IS ANTIBIOTIC RESISTANCE THE NEXT INSIDIOUS PANDEMIC?

Antibiotic resistance is on the rise worldwide and is one of the greatest global health challenges today, not only in terms of medical progress but also for the economy. What action must be taken immediately and which novel drugs against multidrug-resistant bacteria can stop this insidious pandemic?

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Bio^{M}: With the discovery of the first antibiotic, penicillin, in 1928, Alexander Fleming eliminated the horror of many bacterial infections. Almost 100 years since this milestone in medical history, a new danger is emerging that Fleming had already warned against: escalating antimicrobial resistance. This is increasing worldwide and is currently one of the greatest challenges to global health. Now that the SARS-CoV-2 virus has dominated our lives for many months, in fact almost two years, have we lost sight of other pathogens?

Dr. Meyer: Firstly, I think it's clear and evident that a huge, menacing wave came at us in the form of SARS-CoV-2. It was therefore good and very wise to focus on putting resources in place to intercept this wave and save lives. We've managed this very well in many cases. Of course, we realize that other diseases would like the same attention and would also deserve it. But that has only been possible to such an extent in this specific case. What we are seeing, however, is that the technologies developed during the SARS-CoV-2 pandemic, such as RNA vaccines, are paving the way for innovations that will help and will lead to advances in other diseases. From the perspective of infectious diseases, it has to be said that SARS-CoV-2 has brought the threat of infectious diseases back into the consciousness of society. For a long time, we had forgotten how threatening and how difficult such situations can be, and this has definitely now returned to the fore. We are experiencing not only the disadvantages, but also the opportunities that evolve from the situation.

According to a recent study, at least 1.27 million people worldwide died from drug-resistant bacterial infections in 2019. The United Nations has warned that by 2050 multidrug-resistant bacteria could be responsible for killing 10 million people a year. That would exceed the number of deaths from cancer at present. How and why do bacteria develop resistance to antibiotics?

We need to go very, very far back in time: These microorganisms existed long before humans. Each microorganism tries to shape its environment in such a way that it has the best possible conditions. It therefore develops substances to keep other microorganisms out of this environment and thus secure resources for itself. To fight for these resources, the other microorganisms respond by building up resistance. The mechanisms by which microorganisms generally defend themselves against antibiotics can be divided into four major groups: firstly, microorganisms can prevent their cells from absorbing antibiotics. Keyword porins: aqueous channels through which certain antibiotics can be absorbed. If a bacterium has fewer channels or if the channels are altered so that they no longer allow this antibiotic to pass through, it is protected from uptake. Conversely, we also have efflux pumps that do the opposite: these send or pump out anything that has infiltrated a microorganism that might be unwanted. Both mechanisms, uptake and expulsion, regulate the concentration of these antibiotics – potentially to the point where they can no longer function. Other mechanisms exist that are specific to certain antibiotics. The target structure being attacked by the antibiotic could be altered such that it can no longer work. There are also mechanisms that chemically destroy antibiotics in bacteria, also ensuring that they no longer work.

Why is antibiotic resistance such a big problem, and how do you judge its significance compared to the coronavirus pandemic?

The coronavirus pandemic is caused by a pathogen that can change. We are aware of the difficulties. But with resistance, we face a variety of pathogens that are resistant to different antibiotics and cause different infectious diseases. The whole system is much more complex. But more importantly, antibiotics are the basis and the foundation of modern medicine. If we can no longer protect and safeguard patients for treatments with antibiotics, then this clearly compromises our ability to treat other diseases, which of course is the major concern.

Why are multi-resistant bacteria becoming such a global problem and are we acting accordingly? Are we acting globally in this respect?

We have seen with COVID-19 how quickly infectious diseases spread worldwide. It may not be quite as fast, but in principle, the same is true for antibiotic resistance. Furthermore, antibiotics are the 'fire extinguishers' of modern medicine. In many clinical interventions, we need to safeguard the patients against bacterial infections. If antibiotic resistance speeds, some treatments will bear a much bigger risk for the patients. We might lose achievements of modern medicine. Globally, we have a much bigger problem: we have huge problems in parts of the world that are not as economically robust and where there is no access whatsoever to appropriate antibiotics. This is a global issue, and Europe is no exception. Here too, we do not have access to all antibiotics. We know that we need to act globally, but solutions are very difficult to find.

What's the biggest issue? When you say globally, are there regions that are not keeping up?

Yes, it's always the parts of the world that are already in a rather difficult economic position. It's in Africa and the Indian subcontinent where we are seeing serious problems with resistance. We see resistance problems in South America, but also in China and Russia. In other words, wherever people are already facing challenges they no longer have ways to get access. We must be clear about one thing: To date, more people have died from a lack of antibiotics than from resistant infections.

What global consequences do you expect?

In addition to the global consequence of people naturally suffering health damage or even dying, we are also faced with the impact on the global economy. Considerations and calculations by the World Bank indicate that an economic loss of up to 5.6 percent can be expected depending on the extent to which resistance has developed and the areas of the world with the corresponding economic power we are looking at. That exceeds the global economic contraction that we experienced in 2008. This will have an impact on people and their quality of life and prove difficult, of course.

We've already hinted at various regions in our conversation. Which ones have it easier and which ones are struggling more?

The classic low- and middle-income countries are affected: South America, Africa, the Indian continent and, of course, Asia. But we also see antibiotic resistance in Russia. The regions of the world that are currently economically strong are doing much better.

Many large pharmaceutical companies have discontinued their antibiotic research programs. Shouldn't the development of new antibiotics be worthwhile for companies when so many people are falling ill with untreatable infections every year?

Indeed, it should, but antibiotics are a very difficult class of drugs. On the one hand they are traditionally inexpensive, but on the other hand the treatment period is very short. Consequently, the patient - if the antibiotic works - recovers completely. Thirdly, we have the problem of resistance. All three points naturally make it unattractive for the pharmaceutical industry to invest in the development of antibiotics. The investment periods are long: 14 years with costs of up to EUR 1.8 billion. In the end, you don't get much in return.

The public always likes quick solutions. We have now seen that with COVID-19. Is the development of new antibiotics even feasible over a short period?

Well, quick solutions are very, very difficult because we are dealing with two organisms at the same time: the bacterium that we want to fight and the human being who at the end is supposed to tolerate the treatment. That is more difficult or a different challenge with antibiotics than with viral diseases. But yes, I agree: the pharmaceutical industry should get involved again, and there are early signs that this is the case. There is the AMR Action Fund, which was launched in 2019. The pharmaceutical industry has contributed EUR 1 billion to the development of antibiotics along with its expertise. I am therefore confident that this is going in the right direction.

Would different or novel regulations and reimbursement models be needed to make antibiotic research more attractive to biotechnology and pharmaceutical companies?

Absolutely. We have seen that it is precisely small and medium-sized companies that drive such developments. Once they have successfully launched an antibiotic, it usually only takes a few months before these pharmaceutical companies or small businesses become insolvent because they simply can't make the sales. The problem is that the new antibiotics are reserve antibiotics. We should use them very, very, very sparingly, ideally not at all, and keep them in reserve as a safeguard. A product on which EUR 1.4 to 1.8 billion is spent on development, but ultimately is not used, is of course not economically viable. That's why we need new reimbursement options. This is a topic that is being widely discussed. We need to move away from volume-based reimbursement, i.e., the more I use, the more I earn and the more profit I make, to reflect the value of antibiotics for society and for patients, regardless of how often the antibiotic is used.

With your Frabiotics spin-off project, you are researching small molecules that should enable the treatment of infectious diseases. Can you explain your approach? What makes it special?

We are working on combating so-called WHO1 pathogens. These are the ones for which we urgently need to develop new treatments, because they are particularly difficult to treat. Furthermore, thesehese pathogens have one special feature: they are carbapenem-resistant, which means they are resistant to the most important class of antibiotics we have and the treatment options are therefore extremely limited. Carbapenem resistance is mediated by enzymes that act like scissors. They simply cut open the beta-lactam ring - the core structure of those antibiotics - and subsequently the antibiotic is no longer functional. Frabiotics is developing a stone to match these scissors, so to speak, that will block them. The unique feature of this stone is that it can block two types of scissors, as these enzymes come in two different forms at the same time: nail scissors and hedge clippers. In addition, the molecule has another property: independent antibiotic activity. This dual mode of action, namely protecting the beta-lactams on the one hand and acting as an autonomous antibiotic in its own right on the other, obviously offers huge advantages when it comes to the future development of resistance. As far as we know, this is unique.

You won the m4 Award with your Frabiotics team in 2019, which is endowed with a total of EUR 2.5 million. This competition is aimed at academic research groups from Bavaria with spin-off potential. It is coordinated by Bio^{M} and funded by the Bavarian Ministry of Economic Affairs. How important are such programs and other forms of research funding in your field?

These programs are of utmost importance. The m4 Award really helps us to move the project forward and gives us a lot of visibility. The BMBF, the Ministry of Research and the German Center for Infection Research also have funding programs. Without these programs, we could not exist at all, and the development program would already have ended.

To put it a trifle more pointedly, is it possible that at some point no single effective antibiotic may even exist?

We encounter individual infections where we are really at our wits' end. However, I am optimistic that we can prevent this from happening across the board. The problem has become very visible. A lot of work is going on, a lot of research. In politics, we have visibility with this topic. I am confident, therefore, that in time we will develop solutions.

What are the most important short- and long-term measures you are calling for to counteract the increasing development of multidrug-resistant bacteria? What role can preventive measures play in this?

We have a whole portfolio, a potpourri of preventive measures that we all need: It

starts with hygiene, from access to clean water and sanitary facilities to hospital hygiene. It's about ensuring that the production of new antibiotics is set up in a way that wastewater containing antibiotic substances is no longer released into the environment where it encourages the development of resistance. There must be a change in veterinary medicine: Three-quarters of the world's antibiotic production is still used for animal breeding, and in agriculture. Here, too, we must rethink and prevent the emergence of resistant bacteria. In other words, take preventive action. Prevention in human medicine with appropriate diagnostics and appropriate antibiotic stewardship programs is another aspect, making the use of antibiotics in human medicine a targeted and truly effective concept. We need a global approach. This is also a means of prevention, so that we do not target resistances in one corner of the world which then lead to problems in another. Lastly, we also need to expand basic research in this area. An initial approach has been made with the Bayresq.net program, for example, which is also strongly supported and accompanied by Bio^{M}. We must start designing new concepts now and, on this basis, we can develop new therapies in the future. To be clear: The game between antibiotics or antibiotic substances and the corresponding development of resistance, which I described earlier, continues.

What would have to happen quickly?

What would have to happen quickly? The market would have to be regulated rapidly so that products which are in the pipeline reach the patient. Hygiene measures can also be implemented relatively quickly.

And what do you need to factor in for the long term?

Well, in the long term, as I said, veterinary medicine needs to change, as do animal breeding and agriculture, so that fewer antibiotics are needed. Longer-term perspectives are certainly to regulate global access to antibiotics. It's a huge and complex subject. And, of course, basic research: aimed not at tomorrow, but rather the day after tomorrow.