SEEKING THE NEW SILVER BULLET AGAINST BACTERIA

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Antibiotics were long considered the ultimate remedy, a cure-all against bacteria. Increasingly often nowadays they fail at their task – because bacteria are learning to resist their powers.

The very first antibiotic, penicillin, was discovered as the 20th century drew to a close. Seen from today's vantage point this was the pre-eminent milestone in the history of medicine. It came about from observations that certain fungus moulds could kill bacteria. In 1941, substances developed from the "penicillin" fungus were first employed in medicines. Since then, these products have further advanced and today several thousand antibiotic substances are manufactured which can overpower the lethal hazards of life-threatening diseases, e.g. tuberculosis, pneumonia and tonsillitis.

And yet, these miraculous medicines have borne an intrinsic weakness since the day of discovery. Shortly after penicillin triumphed in the medical market, pathogens "learned" how to become resistant to it. Nowadays, all over the world, the number of pathogens capable of resisting antibiotics is skyrocketing. Simple infections and minor injuries which have been supremely treatable for decades have regained the power to kill human beings, as Keiji Fukuda, Deputy Director of the World Health Organization (WHO), warned publicly last year. This is not just apprehensiveness or fear, it is already a fact, elucidated WHO: "It is happening this very moment in every region on earth and can strike anyone of any age in any country".

Shrugging off such statements as attempts to push the panic button is far off the mark, says Michael Borek, Therapeutic Area Head Medical Office at Sandoz: "The situation is genuinely alarming." There are already cases being registered in the fields of oncology and transplants, for example, where patients cannot be treated with medicines, since they have picked up resistant germs. "Particularly in hospitals, the situation is quite critical," says Borek. As a result of the massive use of antibiotics in hospitals, extremely high numbers of multi-resistant bacteria have been colonized. The most well-known among them is the methicillin-resistant *Staphylococcus aureus* (MRSA), less-than-fondly nicknamed the "hospital microbe". To make matters worse, the immune system of hospitalized patients is already severely weakened, which impedes the body's own immune system from coming to the rescue.

Resistance shift and switch

Even in the external zones of physicians' private practices, doctors are now more than ever fighting a losing battle against resistance. The invisible obstructions have made themselves felt, more than anywhere else, in skin, lung and urinary tract infections, according to Borek, and massively so. "In the case of respiratory infections, our portfolio is still sufficiently large and sufficiently effective," says the expert.

And to reflect on how it all started so promisingly: when Alexander Fleming discovered penicillin in 1929, the battle against dreaded infectious diseases seemed to be won. Penicillin was developed further and further. Most antibiotics were researched between 1940 and 1960. Infections were able to be treated with ever greater success. As statistics prove, Europe's mortality rate from infectious diseases was approximately 35% in 1910; by 1990 it had been reduced to 1–4%.

Thousands dead, ever higher costs

And now, things have changed radically. According to current estimates in the European Union, 25,000 people die annually of infections from multi-resistant germs and 400,000 become infected. The costs of the increasing care for patients who are suffering from this, and the loss of human productivity as an ancillary consequence, are assessed at 1.5 billion Euros annually. In the United States 23,000 deaths annually can be attributed to multi-resistant microbes, according to CDC, the Center for Disease Control, and two million people come down with an infection.

Back to square one

But why have we been thrown back to the starting line, right where we were a hundred years ago? "The more antibiotics in use, the higher the resistances," says Borek. It is a piece of wisdom which has been known since the 1940s. And the deployment of antibiotics is enormous indeed: experts estimate that every second antibiotic is being swallowed unnecessarily. "Frequently, antibiotics are prescribed for infections of the upper respiratory system, even though 80% of such infections are caused by viruses," says Dorothea Orth-Höller, Director of the Diagnostic Laboratory for Bacteriology, Mycology and Parasitology at the Department of Hygiene and Medical Microbiology at the Medical University of Innsbruck. The fact that doctors reach for antibiotics so quickly can in part be attributed, in her opinion, to fulfilling the express wishes of patients themselves. While at the same time, doctors are hedging their bets and guarding against unseen risks.

Furthermore, incorrect use and doctors' and patients' mishandling of antibiotics practically forces resistances to evolve. "Patients tend to stop taking antibiotics as soon as they feel better," says Orth-Höller. Yet only the full-fledged, lengthy dosage covering the entire specified period can ensure that the pathogen is destroyed and resistances prevented. Moreover, it is at least as important to have precisely the right antibiotic prescribed, should one become necessary, is Borek's own conviction. It need not always be the wide-spectrum antibiotic, sometimes a simple medicine is far superior in its healing effects. "In hospitals it unfortunately occurs too often that prescriptions are written by the on-duty specialist and not experienced doctors," the expert criticizes. It is also extremely helpful when selecting the appropriate active agent of an antibiotic to use tests that identify the particular strain of bacteria involved. There is also a test to verify whether an infection has been caused by bacteria or a virus.

Not only in human medicine do practitioners reach too quickly for antibiotics. "A gigantic factor is also their use in animal breeding and fattening," both Borek and Orth-Höller concur in unison. Although employing antibiotics as a growth-enhancer in animal husbandry has been legally prohibited in the European Union since 2006, the ban is often circumvented. As consumer demand for meat rises, greater amounts of antibiotics are fed to the animals being bred all around the world. Today, 172 milligrams of medicines go into each and every kilo of pork. By 2030, a further increase of 67% is anticipated, compared with today practices, forecasts an international team of researchers in a recent edition of "Proceedings" journal. The problem is crystal-clear: via the excrement of animals, as much as 90% of the active substances in the medicines are absorbed into the soil, either through fertilization with dung or liquid manure, seeping thereby into the groundwater. It also goes directly into the human body through the consumption of the meat itself. Incidentally, resistant bacteria are also found in animals which make the administering of antibiotics a vain exercise as well.

Bundled measures

The threat of an "Antibiotic Armageddon" has sent a wake-up call to politicians as well. In the meantime: United States President Barack Obama has allotted approximately US$ 1.2 billion to the fight against multi-resistant bacteria in the budget for 2016. According to Obama's plan, hospitalized patients should receive 20% fewer antibiotics and outpatients 50% fewer. The European Union has also taken up the banner against resistant pathogens with a 12-point plan, measures such as raising levels of sensitivity to the appropriate use of antibiotics, tightening laws on animal medicines and animal-feed pharmaceutical products, introducing guidelines and recommendations regarding more circumspect use of antibiotics in veterinary medicine, ratcheting up measures for infection prevention and stricter controls in hospitals and other stationary patient care centres.

Whether or not measures such as these can actually contain and/or curtail antibiotic resistance is not open to doubt; it has been proven through comparisons among European Union countries. "In Europe, a clear-cut North/South divide prevails," says Borek. In Norway, the Netherlands and Sweden, less than 1% of the *Staphylococcus aureus* pathogen (which numbers among the most widespread hospital pathogens worldwide) is resistant against the antibiotic methicillin. In southern European countries, on the other hand, the resistance is 50% or more. One reason for this is the fact that in many countries, e.g. Italy, Greece, antibiotics can be freely purchased over the counter. Another is that northern countries began early on to screen endangered persons. Still another major factor can be found in public awareness: "France had 50% resistance in children, one of the highest rates of all," Borek recalls. Instruction and campaigns to raise public awareness by and for doctors, as well as for patients, sharpened public sensitivity noticeably as regards antibiotics, which in turn swiftly led to a drastic reduction in resistance. Sandoz, too, places its bets on heightened awareness. In South America, the company is sponsoring a programme called "Better Care More Health", to educate people in their use of antibiotics and

to raise both public awareness and individual responsibility.

Prevention really matters

Another significant aspect to reduce resistance, in the opinion of experts, lies in prevention. "Human hands number among the all-time great carriers of multi-resistant pathogens from one patient to another," says Orth-Höller. "Even sickbed visitors are victimized". The screening of patients referred to above is an integral part of prevention. In some places, e.g. at the Innsbruck University Clinic, patients from abroad are isolated to start with, then screened via nose, throat and stool samples. Even healthy people can be carriers of resistant pathogens. For example, in some babies' very first bowel movements after birth, bacteria utterly resistant to all antibiotics has been found. "Whether these were transferred during the process of birth, were previously inside the mother's womb, or were contracted from the environment following birth, has not been answered," says the bacteriologist. An equally important subject of research is the question for how long a patient can carry multi-resistant bacteria. "We simply don't know how long a patient carries them around. Whether they abide, depart, or are merely below our threshold of detection."

Research: Full steam ahead

In laboratories around the world we are witnessing a resurgence in antibiotics research with new antibiotics being sought all year round, around the clock. Whereas between 1983 and 1987, a total of 16 newly approved antibiotics entered the marketplace, between 2008 and 2013 there were only two, reports Borek. Overall, there are more than 80 antibiotics in 20 different classes currently on the market. Borek comments that: "It is being seriously considered not to develop a product for a specific illness, but for the particular germ which causes it."

In the midst of this complex struggle, alternative therapies gain new importance. For example, viral phage therapy is becoming increasingly significant. Tracking other active substances, e.g. adhesion molecules of bacteria through which they cling to their host cells, are also new ideas in the pipeline. Uncovering new antibiotics through special project research and by obtaining subsidies to that purpose are the goals of an initiative known as NewDrugs4BadBugs (ND4BB). Approximately 50 universities and research institutes, as well as 20 international pharmaceutical companies, are participating in this research programme from the Innovative Medicines Initiative (IMI), a Public-Private Partnership developed by the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

Nevertheless, in the fiercely competitive race between researchers and the bacteria, the antagonists are currently winning. Bacteria, too, are constantly developing new paths, new methods and new strategies to paralyze and shut down antibiotics. They do this through altering their genetic makeup or through handing on the substances which contain the codes about resistance to other bacteria. "The biggest problem is time," says Borek. The development of an antibiotic which can stay the course all the way to market approval takes about 10 years, whereas bacteria can develop resistances as early as the clinical testing phase.

Old but good

In the battle against dangerous and formidable microbes, we are currently reaching back to old antibiotics. They were tried and tested, approved decades ago, but then were not developed any further. "Data about correct dosage, about indications and/or toxicity are lacking," says Orth-Höller. Frequently these medicines are simply no longer available, having been removed from the market shelf when the patent ran out.

The momentous impact of antibiotics over the last 70 years remains undisputed. In earlier times, when medicines were unknown, patients died of their infections. And as grave as the situation is today, we cannot forget the fact that today's antibiotics continue to provide enormous benefits in medicine and continue to save the lives of countless human beings year after year. However, the problem of resistance is one of the most pressing medical challenges of our times and urgency is paramount. By continuing to pursue and develop new substances, researchers all over the world are working unflaggingly so that the battle against infectious diseases which had seemed already won does not, in the end, force us to capitulate. However, not only do research efforts need to be stoked up, the avoidance of newly arising resistance also plays a crucial role. To this end, the education of patients is every bit as important as responsible deployment and correct usage of already existing substances. Most importantly, as we have seen with other major global health challenges, success will only come through a sustained and unwavering commitment from governments, the pharmaceutical industry and other health-care organizations. •

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