria.[15] Furthermore, governments are shepherding pharmaceutical companies back into antibiotic research with new schemes and incentives such as rapid FDA approval under the GAIN act[9] and the Innovative Medicines Initiative partnership between biotechnology, pharmaceutical and academic industries—endearingly named 'New Drugs for Bad Bugs'—so new discoveries may be on the horizon. Indeed such initiatives have already begun showing results: six new antibiotics were licensed in the second half of 2014 alone.

Important changes are starting to be implemented: Brazil and Mexico banned the sale of antibiotics without a prescription in 2010, with a number of Latin American countries since following their example.[17] The WHO produced the first ever global report on antimicrobial resistance in 2014, highlighting the importance of changing our patterns of antibiotic use on a global scale.[18] This increasing global awareness of antibiotic resistance provides hope that governments, doctors, farmers and the general public will change their attitude to bacterial infections, since acknowledging the problem is the crucial first step in finding a solution.

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