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Thematic Insights: Robotics, Security & Safety



The rise of antibiotic resistance

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"If you use penicillin, use enough"

Sir Alexander Fleming, Nobel Laureate¹

On 28th September 1928 a piece of mould fortuitously contaminated a petri dish in Alexander Fleming's laboratory at St Mary's Hospital in Paddington, London. He discovered that it produced a substance that killed the bacteria he was examining. After months of calling it "mould juice", he named later the substance *penicillin* (from the Latin *penicillus*, "paintbrush," in reference to the shape of the mould cell structures). Over the following decades penicillin became a "wonder-drug," curing millions of patients suffering from bacterial infections. Other compounds with anti-bacterial, or "anti-biotic", properties were later discovered and revolutionized healthcare, forming the bedrock of many of the greatest medical advances of the last century. Many infectious diseases, such as pneumonia and tuberculosis, which had often proved fatal, could now be treated effectively. The likelihood of a small cut or injury proving fatal if infected was greatly reduced, and routine surgery and childbirth also became much lower risk events. Together with Howard Florey and Ernst Boris Chain, Alexander Fleming received the Nobel Prize in Physiology or Medicine for their work in the field of antibiotics in 1945.

During his Nobel lecture on 11th December 1945, Alexander Fleming sounded a warning: *"There is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant. Here is a hypothetical illustration. Mr. X. has a sore throat. He buys some penicillin and gives himself, not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects his wife. Mrs. X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies. [...] Moral: If you use penicillin, use enough."*¹

¹ Source: Fleming (1945): Penicillin, Nobel Lecture, Dec. 11th 1945, p. 11, URL: https://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.pdf, 5.2.2017.

There is no doubt that penicillin and other antibiotics are amongst the greatest inventions in the field of medical science. Yet Fleming's warning has always haunted their success. Antibiotic resistance is today a costly and dangerous problem. Some people fear there may be worse to come: a strain of resistant bacteria for which no treatment is currently available might start an epidemic. In such a scenario, elective surgeries, such as a hip replacement, bariatric surgery or colectomy, may come to be seen as unacceptably risky. Non-elective surgeries would also become more dangerous and the risks of procedures which suppress the immune system, such as organ transplants and cancer chemotherapies, would increase.

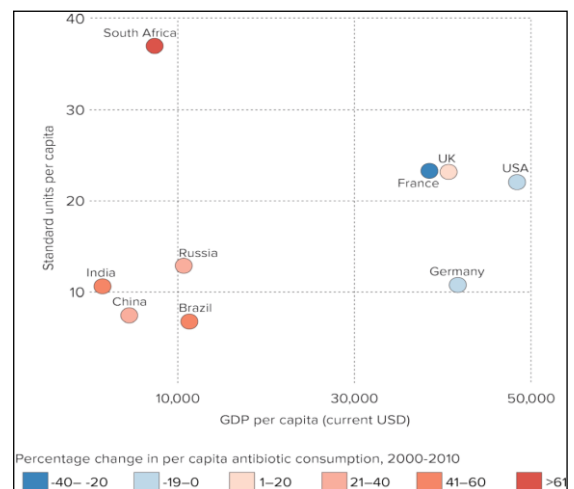
What are the consequences of antibiotic resistance?

Antibiotic resistance is the ability of a microbe to resist the effects of medication previously used to treat them. Resistance arises in one of three ways: (1) Natural resistance in certain types of bacteria, (2) Genetic mutation, or (3) one species acquiring resistance from another. Resistance can appear spontaneously (e.g. random mutations), but more commonly builds up gradually over time, and this may be caused by misuse of antibiotics. According to the Center for Disease Control and Prevention, at least 2 million people in the US become infected with bacteria resistant to antibiotics every year, and at least 23,000 people die as a direct result of these infections.² Already the cost to the US healthcare system of dealing with infections resistant to one or more antibiotics is USD 20 billion a year.³ Worldwide the annual mortality rate from antibiotic resistance is more than 700,000 people and by 2050 this number could rise to 10 million.⁴ Without global action, the implied economic cost of drug-resistant infections would be at least USD 100 trillion and could cut the annual world's GDP by 2 - 3.5% by 2050. These figures almost certainly underestimate the actual costs, because they are based on the direct costs of disease and on deaths caused by the most important drug-resistant pathogens, but the additional secondary health effects could be just as large.⁵

Antibiotic resistance is often a direct result of rising antibiotic use. The greater the volume of antibiotics used, the greater the chances that super antibiotic-resistant population of bacteria will prevail in a "survival of the fittest" contest between the bacteria. Two trends are contributing to a global rise in antibiotic consumption⁶:

- Rising affluence as well as expanding insurance coverage increases the access to antibiotics. On one hand this saves lives, but on the other, the increasing usage also drives up resistance.
- Increased demand for animal protein and resulting intensification of animal production for food is leading to a greater use of antibiotics in agriculture. This increase in usage also drives up antibiotic resistance.

Fig. 1: Antibiotic use per capita by income in selected countries (2010)



CDDEP (2015): The state of world's antibiotics, 2015.

Trends in antibiotic use

Between 2000 and 2010 total antibiotic consumption grew by more than 30%, from approximately 50 billion to 70 billion standard units (SU).⁷ Penicillin and cephalosporins accounted for nearly 60% of total consumption in 2010,

² Source: Centers for Disease Control and Prevention (2017): About Antimicrobial Resistance, Jan. 5th 2017, URL: <https://www.cdc.gov/drugresistance/index.html>, 5.2.2017.

³ Source: Economist (2016): Antibiotic resistance: The grim prospect, in: The Economist, May 21st 2016.

⁴ Source: AMR Review (2014): Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations, Dec. 2014, p. 5, URL: https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf, 5.2.2017.

⁵ Source: Financial Times (2014): Drug resistance to cost \$100tn by 2050, study finds, in: The Financial Times, Dec. 14th 2014.

⁶ Source: CDDEP (2015): The state of the world's antibiotics 2015, p. 8, URL: https://cddep.org/sites/default/files/swa_2015_final.pdf, 6.2.2017.

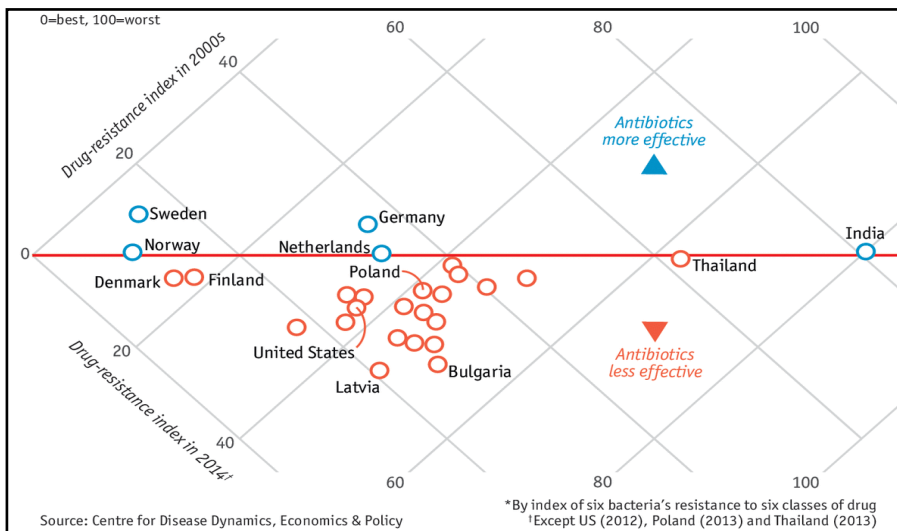
⁷ A standard unit is a measure of volume based broadly on the smallest identifiable dose given to a patient, dependent on the pharmaceutical form (a pill, capsule, or ampoule).

an increase of 41% from 2000. The countries consuming the most antibiotics overall in 2010 were India (13 billion SU), China (10 billion SU) and the United States (7 billion SU). Figure 1 shows in this consumption on a “per capita” basis: The United States led with 22 units per person (2010), compared with 11 units in India and 7 units in China. Per capita consumption is generally higher in higher income countries, but the greatest increase in the use of antibiotics between 2000 and 2010 was from the Emerging Markets, and consumption continues to rise.

In most countries, about 20% of antibiotics are used in hospitals and other healthcare facilities. 80% are used in the community, either prescribed by healthcare providers or purchased directly by consumers without prescription. Perhaps half of all use is inappropriate and avoidable. The use against mild coughs and the common cold is typically ineffective, but it adds to the growing global resistance to antibiotics.⁸

The Centre for Disease Dynamics, Economics & Policy (CDDEP), a think-tank, developed a drug resistance index (shown in Figure 2). The index aggregates information about antibiotic resistance and antibiotic use into a single composite measure that quantifies the decay of antibiotic effectiveness over time. The index runs from zero, meaning that antibiotics are fully effective, to 100, which means pathogens are fully resistant. In 27, mostly European, countries CDDEP calculated the index between the years 2000 and 2014. It shows that the effectiveness of antibiotics has declined in 22 of these 27 countries. Only Germany and Sweden actually buck the trend and improve. In India, the poorest country in the group, the index suggests that antibiotics used to treat most bacterial infections now fail to work.

Fig. 2: Effectiveness of antibiotics in selected countries*



Source: The Economist (2016): The rise of drug resistance, in: The Economist, Sept. 23rd 2016.

The prevalence of sepsis is another indication that global antibiotic resistance is on the rise. The number of cases of sepsis rose from 621,000 to 1,141,000 between the years 2000 and 2008, and number of patients who died from sepsis also rose from 154,000 to 207,000. One reason for this is the emergence of “MRSA” (methicillin-resistant staphylococcus aureus), a bacteria which is no longer susceptible to methicillin (a descendent of penicillin).⁹

What can be done against antibiotic resistance?

To stop the global rise of drug-resistant infections, there is a supply and demand problem that needs to be solved. According to the Review of Antimicrobial Resistance, the following steps should be taken (summarized):¹⁰

1. Reduce unnecessary use of antimicrobials in agriculture: There are circumstances where antibiotics are required in agriculture and aquaculture, such as to maintain animal welfare as well as food security.

⁸ Source: CDDEP (2015): The state of the world's antibiotics 2015, p. 10, URL: https://cddep.org/sites/default/files/swa_2015_final.pdf, 6.2.2017.

⁹ Source: The Economist (2016): Antibiotic resistance: The grim prospect, in: The Economist, May 21st 2016.

¹⁰ Source: The Review on Antimicrobial Resistance (2016): Tackling drug-resistant infections globally: Final report and recommendations, May 2016, p. 6.

However, much of their global use is not for treating sick animals, but rather to prevent infections or simply to promote growth.

2. Improve global surveillance of drug resistance and antimicrobial consumption in humans and animals: Surveillance is one of the cornerstones of infectious disease management, which has been until recently often ignored. Learning the lessons from Ebola outbreak in West Africa back in 2015, countries have started to increase funding in this area recently, in particular in the US and in the UK.
3. Promote new, rapid diagnostic instruments to cut unnecessary use of antibiotics: Rapid diagnostics could transform the way we use antimicrobials in humans and animals. Reducing unnecessary use of antibiotics could slow the development of its resistance. If practitioners could analyse whether an infection was viral or bacterial, they would no longer be tempted to automatically prescribe antibiotics. If they knew which antibiotics would eradicate an infection, they would avoid prescribing a drug that suffers from partial resistance, and thereby limit the further selection of resistant strains.
4. Promote the development of vaccines: Vaccines can prevent infections and therefore lower the demand for therapeutic treatments, reducing use of antimicrobials and therefore slowing the rise of drug resistance.
5. Better incentives to promote investment for new antibiotic drugs: Currently the commercial return for developing antibiotics looks unattractive: The total market for antibiotics is about USD 40 billion of sales per annum. But only around USD 4.7 billion of this amount is from sales of patented antibiotics (that is about the same number as the yearly sales for one top-selling cancer drug). So it is not surprising that companies are not investing in antibiotics despite the very high medical needs. New commercial models are needed to encourage innovation.

Conclusion

Demand for antibiotics is likely to continue to grow both from legitimate uses and inappropriate over usage. It is a sad irony that while many people in the world continue to use antibiotics excessively, the same drugs are often not available to people who would greatly benefit from them. For example, in 2013 pneumonia alone was responsible for an estimated 935,000 deaths of children under the age of five worldwide. If effective antibiotic treatment had been available to them, it is estimated that most of these children would not have died.¹¹

While there are several solutions to stem the growth of antimicrobial resistance, the rising threat of antibiotic resistance remains a very serious issue for our entire society. We believe that a number of leading companies in the field of health diagnostics, genetic sequencing, big data analytics, as well as automated systems to monitor for disease and epidemics, will invest in R&D to develop innovative new solutions and therapies to tackle this problem and other long term issues which threaten the safety and security of humankind. Many of these solutions are likely to be automated and therefore we also believe that this is another example of how the theme of security and safety dovetails with the theme of robotics and automation. We believe we are in the early stage of a secular growth cycle in the security and safety theme, and are confident that investments in these areas are likely to increase going forward due to the long term structural drivers of demographics, digitalization and globalization. As a consequence we are shareholders of leading companies in the investment themes of Security and Robotics.

For further information (such as current fund factsheet, performance or quarterly comments) please click [here](#) (security & safety) or [here](#) (robotics).

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¹¹ Liu et al. (2015): Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: An updated systematic analysis, in: The Lancet, January 31st 2015, p. 430, URL: <http://www.who.int/immunization/diseases/tetanus/Lancet-2013-Global-child-mortality.pdf>, 6.2.2017.

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