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Resistant pathogens

A threat for humans, animals and the environment

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RESISTANT PATHOGENS: A THREAT FOR HUMANS, ANIMALS AND THE ENVIRONMENT

Resistant bacteria are spreading worldwide. In collaboration with partners in India, Tanzania, South Africa and Germany, we have investigated the causes and consequences of this spread.[2] This Pharma-Brief Special presents the results. It examines the risks for humans, animals and the environment. It focuses on local problems and approaches, international interactions and the responsibility of doctors, farmers and consumers.

> *"Antibiotic resistance is not a faraway threat but one that is happening now. In hospitals and clinics all over the world, patients are being given antibiotics that are failing to work."*[1]
>
> *Madlen Davies, Bureau of Investigative Journalism, Great Britain*

The World Health Organization (WHO) is sounding the alarm: without swift, coordinated action, the world is heading for a post-antibiotic age. Not only widespread infections, even minor injuries could become a deadly danger. This is true for patients in Germany, and even more so for those affected in India, Tanzania or South Africa, where people fall ill more frequently, and the necessary specialists, diagnostics or therapies for the treatment of multi-resistant infections are available at best in large cities.
According to WHO estimates, at least 700,000 people worldwide already die of resistant germs every year. They spread in hospitals as frequently as in pig and chicken houses. And, most dangerously, the pathogens do not stop at borders.

Careless use and research gap

The first strains of pathogens against which no single remedy is effective any more are already appearing in various parts of the world. They are spreading from country to country through travelers, exports of goods, in the air or in water. On the one hand, they bear witness to decades of careless use of antibiotic agents, which has accelerated the development of resistance. On the other hand, the misery reveals the failures of a largely privatized research system based on profit rather than need: no new drugs are in sight.[3,11] Most of the large pharmaceutical companies have stopped

Patients in poor countries are often denied access to expensive and newer drugs.
Photo: CC Monusco Photos

> ***"Humans have created an unequal world with unequal distribution of wealth and power, and all this in turn is leading to unhealthy living conditions for millions. The dirt and unhygienic living conditions have helped the microorganisms to thrive and develop resistance. Most unfortunately, global leaders are not even aware (or just pretend being not aware) about this huge problem that the world is facing."*** [1]
>
> *Dr. Gopal Dabade, Indian doctor and activist, founder and board member of Jagruti/India*

antibiotics research because it is hardly possible to make a profit from it. Bristol-Myers Squibb, Abbott, Eli Lilly, Wyeth, Aventis and Bayer left more than ten years ago. Recently, AstraZeneca, Sanofi and Novartis have stopped development, and Johnson & Johnson is now also giving up.[4] Only a handful of companies are still involved in antibiotics research, including GSK and Pfizer. In addition, the few new substances that exist are hardly available: there are 13 antibiotics that are still under patent protection. In most poor countries, manufacturers have not even applied for approval for these newer preparations. Only three are registered in at least 10 of the 102 countries with a particularly high demand. Older, sensible treatment alternatives are also lacking in many places because they are not available on a nationwide basis.[5]

Poverty: a breeding ground for resistances

The fact that poverty and wealth have an immense influence on health is nothing new. The issue of antibiotic resistance confirms this connection once again, and will exacerbate this inequality. This is because resistant germs encounter weak health systems in the Global South where infectious diseases are among the main causes of death. Poor housing conditions – especially in urban slums or in refugee regions – accelerate the spread of the super germs.[6] With significant social and economic consequences: the treatment of resistant forms of the disease takes longer, is far more expensive and has more side effects. The chances of cure are also poorer. All of this puts a strain on both the public funds and the private purse.

Innovative approaches are needed at national and international level, in hospitals and medical practices as well as in agriculture. Consumers and patients can contribute a great deal to their success – through the critical use of antibiotics and sustainable meat consumption.

Poverty and poor housing conditions favor the spread of super germs. Photo: CC SuSanA

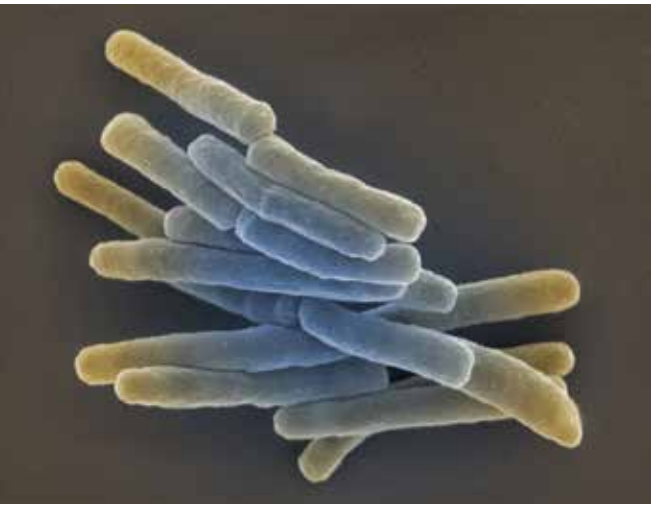
USEFUL HELPERS OR DEADLY ENEMIES?

Bacteria have lived on earth for over 250 million years. In our body they play an important role and are essential for survival. On the other hand, they can sometimes cause diseases such as urinary tract infections, pneumonia, wound infections or blood poisoning.

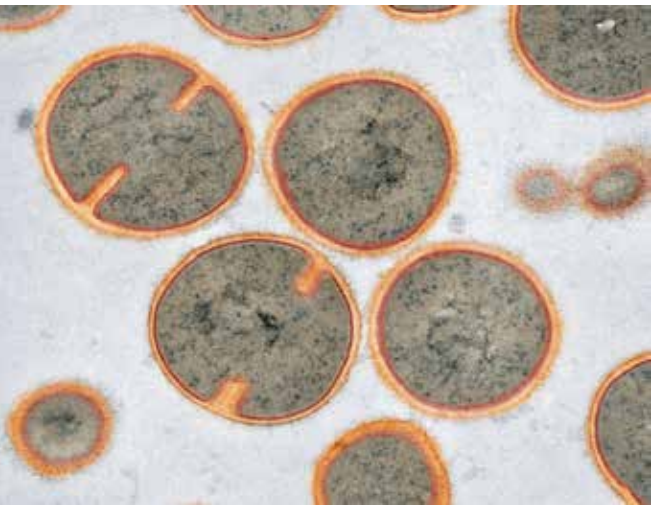
Every human being carries 1-2 kilos of bacteria. The intestinal flora is responsible for digestion. On the skin, in the mouth-throat area and on the genitals, microorganisms are part of the immune system. But they can also cause diseases – especially when our immune system is weakened – for example after an operation or through poor nutrition.[6]

Before the invention of antibiotics, bacterial diseases repeatedly caused devastating epidemics. For example, the plague, also known as the "black death", killed over 20 million people in the 14th century. The pathogen had spread along the trade routes from Asia to Europe and depopulated entire regions.

Bacteria are very different from viruses, which do not have their own metabolism and are not living organisms. Antibiotics are ineffective against viruses.



Mycobacterium tuberculosis is a gram-negative rod-shaped bacteria. Photo: © RKI



Staphylococcus aureus is a spherical bacterium. Photo: © RKI

There are Gram-negative and Gram-positive bacteria. The name goes back to the Danish scientist Hans Christian Gram, who discovered that the two groups of bacteria can be stained differently. This is helpful in the diagnosis of bacterial diseases, and crucial for choosing the right antibiotic. Antibiotics can have a bacteriostatic effect, i.e. prevent the bacteria from multiplying, or a bactericidal effect, i.e. they kill the bacteria. Currently, about 80 different antibiotic agents are used.[6]

Reserves: aces up our sleeve

Broad-spectrum antibiotics are effective against many different types of bacteria (e.g. amoxicillin) and are therefore frequently used. In many cases, however, they are not the best choice. In most cases, a targeted therapy with an active substance of the first therapy line makes more sense. A good diagnosis is necessary to determine the pathogen exactly and to check whether an antibiotic is effective. In addition to the agents that are used as standard, there are so-called reserve antibiotics. These are reserved for difficult therapy situations, e.g. for resistant pathogens when the usual treatment is no longer effective. So far, however, there is no generally valid list that classifies all antibiotics. Some orientation is provided by a list of the WHO, listing all active substances that are particularly important for human medicine and should therefore be used with extreme restraint in animals.[7] Among the antibiotics described by the WHO as "critically important" are macrolides, fluoroquinolones or cephalosporins, all of which are also approved here as veterinary medicines. The same applies to the reserve antibiotic colistin. This drug is currently considered the last trump card in the treatment of severe, multi-resistant infections with gram-negative germs.

True survival specialists

Bacteria react extremely quickly to changing living conditions. When they multiply, genetic mutations always occur. This can result in organisms that differ from their parents: they become resistant. If these resistant germs then come into contact with antibiotics, they have a better chance of survival and can multiply more rapidly. Resistance formation is therefore a natural and evolutionary process. However, frequent contact with antibiotics accelerates it considerably. Resistances develop primarily where there are many antibiotics in circulation, e.g. in hospitals or in factory farming.[6] A continuous input of antibiotic residues into the environment also increases the occurrence of resistant germs in soil, air and water.[8,9] Bacteria can also pass on resistance to other bacteria by exchanging genetic material. They can even take up several resistance genes that protect them against different antibiotics. This leads to the development of multiple or multi-resistant pathogens (MRP) that can resist a variety of antibiotics.

Resistant pathogens can be transmitted in many ways: from person to person, for example by coughing or shaking hands; in close contact between humans and animals or via air, water and food. Drinking water contaminated with faeces, for example, plays a major role in the spread of resistant coliform bacteria in many poor countries. Bacteria can be transferred to meat products during slaughter and meat processing. But resistant germs can also be found on vegetables: they are spread on the cultivated areas with liquid manure or fermentation residues from biogas plants. The resistance genes can survive for years in the soil and be transferred to pathogens that cause diseases in humans or animals.[9]

Resistant germs can also be transmitted during meat processing.
Photo: © iStock

No problem for healthy people

For healthy people, resistant pathogens are usually not a problem. Many people are carrying such bacteria without even noticing it. Only when the immune system is weakened, or when these pathogens penetrate deeper into the body, for example during an operation, it can become critical.

The multi-resistant Staphylococcus aureus (MRSA) germ, for example, lives on the skin or mucous membranes. It can cause skin and wound infections, but is really dangerous in surgical wounds or pneumonia. The VRE pathogen (vancomycin-resistant enterococci), on the other hand, colonizes the intestines. The resistant germ occurs mainly in hospitals, and can cause urinary tract infections, peritonitis or blood poisoning in immunocompromised patients.

Resistant Staphylococcus pathogen
Photo: CC Bill Branson

Dirty tricks

Bacteria use different mechanisms of resistance formation. They form enzymes (β-lactamases) that react with an important component of many antibiotics (β-lactam) and chemically alter it. This renders the drugs ineffective. There are different types: ESBL deactivates antibiotics such as penicillins, but also cephalosporins. E. coli is one of the pathogens that often master this trick. It colonizes the intestines and can cause urinary tract infections, pneumonia, blood poisoning or wound infections after operations. Even Klebsiellae – also natural inhabitants of the digestive system – are increasingly showing the ESBL resistance mechanism.

Carbapenemase-producing bacteria are resistant to carbapenems and other reserve antibiotics. Such bacteria are even more difficult to treat, and are considered extremely resistant. In Germany, they are currently only found in hospitals.

Antibiotics: as much as necessary and as little as possible! Photo:© Health-e

"One of the most important aspects of avoiding antibiotic resistance is the accurate measurement and reporting of antibiotic consumption – both in humans and animals. In far too many countries, such data is not collected, not made public or not used to inform policy-makers and medical personnel. It is essential to use standardized procedures, using the daily dose defined by WHO and a uniform methodology."[1]

Andrew Gray, Professor of Pharmacy at the University of KwaZulu-Natal in Durban/ South Africa

ACTING GLOBALLY

The World Health Organization plays an important role in the global fight against antibiotic resistance. For two decades it has been pointing out the immense risks, and urging states and governments to act quickly.

As early as 2001, the WHO presented a global strategy for the containment of antimicrobial resistance. At that time, however, the issue received little attention. Only in recent years has there been some movement, as reports of uncontrollable resistant forms of disease have become increasingly overwhelming. In 2015, the 194 countries represented in the WHO agreed to a Global Action Plan against antimicrobial resistance.[10] They thus committed themselves to introducing action plans and establishing monitoring systems at national level. But in many poor countries in particular, their implementation has so far failed due to insufficient financial and human resources or a lack of infrastructure.[11]

One Health: thinking holistically and globally

The WHO action plan pursues a holistic approach: The One-Health concept takes into account the complex interrelationships of resistance formation between humans, animals and the environment, and strives for close cooperation between all actors in order to develop solutions.

And the global dimension is also in focus, because resistance is not limited to individual regions and populations. Worldwide interactions and similar trends are obvious: resistance rates are increasing everywhere, the same drugs are used worldwide, and similar behavior patterns can be found among doctors and patients worldwide, which must be overcome. Finally, the One-Health approach is also a response to globalization. International trade and growing

mobility help resistant bacteria to overcome geographical borders in the shortest possible time.[6]

Reporting and monitoring resistance rates

Knowing where which pathogens appear and what resistance they carry is crucial. This is the only way to identify transmission paths and develop countermeasures. This is why the WHO launched a worldwide reporting system for monitoring antimicrobial resistance in 2016. The Global Antimicrobial Resistance Surveillance System (GLASS) is designed to provide reliable data on the global resistance problem and thus support national, regional and global action plans.

But reporting and monitoring systems require well-equipped laboratories and trained personnel. It is also important to have a collection system as uniform as possible so that the data collected is comparable. So far, all this has been lacking and the global reporting system GLASS is piecemeal. Only 49 countries currently report data on the resistance situation – often they come from only a few large hospitals.[12] "[Resistance] monitoring is still in its infancy," says Dr Carmem Pessoa-Silva, who coordinates the GLASS project.[13] This makes it all the more important to expand the reporting system in order to effectively address the resistance problem.

The focus of GLASS has so far been on human medicine. Resistant germs in the environment or in the food chain are currently only being investigated in pilot projects at best.[13]

Focus: human medicine

For the GLASS Report 2018, 22 countries reported resistance rates to the WHO. The data show: "Some of the world's most widespread – and potentially most dangerous – infections show resistance," says Dr Marc Sprenger, Director of the WHO Secretariat on Antimicrobial Resistance.[13] Infections with resistant coliform bacteria, Klebsiellae, MRSA, pneumococci and salmonella were particularly common. Data on resistant tuberculosis, which affected half a million new cases in 2018 alone, are not recorded by GLASS because the WHO has established its own reporting system for this.[14]

Up to 82% of all sepsis cases in some countries showed resistance to at least one standard antibiotic. Penicillin – an antibiotic that has been used successfully for decades to treat pneumonia – fails in half of all cases in some places. The E. coli pathogen, a frequent trigger of urinary tract infections, shows resistance rates of up to 65% to the reserve drug ciprofloxacin.

The WHO also sees major treatment problems in sexually transmitted diseases such as gonorrhea.[15] With 78 million cases per year, it is the second most common sexually transmitted disease with particularly high infection rates in Africa. In women it can lead to pelvic inflammation and ectopic pregnancies. It also increases the

Well-trained personnel are needed to detect resistance and to expand the detection systems worldwide. Photo: CC Benoît Marquet, DNDi

Focus on human medicine: resistant germs complicate the treatment of many diseases. Photo: © Health-e

Veterinarians are rare in many countries and antibiotics are administered without diagnosis. This also promotes the development of resistance.
Photo: CC J. Kabluyen, USAF

risk of HIV infection. Resistant forms of the disease now make the treatment of gonorrhea extremely difficult worldwide.

Focus: veterinary medicine

All over the world, the quantities of antibiotics administered to pigs, cows and chickens have been increasing for years. Disease susceptibility through mass production and breeds bred for high performance are important driving forces. Especially in poorer countries, the use of antibiotics is growing rapidly – with serious consequences. A review study by Van Boeckel et al. evaluated data from more than 900 scientific studies on various resistant pathogens such as E. coli, Salmonella or Staphylococcus aureus in poorer countries.[16] This revealed worrying trends: between 2000 and 2018, the effectiveness of antibiotic agents against these pathogens in pigs, chickens and cattle decreased significantly.

Hotspots of resistance development are regions of the world that are used particularly intensively for agriculture, e.g. northeast India, northeast China, northern Pakistan, the southern coast of Brazil or the Red River Delta in Vietnam. Other problem regions include conurbations such as Mexico City or Johannesburg.

If many animals are kept in a confined space, this affects their health and the need for antibiotics is high.
Photo: CC Shpernik

Poultry production – hightly profitable

In particular, poultry production poses a high risk of developing resistance. Chicken farming is particularly widespread in poorer countries and commercial poultry fattening is highly profitable – partly because it does not take up much space. But chickens are given more antibiotics than any other farm animal.[17]

Solutions are sorely needed: how can food security succeed in the long term with a growing world population? Are there realistic alternatives for producing sufficient animal protein sources without intensive animal husbandry and thus without the mass use of antibiotics?

Antibiotic substances are found in water bodies and rivers all over the world. Photo: © iStock

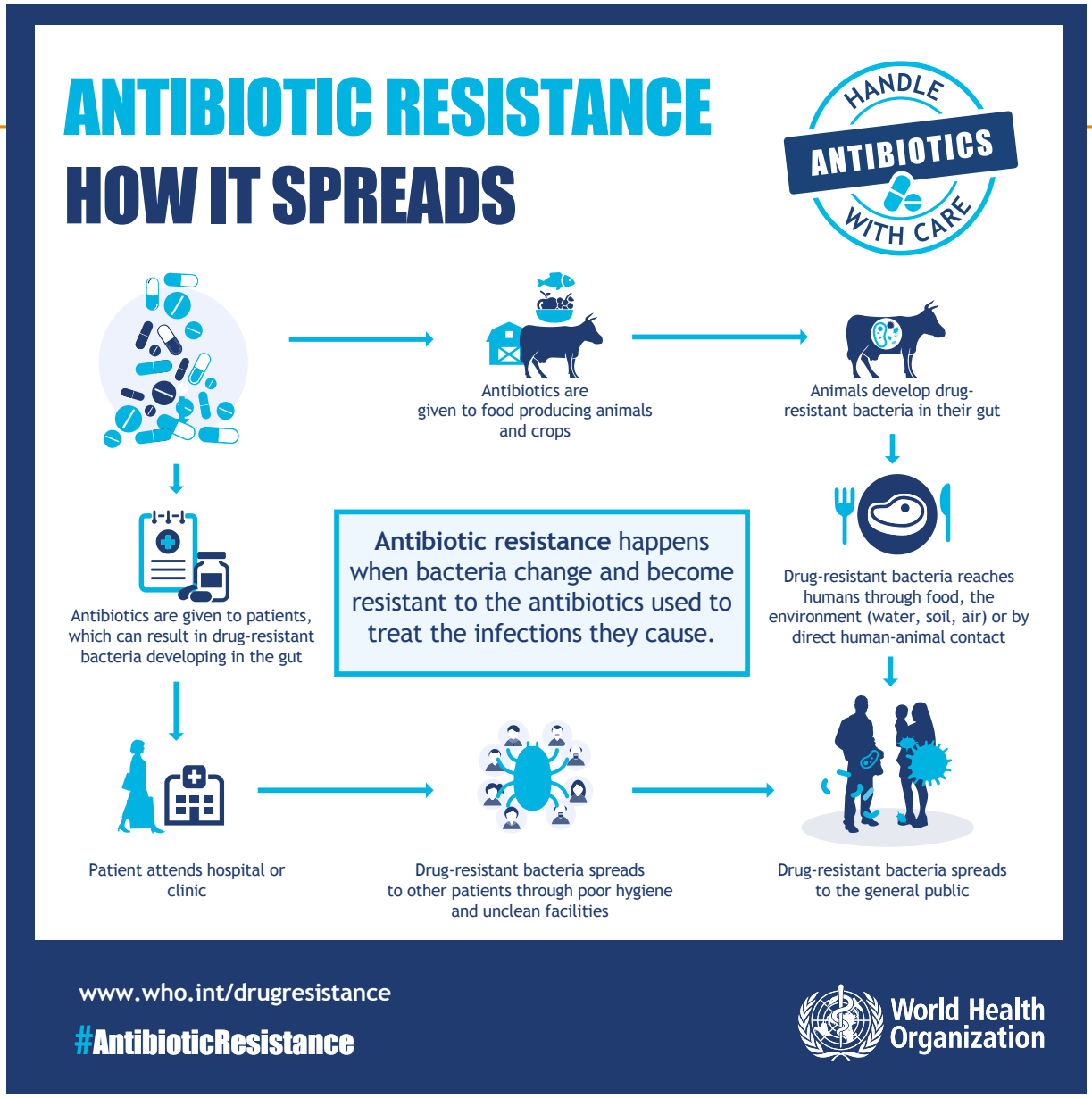
Focus: environment

Intensive agriculture and wastewater from hospitals and pharmaceutical production result in large quantities of antibiotics ending up in soil and water. The contamination of the environment with antibiotic substances promotes the development of resistant pathogens, which can also be dangerous to humans.

In addition to soil and water, the importance of air as a reservoir of resistant germs has recently come to the forefront of science. A study from the Netherlands examined the surroundings of 61 farms and found high concentrations of E. coli and staphylococci pathogens as well as resistance genes in airborne dust particles in the vicinity of the farms. Ventilation systems ensure that germs are transported outside with the stable air. Even at a distance of more than one kilometer, bacteria with resistance genes were detectable. The contamination was particularly high where there were many pig and chicken houses.[18]

The long-term effects of the massive introduction of antibiotics into the environment have so far hardly been investigated. Yet there are probably enormous differences between individual regions. In any case, the estimates and guidelines that apply to industrialized nations are miles away from the reality in poor countries.[19]

Whoever wants to win the battle against the spreading multi-resistant germs must involve the population, demands the WHO. Our country studies show exactly that: patients are just as much responsible for avoiding antibiotic resistance as doctors, farmers or consumers.



Infographic: © WHO

Endnotes

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2 *All partners are introduced on page 66-67.*
3 *WHO (2020) Lack of new antibiotics threatens global efforts to contain drug-resistant infections. www.who.int/news-room/detail/01-17-2020–01-17-2020-lack-of-new-antibiotics-threatens-global-efforts-to-contain-drug-resistant-infections [Access 27. 1.2020]*
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Protective suits in the high security laboratory of the Robert Koch Institute. They are not needed for resistant pathogens but for the treatment of highly infectious diseases like Ebola. The RKI supports partners worldwide with technical equipment and specialist know-how. Photo:© RKI

GERMANY: WELL PREPARED?

Antibiotic resistance has long since entered the public debate: difficult-to-treat super pathogens are worrying doctors and patients alike. Consumer protection bodies are warning of resistant germs on food. Environmental organizations are raising the alarm about antibiotic residues and resistant bacteria in rivers and lakes. What has to be changed? And what are the politicians doing?

Actually, Germany is well prepared: identifying, preventing and combating resistant pathogens is the declared goal of the German Antibiotic Resistance Strategy (DART). It was adopted in 2015 and contains a whole package of measures. DART pursues a one-health approach and addresses both human and veterinary medicine. However, the initiative also relies on international cooperation to implement the World Health Organization's (WHO) global action plan against resistance.[2] The German Robert Koch Institute is involved, for example, in Vietnam, Cambodia or Nigeria, and supports the countries in the further development of the global reporting system for antimicrobial resistance (GLASS).[3]

"Antibiotic resistance is a global challenge that must be managed globally. Resistant bacteria fly inside the gut flora of traveling humans from India to Europe in just a few hours."

Professor Joakim Larsson, Director of the Centre for Antibiotic Resistance research at the University of Gothenburg[1]

Sophisticated monitoring systems

DART has achieved a lot: changes in the law have been initiated and monitoring systems have been expanded. They provide data on the resistance situation and consumption. Such data – used as feedback – can inform doctors about current developments and support them in changing their prescription behavior. The analyses also show whether interventions are working.

Hotspot: animal fattening. Photo: © iStock

In 2014, for example, a special reporting system was established to reduce the use of antibiotics in fattening animals (cattle, pigs, chickens, turkeys). Since then, livestock farmers have been required to report every use of antibiotics above a certain stock size. The data are used to calculate every six months how often which antibiotics were used in which animal species. If a farm shows above-average consumption, the animal keeper has to search for the causes together with a veterinarian.[4]

Data about data

There are also various reporting systems and databases for human medicine, and doctors' practices receive feedback on their prescriptions. For example, since 2019 the Kassenärztliche Vereinigung Nordrhein (Association of Statutory Health Insurance Physicians in North Rhine-Westphalia) has been sending all GPs a detailed report on their antibiotics prescriptions. This enables physicians to compare their prescribing behavior with that of other colleagues.[5]

The threat posed by resistant pathogens in the environment has also become a focus of attention in recent years: with the HyReKA[6] research project, the German government has had resistant pathogens in water bodies investigated. In the process, sewage treatment plants, animal fattening operations and slaughterhouses as well as hospitals were identified as hotspots, and recommendations for political action were formulated.

The problem is, therefore, well known and well documented. It is far more difficult to achieve changes in people's minds – both prescribers and patients. Not to mention the structural changes that would be necessary to improve animal welfare and thus make antibiotics superfluous in many cases. There are still major hurdles to be overcome here. In order to succeed, political will is needed, but also insight and changes in behavior on the part of doctors, farmers and consumers.

One in four is prescribed an antibiotic once a year in Germany. Photo: © Fotolia

TOO MUCH AND WRONGLY PRESCRIBED

Every fourth person receives an antibiotic prescribed by his or her doctor at least once a year. Often it is the wrong one. Often it would be unnecessary. This promotes resistance and harms the patients.

Around 750 tons of antibiotics are used in human medicine in Germany every year.[10] The lion's share (85%) is prescribed in doctors' surgeries. Women receive a prescription far more often than men.[11] Older people and children swallow most. Although Germany is in a relatively good position compared to other EU countries and has been able to reduce its consumption continuously since 2013, Austria or the Netherlands show that it could be even more economical: in Germany, almost 12 out of every 1,000 inhabitants swallow an antibiotic (11.9 DDD, see box) every day, in Austria the figure is 10.4, and in the Netherlands only 8.9. In Greece, on the other hand, a particularly large number of antibiotics are prescribed. Here the figure is 32.4 DDD, in Spain it is 24.3.[12]

The West swallows more

Prescription behavior also varies greatly within Germany: in the West, patients receive significantly more antibiotics than in the South and East of the country. In North Rhine-Westphalia the prescription density is particularly high. Experts complain that many prescriptions are unnecessary and that antibiotics are often wrongly prescribed, e.g. for mild infections or infections where bacteria play no role at all. The choice of drugs is also problematic: far too often, broad-spectrum instead of narrow-spectrum antibiotics are used, even if it makes no sense. For example, doctors often prescribe the reserve antibiotic ciprofloxacin for respiratory

Who collects the data?

In Germany, data on infectious agents and resistances are collected by the Robert Koch Institute (RKI), among others. Laboratories that examine samples from patients from hospitals or doctors' practices report the resistance results. At the RKI, these data are stored centrally, evaluated and also transmitted to the European database EARS-Net.[8] However, participation in the ARS (Antibiotic Resistance Surveillance) reporting system is voluntary. In 2016, only around one quarter of hospitals and a fraction of doctors' practices were connected. The data are therefore only approximately representative.[9] Since the resistance situation is closely linked to the consumption of antibiotics, the RKI also monitors the use of antibiotics in hospitals. Consumption data from the outpatient sector is provided by the AOK Scientific Institute (WidO) and the Central Institute for Statutory Health Insurance Physician Care. Nationwide billing data from medical practices serve as a data source. National consumption is also reported to the European reporting system ESAC-Net. Here, data on antibiotics consumption in the EU member states is collected and compared with each other.

Even in hospitals, antibiotics are often administered for too long or unnecessarily.
Photo: © Flickr Teddy Wade

infections. Amoxicillin would be more effective against pneumococcus, the most common cause of respiratory infections.[13]
Fluoroquinolones such as ciprofloxacin also carry higher risks. They can damage the nervous system or cause tendon tears. The AOK Scientific Institute estimates that of the 3.3 million patients treated with fluoroquinolones in Germany in 2018, around 40,000 were affected by such side effects. For many infections, there are effective, lower-risk substances available.[14]
But even in hospitals, around 30 % of antibiotics prescribed are unnecessary, or the drugs are used for too long or incorrectly, experts say.[13] For example, the prophylactic administration of antibiotics during operations could often be shorter, and stricter adherence to treatment guidelines would significantly reduce consumption in hospitals. In addition, the majority of prescriptions are made without determining the pathogen in the laboratory. Treatment is therefore not targeted. This often happens in smaller institutions in particular because microbiological laboratories are lacking.[15]

Dreaded hospital germs

The medical treatment itself can also cause dangerous infections: pneumonia, wound and urinary tract infections, diarrhea or blood poisoning are some of the most common conditions that patients acquire in hospitals.[16] They are also called nosocomial infections. There are many reasons for this: some patients need, for example, urinary catheters, feeding tubes or artificial respiration. All these are entry routes through which pathogens can enter the body. They often colonize the human skin or intestines before they cause an infection. Hygiene deficiencies, especially hand hygiene, play an important role in the spread of the pathogens.
The burden of disease caused by nosocomial infections in Germany is slightly above the European average: According to RKI estimates, there are 400,000 to 600,000 infections and approximately 10,000 to 20,000 deaths every year.[16] Some of these infections are caused by pathogens that are resistant to antibiotics.
A worldwide dreaded pathogen of nosocomial infections is the methicillin-resistant Staphylococcus (S.) aureus (MRSA). Due to its multi-resistance it is difficult to treat. The pathogen colonizes the skin and mucous membrane of healthy people, especially the nasal mucous membrane. From here it spreads further to the throat, the intestines and the hands. In immunocompromised people it can cause severe wound infections, pneumonia or sepsis. But MRSA isn't only causing problems in hospitals. It is just as common in old people's homes and nursing homes. This is the result of a study in North Rhine-Westphalian institutions.[17] Residents with a urinary catheter had a three times higher risk of acquiring MRSA than the other residents.

What is a defined daily dose?

The defined daily dose (DDD) is a statistical value. The World Health Organization (WHO) has introduced this value in order to be able to compare consumption values regionally and internationally. DDD refers to the assumed average daily intake dose for the main indication of a drug in adults. The dose actually prescribed by the physician may differ.

"Antibiotic prescriptions take place in a social context. The power of experience and habits plays a role there, but also presumed expectations and time pressure."

Dr. Roland Tillmann, AnTiB [6]

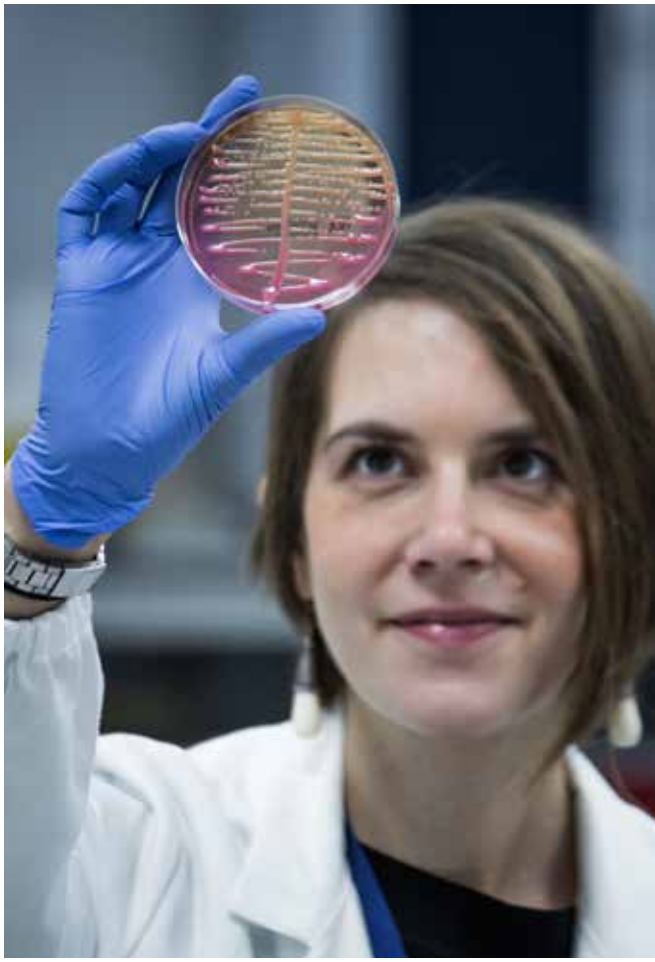
Cause for concern: rising resistance rates

The development of the resistance situation in Germany over the last four years (2015-2018) shows opposing trends:[18] in Enterococci (Enterococcus faecium), resistance to the reserve antibiotic vancomycin has increased sharply and is a cause for concern. The VRE rate in Germany has more than doubled to 23.8 % and is now above the European average, which is also rising significantly.

In the case of methicillin-resistant Staphylococcus aureus (MRSA), on the other hand, the development is declining, and there is also a slight decrease in resistance in the hospital germ Pseudomonas aeruginosa.

The resistance situation of enterobacteria is largely stable with two exceptions: In E. coli, resistance to third-generation cephalosporins is increasing significantly, in Klebsiella pneumoniae resistance to fluoroquinolones. Resistance rates to these gram-negative pathogens are also increasing throughout Europe.

Resistances against carbapenems are rather rare in Germany. These antibiotics are considered to be the last resort when nothing else helps. They are below 0.1 % for the pathogen E. coli and 0.4 % for K. pneumoniae. In particular, carbapenem resistance varies greatly in comparison with other European countries. In some southern European countries the values are above 20 %. It is very clear that national consumption of antibiotics is closely linked to the spread of resistance. In countries with high consumption – such as in southern Europe – resistance also occurs at a significantly higher level.[2]



Resistance to K. pneumoniae and E. coli is increasing throughout Europe. Photo: CC Chiara Marraccini

Resistant pathogens in the luggage

Travels abroad play a major role in the acquisition and spread of resistant germs. Several studies have shown that up to 30 % of travel returnees from Asia are colonized with ESBL-forming E. coli.[19] And increasing medical tourism is also creating problems: patients who seek treatment abroad to save costs or avoid waiting times are carrying resistant germs from country to country. Every year, slightly more than 20 million patients travel abroad for treatment. Germany – just like Switzerland, Turkey, Thailand or Singapore – actively solicits solvent customers. Many citizens from EU countries, the Commonwealth of Independent States and Arab countries seek treatment in Germany. Conversely, medical tourism is also becoming increasingly popular among Germans: 55 % can imagine taking advantage medical treatment abroad.[20]

Resistant pathogens also travel with tourists from country to country. Photo: © iStock

Resistance concerns us all!

Resistance is not only a problem for doctors, but for all of us. We are all jointly responsible for ensuring that the effectiveness of antibiotics is maintained. Hygiene plays just as important a role here as the responsible use of medicines. But communication between

doctors and patients is also crucial. Especially in the outpatient sector, for example, the expectations of patients play an important role and lead to prescription pressure. There is often a double misunderstanding: the doctor thinks that the patient expects an antibiotic and the patient thinks that the doctor wants to prescribe an antibiotic. In the end, the patient gets an antibiotic, although it is not what either of them wanted.[13] It is, therefore, all the more important that doctors communicate the prescription or abstention from antibiotics well.

This is where the project AnTiB (antibiotic therapy in Bielefeld) comes in. Doctors in Bielefeld are working together at local level to develop practical and widely accepted rules for prescribing antibiotics. With the uniform prescription practice, communication strategies were established as to when and how antibiotics are prescribed. This reduces conflicts with patients and between colleagues.[21]

Drinking a lot helps with urinary tract infections.
Photo: CC Shuichi Kodama

Involving patients

It is important to involve patients in the therapy decision. A study showed that the involvement of patients in the decision to take antibiotics has a positive effect. In comparable disease courses, the intake of antibiotics was reduced by almost half.

Urinary tract infections are one of the most common bacterial infections in the outpatient sector, and also one of the most common reasons for prescribing antibiotics. Women are particularly affected. They have the constant feeling of "having to go" even though the bladder is empty, and urination can be extremely painful. In one in four patients, the disease returns every few months. This usually means frequent antibiotic therapy.

However, especially in the case of urinary tract infections, the careful use of antibiotics is necessary. The main pathogen E. coli is becoming increasingly resistant to reserve antibiotics such as fluoroquinolones and cephalosporins. The treatment guidelines now recommend avoiding reserve antibiotics and using older antibiotics. In the case of uncomplicated urinary tract infections, however, it is often possible to avoid them. Studies show that the inflammation subsides on its own after a week in almost half of those affected. Treating the symptoms with the painkiller ibuprofen can be enough in most cases.[22] Even drinking a lot of fluid can give sufferers a good chance of flushing the bacteria out of the bladder.

Although antibiotic therapy can help well, it can also destroy the useful bacteria that protect us from infections. "Antibiotics can weaken our immune defenses in the long term, because they affect the intestinal bacteria. 80 % of all the body's defense cells are located in the intestinal mucosa and the intestinal bacteria train them," explains Dr. Eckhard Schreiber-Weber.[23] Patients should bear this in mind every time they take an antibiotic.

A particularly large quantity of antibiotics is used in chicken fattening. Photo: CC Shpernik088

MAKE ROOM!

99 % of all German chickens come from fattening facilities with over 10,000 animals. More and more animals in less and less space – the use of antibiotics can hardly be further reduced under such husbandry conditions, say veterinarians. Structural changes would be necessary. But the prospects for this are gloomy: farmers are railing against government policy, consumer protectionists against farmers, medical doctors are pointing the finger at veterinarians and vice versa. What is needed is joint action for the welfare of humans, animals and the environment.

In 2017, 82 milligrams of antibiotics were needed in Germany to produce one kilogram of meat – twice as much as in Denmark, Great Britain or Austria.[24] At the same time, consumption has already been significantly reduced over the past decade: in 2017, 733 tonnes of antibiotics were given to veterinarians, about half as much as in 2011, which is roughly the same amount as is used in human medicine. However, the pure quantities delivered in tonnages are not very meaningful. This is because the reduction in consumption is due not least to the more frequent use of reserve antibiotics, which are more potent and administered in lower doses: The reduction in tonnage was particularly marked in the case of tetracyclines, penicillins, macrolides and sulphonamides. In contrast, consumption of fluoroquinolones increased by 20 %. Although the reserve drug colistin, which is important in human medicine, is used in significantly lower quantities today than in 2011, consumption is also rising slightly again. In 2017, four tonnes more were consumed than in the previous year. [4]

"Animal factories need antibiotics to compensate for the lack of housing, breeding, management and hygiene."

Dr. Claudia Preuß-Ueberschär, Doctor for responsible agriculture [23]

Who collects data on consumption?

The Federal Office of Consumer Protection and Food Safety (BVL) monitors the quantities of active ingredients used in animals. Pharmaceutical companies and wholesalers must report every six months how many and which antibiotics they sell to veterinarians. The BVL also reports these data to the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) at the European Medicines Agency (EMA).[10] In addition, large fattening farms report their consumption of antibiotics to the competent state authorities.

Large fattening farms are subject to reporting requirements

Since 2014, larger farms with more than 20 fattening cattle, 250 fattening pigs, 1,000 fattening turkeys or 10,000 broilers have been obliged to report their antibiotic consumption and the number of treatments to the competent state authorities. The frequency of treatment for each fattening animal species in each farm is calculated on the basis of this information for each calendar half-year. The data are recorded and evaluated nationwide. The authorities can order more precise checks and countermeasures in the event of above-average use of antibiotics.

Nationwide data from companies show:[4] from 2014 to 2017, consumption decreased, especially for fattening pigs. The rather low consumption of antibiotics has also fallen sharply again for fattening cattle. For calves, chickens and turkeys for fattening, however, it remained almost constant. In addition, the proportion of critical drug classes was particularly high in chickens and turkeys for fattening. In poultry, such drugs accounted for around 40 % of the consumption volume, while in all other types of use it was less than 10 %. The German Federal Ministry of Food and Agriculture (BMEL) suspects that so-called polypeptide antibiotics such as colistin, are dosed much higher in broilers than required by the approval conditions.[4] The European Medicines Agency (EMA) had already recommended in 2016 to significantly minimize the use of this important reserve antibiotic in livestock farming: to half of what is currently consumed in Germany.[25]

Farm idyll was yesterday. Fewer and fewer farms are keeping more and more animals in Germany. Photo: CC Dietmar Rabich

More and more animals in less space

The influence of farm size is clearly visible for all animal species: antibiotics are used much more frequently on large farms than on small and medium-sized farms. But the trend is towards large fattening farms. Whether cattle, pigs or poultry – more and more animals are kept in less and less space. Between 1999 and 2016, for example, the number of farms with chicken fattening decreased by 72 %. However, the total number of animals increased, and the stables became considerably larger. The share of fattening facilities with more than 50,000 animals has increased approximately eightfold.[26] In 2016, every farm had an average of 28,000 animals. In the new federal states the herds were a good three times as large as in the old ones. Lower Saxony had the highest average stock in the west with 59,000 broilers; the leader in the east was Saxony-Anhalt with 143,000 animals.

Particularly the intensive fattening of chickens and turkeys cannot do without regular antibiotics. The whole flock is treated with the feed or drinking water in case of diseases.

Even feed mixtures sometimes contain antibiotics. Such additives have been banned in the EU since 2006. However, certain antibiotics, which are mainly added to chicken feed, are an exception.[27]

They are used in fattening poultry to prevent blackhead disease or coccidia. These are parasites that can infect the gastrointestinal tract of poultry or ruminants and cause diarrhea. However, it is completely unknown how many antibiotics end up in feed mixtures. This is because the quantities of active substances delivered to feed mills are not recorded in this country. The BVL estimates that the quantity is insignificant. However, data from the European Medicines Agency (EMA) give cause for concern: in 2016, preparations used as feed additives accounted for around 40 % of total sales of antimicrobial substances.[28] Additions of copper and zinc are also problematic. These heavy metals play a major role in the development and spread of resistant germs.

Intensive fattening cannot manage without antibiotics

Several years ago, the State Office for Nature, Environment and Consumer Protection of NRW (LANUV) investigated the use of antibiotics in North Rhine-Westphalian turkey houses and found that in nine out of ten fattening runs (92.8 %), the animals were administered an antibiotic. On average, a turkey received an antibiotic on 20 of 100 fattening days. In the most frequently used and very heavy Big 6 breed, the therapy density was particularly high. Reserve antibiotics were regularly used. In one third of the cases investigated, a preparation was also used which is not even approved for use in turkeys in Germany. Only in individual cases, when no other therapy is possible, may veterinarians prescribe such a medication.[29]

Poultry meat heavily contaminated

"The high resistance rates of isolates from the food chains broiler chicken and turkey for fattening correspond to the high therapy frequencies determined for these types of use," the BMEL concludes in its evaluation report.[4] A high proportion of E. coli and Campylobacter spp. isolates from poultry meat is resistant to at least one active substance. Colistin resistance in broilers or the increase in fluoroquinolone-resistant E. coli pathogens in turkeys is striking.[30] The organization Germanwatch wanted to know what the poultry meat from German supermarkets was like and had test purchases laboratory-tested. The result: every second meat sample from the shelves of Lidl, Netto, Real, Aldi and Penny was contaminated with resistant germs. Every third sample contained bacteria that were resistant to important reserve antibiotics. 20 % of the samples even showed resistance to three different classes of antibiotics.[28]

At best, laying hens still run on the green field today. Broilers are being crammed in by the thousands. Photo: CC Ikarus Busenbach

Every German consumes around 6 kg of turkey meat on average per year. A large part of this is produced in North Rhine-Westphalia and Lower Saxony. Over half of all large farms with more than 10,000 animals are located in these two federal states. Photo: CC USMC

Who collects the resistance data?

Two surveillance programs are in place at national level for pathogens present in animals and in meat. In the case of representative samples, the state authorities collect bacterial pathogens and forward them to the Federal Institute for Risk Assessment (BfR). The BfR tests the isolates for antibiotic resistance, publishes the results, and also reports them to the European Food Safety Authority (EFSA).[31]
Nationwide, the Federal Office of Consumer Protection and Food Safety (BVL) also continuously takes random samples from the food chain and tests them for resistance as part of the GERM-Vet [32] *program. The isolated animal-pathogenic bacteria are tested for their sensitivity to 24 antibacterial substances. The resistance data are evaluated separately according to animal species and pathogen.*[9]

Resistant pathogens can be transmitted by close contact between humans and animals. This is well documented for MRSA. Photo CC Izvora

Transmission to humans

Resistant bacteria or their resistance genes can be transferred from animals to humans.[33] This is well documented for MRSA, for example. A special strain of the pathogen, which occurs in conventionally kept fattening animals, very often colonizes people who have close contact with the animals – for example farmers or butchers. In regions with a high density of fattening facilities, this germ is widespread among the population.[34]
People can also ingest resistant pathogens through raw meat. Special care and hygiene is therefore required in the kitchen. This is because microorganisms can, for example, pass from meat to other foods when they come into contact with each other. Indirect transmission via hands, work surfaces, knives or other kitchen utensils is also possible.[35]

Cheap poultry meat from Europe is also exported to Africa. There it competes with the domestic producers. Photo: © iStock

Exports to Asia and Africa

Meat exports from Germany also contribute to the worldwide spread of the resistant germs. They go to neighboring EU countries, but also to Asia or Africa. In the case of pork, for example, East Asian countries play a special role because pig ears, tails and feet are delivered there which are not used in Germany.[36] After pork, poultry is the most commonly produced meat in Germany. In particular, frozen chicken parts go to various African countries. However, German exports to South Africa have collapsed due to the poultry flu and the associated export bans.[37] In 2016 around 17,000 tonnes were exported to Africa.

With the liquid manure, antibiotic residues get onto the fields and into the soil. Photo:© iStock

TRACKED DOWN

In principle, resistant bacteria in the environment can also be dangerous to humans and animals. They can pass on their resistance genes to pathogens that cause diseases in humans or animals. In this way they contribute to antibiotics losing their effectiveness. It is still difficult to estimate the actual risk of contaminated soil and water.[34]

Liquid manure from agriculture, fermentation residues from biogas plants and sewage sludge play a special role in the spread of antibiotic resistance in the environment. On the one hand, they contain high concentrations of antibiotics because the drugs are only partially metabolized in the body of humans and animals. Depending on the antibiotic, 10 to 90 % of the active ingredient is excreted again. On the other hand, many resistant bacteria are found in the excretions of animals and humans treated with antibiotics.[34] So far, there is no comprehensive monitoring of antibiotic residues or resistant germs in the environment in Germany. In 2015, however, the BMBF launched the HyReKA research project.[6] The investigations should show how high the exposure is, where the greatest problems lie and how great the danger for humans is.
The Federal Environment Agency also carried out two research projects in regions with intensive livestock farming. Antibiotics were found in groundwater at 9 of 38 monitoring sites in northwest Germany. The inputs with high antibiotic concentrations came from animal husbandry or from nearby small sewage treatment plants.[38]

Loaded with resistant germs? Creek in Münsterland. Photo: CC Dietmar Rabich

Most wastewater treatment plants cannot eliminate antibiotic residues and resistant germs. This would require a fourth purification stage. 13 wastewater treatment plants in Baden-Württemberg are now equipped with this. The additional costs for the improved wastewater treatment are borne by the population. Photo: © iStock

Better technology is expensive

Antibiotics and germs get into the wastewater and sewage treatment plants via fattening facilities, slaughterhouses, clinics or nursing homes. From there they make their way into rivers and lakes. This is because conventional treatment technology is not sufficient to filter out resistant germs or antibiotics. The mechanical and biological purification stages only reduce antibiotic concentrations by about 30 %. Even resistant germs are not sufficiently reduced. New processes do exist and are also in operation sporadically, but the technical effort is expensive.[39]

In 2018, the State Office for Nature, Environment and Consumer Protection (LANUV) examined ten bathing waters in North Rhine-Westphalia for antibiotic-resistant bacteria and antibiotic residues. Of the samples taken, only two showed resistant bacteria. "However, the quantities found were so low that healthy people were not exposed to any danger."[41]

BUND, however, sees a clear need for action. The nature conservation organization also searched for resistant germs in rivers and lakes in NRW – and found them. Particularly noticeable is the pollution behind sewage treatment plants with affiliated hospitals.[42] BUND demands clear legal requirements, better control and an expansion of wastewater treatment.[43]

Calling polluters to account

In order to reduce the risky freight of pathogens and drugs, the polluters would also have to be made more accountable: hospitals, fattening farms or slaughterhouses must take measures to reduce the load in their wastewater. On the other hand, decentralized treatment of wastewater before it is discharged into the public sewerage system would be useful here.[44]

An accident with serious consequences

In 2017 a man in Frankfurt am Main had fallen into a stream and almost drowned. Shortly afterwards he died in hospital as a result of the accident. In addition to water and leaves, the hospital doctors found extremely dangerous germs in his lungs, against which almost no antibiotics were effective. The super germs also spread in the intensive care unit of the hospital. They had probably been introduced by this patient because the stream in which the man had almost drowned was teeming with multi-resistant bacteria. Martin Exner, Director of the Institute of Hygiene at the University Hospital in Bonn, who investigated the case, believes it is absolutely necessary to further investigate the spread of multiresistant bacteria in the environment.[40]

Here in lake Elfrath and also in the lake Baldeney the LANUV made a find: resistant E. coli pathogens were found in both lakes.
Photo: CC Magnus Manske

Polluted soils

However, not only water bodies, but also arable soils are now sometimes heavily contaminated with resistant germs and their genes. When comparing today's soils with archived soil samples from the 1940s, an increase of more than 15 times was found for individual resistance genes. Such developments ultimately also have an impact on human medicine: they can, for example, weaken the effectiveness of important reserve antibiotics. For carbapenems and colistin, two active substances of particular importance in human medicine, the spread of resistance and its origin from environmental bacteria is well documented: The resistance gene has been detected in hospital effluents. Bacteria that are primarily found in the environment exchange resistance genes with the pathogens from hospitals. And samples from soil bacteria also showed resistance genes of human pathogenic bacteria.[34]

Heavy metals also promote resistance

Pesticides such as zinc or copper are also problematic. They can create a strong selection pressure on bacteria and accelerate the development of resistant germs. Liquid manure should therefore not be applied to soils that have been treated with heavy metals – especially if the land is intended for growing lettuce and fresh vegetables.

Biocides such as zinc and copper are used in conventional agriculture and to a lesser extent on organic farms – for example in fruit growing.[34] Because of their antimicrobial effect they are also added to the feed for pigs and turkeys. Although the consumption of antibiotics can be reduced by such practices, this does not help to prevent resistance.

Even fresh vegetables can be contaminated with resistant germs. Photo: CC Gerhard Giebener

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Intensive agriculture in southern Rajasthan.
Photo: CC Iamg

HOTSPOT INDIA

India is one of the countries with the highest resistance rates worldwide. In human medicine, resistant pathogens cause deadly infections in newborns or make the treatment of tuberculosis and cholera more difficult. Animal fattening and fish farming use large amounts of antibiotics in a largely uncontrolled manner, and food is highly contaminated with resistant germs. The environment is also at risk: international pharmaceutical manufacturers who have their antibiotics produced cheaply in India are to blame.

A farmer carries his harvest on a bike.
Photo: © Gopal Dabade

The thoughtless use of antibiotics in humans and animals, but also the improper treatment and disposal of wastewater, fuel the resistance problem in India. Sewage sludge used to fertilize the fields or illegally dumped waste from the meat and fish industry probably also contribute to the development of resistance – data on this is still unavailable.
But effective action requires a good data basis. And it is precisely here that there is still an urgent need to catch up, especially with regard to resistant germs in veterinary medicine and in the environment: of the 2,152 studies on resistance carried out by Indian institutions, almost half dealt with human health. 3% of the studies looked at animal health and 4% at the environment. The rest concerned new therapies, diagnostics and other issues.[2]

"The problem of microbial resistance is probably more threatening in India than in any other country in the world. Many antibiotics that worked well 5-10 years ago are almost ineffective today." [1]

Ramanan Laxminarayan, director des Centre for Disease Dynamics, Economy and Policy, New Delhi.

National plan of action

The Indian government has made great efforts to combat antimicrobial resistance (ABR) with its National Action Plan. However, it is still in its infancy here. India's National Health Policy of 2017 aims at a rapid standardization of guidelines for the use of antibiotics. It aims to curb the over-the-counter sale of the drugs and their use as fattening accelerators, and to promote the safe use of antibiotics.[2] A national network for resistance monitoring has existed for several years. In 2017, 21 laboratories reported data from 55 major hospitals to the WHO's GLASS database, which is trying to record resistance worldwide.[3]

In 2018 there were 130,000 new cases of multi-drug-resistant tuberculosis in India. Photo: Flickr

"WE'RE IN TROUBLE"

The diagnosis and treatment of resistant germs pose a huge challenge to the Indian health care system. The burden of infectious diseases is high and there are many gaps in the healthcare system – including laboratory technology for determining the germs. Old scourges such as tuberculosis and cholera are far from being conquered and now show high resistance rates. At the same time, new super germs are causing problems for doctors and patients alike.

Babies are particularly susceptible to infections. Photo: Santhoshwideangles

In 2018, for example, more than two and a half million Indians fell ill with tuberculosis. According to WHO estimates, a quarter of all TB patients do not receive any therapy, and only 80 % of those treated are cured.[5] Resistant pathogens are a frightening scenario against this background alone. They make the treatment more complicated, have more side effects, extend the duration of treatment from six months to up to two years, cause extreme costs, and significantly reduce the chances of cure.[6] In 2018 there were 130,000 new cases of MDR-TB in India according to the WHO.

Resistance in pneumonia, typhoid and cholera

In Indian hospitals, Gram-negative bacteria show high resistance rates with growing insensitivity to broad-spectrum antibiotics and also to important reserve antibiotics.[7] According to official data, more than 70% of isolates of E. coli bacteria are insensitive to broad-spectrum antibiotics such as third-generation fluoroquinols and cephalosporins. The same applies to the hospital germs Klebsiella pneumoniae and Ancinetobacter baumanii, both a common cause of hospital-acquired pneumonia and other infections. Half of all isolates of the Pseudomonas aeruginosa pathogen – another im-

portant hospital germ – were also resistant to the broad-spectrum antibiotics. Various resistance genes are increasingly rendering the hospital germs insensitive. Gram-negative bacteria also proved to be highly insensitive to active substances from the carbapenemes group – an indispensable last reserve for treating serious bacterial infections. A. baumannii bacteria showed the highest resistance rates with around 70 %, followed by K. pneumoniae (56.6 %).[8] Resistance to the important reserve antibiotic colistin is also a cause for concern. Many hospital patients die for lack of other treatment options. Blood poisoning caused by hospital-acquired pneumonia is fatal in 70 % of cases because colistin and carbapenems are no longer effective.[8] Bacterial pathogens of dysentery, salmonella or cholera are also increasingly developing resistance to standard therapies. Resistance rates of 28 % and 82 % respectively have been found for Salmonella Typhi and Shigella species. For cholera pathogens, resistance rates ranged from 17 to 75 % in different parts of the country.

MRSA widely spread

In Gram-positive bacteria, MRSA, the multi-resistant Staphylococcus aureus germ, but also resistant pneumococcus germs cause problems.[8,2] MRSA is often acquired in India on an outpatient basis or in the home, and is widespread in the general population. Studies found an incidence rate of 10 %.[9] It is increasingly observed that the germ is also invasive and contagious outside the hospital. It can cause skin and wound infections, but also life-threatening infections such as septic shock and severe forms of pneumonia.[10]

Newborns die from sepsis

For some years now, infant mortality due to resistant germs has been the focus of public attention in India. It is estimated that 58,000 newborns die of resistant infections there every year.[14] Because their immune system is not yet developed, they are particularly susceptible to infections. Once the infection enters the bloodstream, it causes a dangerous inflammatory reaction. In South Asia, such cases of neonatal sepsis are very common and 4 to 10 times more frequent than in rich countries. The main reason for this is a lack of hygiene during delivery in the delivery room, during Caesarean sections or in the infant wards.[15]

However, especially in the case of early sepsis, the infection may also have been transmitted from mother to child. Most infections in India occur within the first 72 hours after birth. Sepsis is often triggered by Klebsiella pneumoniae or E. coli bacteria, but also by Staphylococcus aureus germs. They all show high resistance rates.[16],[17] "In most major hospitals where babies are treated for sepsis, standard antibiotics are no longer effective," said Suman

Unlimited mobility: a super germ from India conquers the world [11,12]

In 2009, a 59-year-old Swede of Indian descent visited a hospital near Stockholm. The patient was diabetic and needed treatment for pressure sores and a urinary tract infection. He had just returned from India, where he had also been treated in a hospital – for an abscess on his buttocks. He was operated in the Indian hospital and then returned to Sweden.

The abscess was not unusual – they often occur in diabetics. The patient had probably contracted the pressure ulcers and the urinary tract infection in the hospital in Delhi. But there was something strange about this pathogen: no antibiotic seemed to work. Not even an antibiotic from the group of carbapenems, the most effective drugs.

A urine test showed something very unusual: the bacterium that had caused the infection was indeed related to Klebsiella pneumonia, a hospital pathogen that often causes pneumonia and blood poisoning. However, it had a gene that was previously unknown. This made it insensitive to almost all antibiotics.

The discovered gene was named NDM-1 (New Delhi Metallo-beta-lactamase-1) after the city where the patient probably caught the super germ. It turned out that it not only defies common therapies. It can also spread very quickly and effectively by jumping from one bacterium to another, thereby rapidly increasing the resistance of the infection.[13]

Within a year, NDM-1 spread worldwide. The resistance gene was found in patients in the USA, UK, Canada, Japan and China. It has now been discovered in 75 countries. Some of the patients had been in India and had been treated there, but many had never been there. So the gene is spreading further within the affected countries.

Doctors are concerned. The number of resistant infections is particularly high in India. Photo: CC DFID

58,000 newborns in India die of resistant infections every year. Photo: © M. Davies, Bureau of investigative Journalism

Chaurasia, pediatrician and sepsis researcher at the All India Institute of Medical Sciences, a leading state university hospital in Delhi.[1] He and his colleagues examined 13,530 newborns at three state hospitals in Delhi from July 2011 to February 2014. 15 % of the babies suffered from sepsis – the disease was responsible for a quarter of all deaths in newborns.[18]

50-88 % of the isolates causing sepsis showed resistance to standard antibiotics in the study. One of the pathogens was Acinetobacter, a bacterium with widespread distribution in soil and surface water as well as in drinking and waste water. It had a resistance rate of 82 %. Two thirds of the babies infected with the germ died.

Bleak outlook

One reason for the poor chances of survival is the lengthy diagnosis. "As soon as the babies show signs of sepsis, we have to treat them, otherwise we lose them," says Indian pediatrician Dr. Achut. "But we only get the laboratory results of blood and urine tests after three to four days. So we have no choice but to rely on our experience when choosing antibiotic therapy."[19] Better diagnostic facilities and rapid tests at all levels of healthcare would therefore be extremely important.

"We are in a tight spot and the outlook is bleak," sums up Dr. Chaurasia. This is, he says, because even reserve antibiotics are increasingly losing their effect. In adults with sepsis, it was possible to switch to older drugs or combinations that were originally intended for other indications. However, there was too little data on how these drugs work in the body of newborns. "Our biggest concern is what drugs we have left. How will we treat babies in the future if drugs like Colistin are taken out of our hands?"

Poverty fuels the resistance problem

Factors such as poverty, lack of education, cramped housing conditions and malnutrition further fuel the resistance problem. They encourage the spread of infectious diseases and also the misuse of antibiotics. The consumption of antibiotics in human medicine has more than doubled between 2010 and 2015. Self-medication or the prescription of antibiotics by healers or informal doctors – especially in rural India – are the order of the day. Self-proclaimed doctors offer their services at low cost, and are often the only chance for poor people to receive medical care.[20] An evaluation of more than 15,000 prescriptions from such practices showed that 95 % of antibiotics prescribed were broad-spectrum antibiotics; frequent indications were dental problems, fever and respiratory diseases.[21] However, even trained physicians too often prescribe reserve antibiotics – also because there is a lack of suitable diagnostics and laboratory technology to determine the pathogen and its sensitivity. In hospitals, in turn, there is a lack of guidelines for the effective

Antibiotics are often available in pharmacies without a prescription. Photo: Flowcomm

prevention and control of resistant germs. Important essential antibiotics are sometimes not available in hospital pharmacies, while others are easily available without a prescription.[22] The problems are complex, as our partner Rahul Meesaraganda points out: „The huge profit margins in the sales of antibiotics and the lack of regulation and accountability here is a perfect mix for bacteria to evolve and beat the existing antibiotics."[23]

India's National Action Plan on antimicrobial resistance is certainly addressing these problems. It aims to raise awareness of antibiotic resistance, improve resistance monitoring and data collection, reduce infection rates, and promote sustainable use of antibiotics. However, implementation of this huge project is progressing only slowly – partly because there is a lack of solid funding, and meaningful new initiatives and projects have to take a back seat to other pressing tasks.[24]

When you consider that there are five times the number of rural medical practitioners in India as there are trained medical doctors, it should come as no surprise that the majority of antibiotics reach patients through this channel. (...) There is a need to balance access to antibiotics, which these practitioners provide, and also prevent overuse and inappropriate use and therein lies the challenge."[4]

Prof. Ramanan Laxminarayan, Director Centre for Disease Dynamics, Economics and Policy (CDDEP)

Poultry production in India is growing rapidly .Photo: © Gopal Dabade

ANTIBIOTICS IN MEAT AND FISH

Industrial methods of animal husbandry and fattening and intensive aquafarming have exploded the consumption of antibiotics in Indian agriculture. The weak regulation of the market endangers not only animal welfare but also food safety. But the available data are sparse.

India is the largest producer of milk in the world and the second largest producer of fish after China. The country ranks fifth in meat production.[2] Poultry production, in particular, is experiencing enormous growth due to rapidly increasing consumption in the domestic market. Exports go mainly to the Arab Emirates and to Southeast Asian countries.

„They are using the antibiotics as a substitut to just keep the chicken alive. And the reason people do that now is because antibiotics are very cheep." [25]

Prof. Ramanan Laxminarayan, Director Centre for Disease Dynamics, Economics and Policy (CDDEP)

The meat companies deliver the chicks to the farmers and buy the slaughter-ready animals from them 40 days later. Photo: © Gopal Dabade

15 cents for a chicken

Large industrial enterprises have emerged – with cost-effective, automated husbandry techniques, air-conditioned stables and a high stocking density.[26] Breeds suitable for fast fattening have displaced native poultry species. Chicken fattening – a private affair in the backyard just a few decades ago – has developed into a profitable industry. But so far this market is only weakly regulated. For example, there are no regulations on stocking density and husbandry conditions, as criticised by the Indian Law Commission.[26]
Poultry fattening is not only a matter for large industrial enterprises. Many farmers who grow sugar cane or rice as their main occupation use poultry production to generate additional income. Large meat producers usually deliver the day-old chicks and buy the slaughter-ready birds from the farmers 40 days later. For a two-kilo bird, the farmer receives 12 rupees, the equivalent of 15 cents. The companies provide the necessary feed and medicines. "All we have to do is provide light, water and a barn," explains a chicken farmer in an interview with our Indian partner.[27]

Depending on the meat industry

Most farmers know very little about the drugs supplied and rely entirely on the recommendations of the companies.[28] Information material in the local language is not available. In the state of Karnataka, the state government is trying to remedy this situation. It offers free training in chicken farming to break the dependence of farmers on the large meat producers and to preserve traditional poultry breeds.

The meat producers regularly visit the animal owners and send the company's own veterinarian if necessary. However, the diagnostic possibilities of the veterinarians are very limited. A veterinarian from Kwality Company, which also supplies snack chains such as McDonald's and KFC, told our Indian partner that the only thing available to him are scissors to examine animals post mortem.[29] His company has not used antibiotics for two and a half years, the veterinarian initially emphasized. However, after persistent drilling, he admitted that his company does use antibiotics when animal populations are infected with salmonellosis, poultry cholera or E. coli pathogens. Just as in Germany, broad-spectrum antibiotics such as enrofloxacin and ciprofloxacin are used in this case, which also play an important role in human medicine. Quality control or testing for resistant germs in meat does not take place, but is carried out by customers such as McDonald's, the veterinarian of the meat producer claimed.

Day labourer on a poultry farm.
Photo: © Gopal Dabade

Many small farmers operate poultry fattening as a sideline. Photo: © Gopal Dabade

Colistin prohibited as a veterinary medicine

There are as yet no binding and uniform regulations on the use of antibiotics in agriculture, nor are there any resistance monitoring or national data on consumption.[30] There are various guidelines that aim to reduce the consumption of antibiotics in Indian meat and fish production. However, their consistent implementation has so far failed because effective control measures are lacking and producers and veterinarians are not very aware of the problem.

As early as 2013, the government has instructed all federal states to provide comprehensive advice to veterinarians, feed manufacturers and all persons employed in animal husbandry on the correct use of antibiotics.[26] Since then, the labels of veterinary medicinal products must also indicate a withdrawal period that must be observed in order to prevent residues of the active substance in food. In 2015, the Food Safety and Standards Authority of India (FSSAI) issued guidelines to reduce the use of antibiotics in animal production, but they are still in the implementation phase.[26]

Since July 2019, India has banned the use of the important reserve antibiotic colistin in veterinary medicine – because of incalculable risks to human health. In the Indian fish and poultry industry, the drug was used up to recently on a massive scale and was freely

Chickens are cut up at a meat market in Calcutta. Photo: CC Kritzolina

Small farmer offers eggs from traditional breeds. The government of Karnataka tries to protect local poultry diversity. Photo: © Gopal Dabade

available for sale.[31] Now it can no longer be manufactured, sold or circulated as a veterinary medicinal product and is prohibited in all formulations for livestock, poultry, aquafarming and as an additive in animal feed. India is thus – at least on paper – one step ahead of the EU.

Pharmaceutical companies under criticism

The consumption of antibiotics in livestock, poultry and fish farming remains high and unregulated despite all efforts, Walia et al. conclude in the Indian Journal of Medical Research.[30] This is also confirmed by the research of our Indian partner: in the office of the Kwality veterinarian, for example, a veterinary drug was found that contained the antibiotics levofloxacin and colistin in addition to the cough medicine bromhexine. The veterinarian explained that he had received the now banned drug from a pharmaceutical sales rep.

It is not least the manufacturers of pharmaceuticals who contribute to the misuse and overuse of antibiotics with aggressive marketing. In October 2018, for example, the British Bureau of Investigative Journalism revealed that Zoetis, a former subsidiary of Pfizer and the world's largest supplier of veterinary medicines, was operating with double standards. While the pharmaceutical giant upheld the ban on reserve antibiotics in animal fattening in the US, it promoted and sold the drugs in India as growth promoters to Indian farmers.[32] In January 2019, the company responded to public criticism and discontinued this practice. However, this is unlikely to be the end of the problem. The use of antibiotics as fattening accelerators is particularly widespread in poultry.[30] Although the GOI intends to put an end to this practice, a general ban exists so far only in the second largest state, Maharastra.

Milk, meat and fish highly contaminated

Studies show that various bacteria that cause infections in chickens (Staphylococcus, Pasteurella multodica) are now 100 % resistant to some antibiotics. In pigs, isolates of the pathogen Pasteurella multocida showed a 70 % resistance to standard antibiotics.[33]

Various studies show that Indian food such as milk, meat or fish are also heavily contaminated with resistant germs. Investigations on poultry meat in various states revealed highly resistant E-coli and salmonella pathogens. An investigation in 18 poultry farms in the Indian state of Punjab also found highly resistant enterobacteria there – the resistance rate in fattening farms was more than twice as high as in farms with laying hens. And in the state of Kerala, shrimps, crustaceans and crabs from retail outlets were also tested and showed multidrug resistant cholera bacteria.[2]

Farmed shrimps for the EU

Shrimps are often produced in aquacultures and the high stocking densities make the animals susceptible to diseases. Antibiotics are therefore often administered prophylactically – e.g. chloramphenicol or nitrofuran, the use of which is prohibited in the European Union and many other countries. This is because even small amounts of residues can be dangerous to health. All exports to the EU would actually have to be tested for such substances in the laboratory before export. But the reality is different: since 2009, the EU Commission has had farmed shrimps from India tested for antibiotic residues. Because deliveries were repeatedly heavily contaminated, the inspection density was increased from 10 to 50 % in 2016.[33, 34]

While EU citizens are largely protected by tight import controls and (at least on paper) by existing standards of the goods produced for export, the domestic population is defenseless against the risks. "While we protect the health of our export customers, we are in no way concerned about domestic consumers," concludes the Indian environmental organization Centre for Science and Environment (CSE).[35]

Cow's milk in India is often contaminated with resistant germs. Photo: CC Adam Jones

Also landing on German plates: shrimps from India. Photo: CC Pawar Pooja

The Musi river in Hyderabad is highly contaminated with antibiotic residues and resistant germs. The reason for this are affluents from pharmaceutical production. Photo: CC Mohammed Mubashir

THE INVISIBLE DANGER

Large quantities of antibiotic substances are released into the environment through agricultural inputs or hospital effluents that are discharged untreated into nearby rivers. Domestic wastewater also contributes to the problem, as only around 20-30 % of municipal wastewater is treated in wastewater treatment plants.[2] Not least the boom in the Indian pharmaceutical industry is creating enormous problems: Wastewater from the production of antibiotics contaminates waters and rivers, and promotes the development of resistant germs.

Low and middle income countries with limited focus on waste management or those who produce more drugs and food from animals are likely to have a greater contribution from environmental routes to the rising AMR. These countries will also be impacted more as they are less prepared to tackle AMR and in particular the animal and environmental dimensions of it." [36]

Amit Khurana,Director of the Food Safety and Poisons Program, Centre for Science and Environment (CSE) in Neu Delhi, Indien

A study of waste water in sewage treatment plants in southern India showed particularly high resistance to E. coli bacteria for waste water originating only from hospitals: the resistance rate to third generation cephalosporins was 95 %. If the wastewater was mixed with domestic wastewater, the resistance rate of E. coli isolates was 70 %. For domestic waste water alone the resistance rate was 25 %.[2] Resistant germs have been detected in the major rivers of various federal states: in the two largest Indian rivers Ganges and Yamuna, for example, the resistance rate of Gram-negative bacteria was over 17%. Various resistance genes were also found in river water. In the South Indian river Cauvery, the E-coli bacteria found were 100 % resistant to third-generation cephalosporins. Resistant E. coli bacteria were also found in groundwater and in wells and springs used for drinking water supply.[2]

Antibiotics for the world market

Various studies in India have shown that antibiotic active ingredients are released into the environment with waste water from

the production of medicines. The situation is particularly bad in the vicinity of Hyderabad. The fourth largest city in India is considered a stronghold of the pharmaceutical industry with more than 30 factories. Systematic research initiated by the North German Broadcasting Corporation (NDR) showed that the water around the production facilities is contaminated with antibiotics and resistant germs.[37, 38] Along with China, India is the most important supplier country for antibiotic active ingredients.

However, there is no orderly sewage disposal system for the factories. After pre-treatment on the company premises, the sewage sludge is transported by truck to a municipal sewage treatment plant. From there the wastewater is piped into the city and mixed with domestic sewage before it flows into the river Musi.

Pharma production in Hyderabad. Photo: © NDR

Contaminated water

The research team took a total of 28 samples from sewers, streams, rivers and ponds in the area and also from drinking water. 16 of the 28 samples were also tested for drugs. Only two of them were negative (hotel water and ground water). In all other samples between two and nine antibiotics were detected. The highest number of active substances was found in the water of the river Musi. The reserve antibiotic moxifloxacin was detected in nine samples and the concentration was up to 5,500 times higher than the limit value considered to be harmless.

The high antibiotic load of the water massively promotes the development of resistance. It is therefore not surprising that resistant bacteria were found in 26 samples. Only two samples were uncontaminated – they came from the taps of a four-star hotel. In contrast, the drinking water samples from two settlements and the groundwater sample from a borehole were contaminated with multi-resistant pathogens. All 23 water samples from canals and water bodies also contained various resistant pathogens. Particularly problematic: resistance to carbapenems – antibiotics of the last reserve – was frequently found.

A research team is taking water samples.
Photo: © NDR

Contaminated soils

But industrial agriculture and fish farming also play a significant role in the increase in resistant germs. According to a study by the environmental organization CSE, the soil around chicken farms is heavily contaminated with antibiotic residues and resistant germs. Soil samples from the area surrounding the farms showed similar resistance patterns in E-coli bacteria as the litter of the stables. This is because the farmers use the manure to fertilize the fields.[39]

Especially in the states of Andhra Pradesh and West Bengal, the fish industry is responsible for a massive input of antibiotic substances. The substances are deposited in the sediments of rivers and water bodies, where they have half-lives of more than 10 months.[40]

A farmer in Punjab checks his grain.
Photo: CC Neil Palmer/Flickr

Polluted sewage sludge or manure is often used to fertilize the fields.
Photo: CC Phil Bus

True extent is unknown

Environmental factors probably account for a considerable proportion of the growing threat from resistant germs in India. However, the full extent of this is hardly known. The authors of a review paper published in the Indian Journal of Medical Research describe the topic as "neglected".[2]

Political action is needed to stop the further spread of resistance. And it is not only actors in India who are needed here. German and international companies also bear responsibility when it comes to environmental standards for suppliers from India. German politicians have also recognized this. For example, there are currently plans to introduce a supply chain law that would oblige larger companies to comply with human rights, social and environmental standards if they have their products produced abroad. In the case of pharmaceutical products, environmental standards should be regarded as part of good manufacturing practices and play a role as early as the approval stage. The European Medicines Agency (EMA) would be called upon here. Routine quality controls on site must not disregard environmental risks – especially if they cause considerable medical problems worldwide.

The Indian Ministry of Environment, Forestry and Climate Protection has already drawn conclusions: On 23.01.2020, it published a draft law that sets maximum levels for antibiotic agents in the wastewater of pharmaceutical factories. The new limits could soon apply to all pharmaceutical producers in India.[41]

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Hospital pharmacists not only have a key role in procuring and providing the right medicines. They also assist doctors in making difficult therapeutic decisions. Photo:© Health-e

SOUTH AFRICA: PIONEERING SPIRIT

There is still much work to be done. But the government's action plan introduced in 2014 is beginning to bear fruit. Especially in human medicine, there are promising approaches to improve the responsible use of antibiotics. Such interventions are crucial to reducing the resistance rate. And this is vital in a country where a million people live with HIV/AIDS and are at particularly high risk of contracting the disease.

"Patterns of usage of antibiotics have changed over the years. We started seeing an increasing antibiotic use, multiple antibiotics being used, for durations that were longer than what you would normally expect. And this culture of using antibiotics, or most using antibiotics now needed to stop."[1]

Azraa Cassim Paruk, Senior Pharmacist at Baragwanath Hospital in Soweto, Johannesburg

At the end of 2018, for the first time, the South African Department of Health presented a comprehensive report summarizing all data available to date on antibiotic use and resistance in humans and animals. This was a first step, but there was still a lot to be done, the ministry concluded: "(...) there are significant areas where additional data is needed to inform better policy and decision-making abilities in the future."[2]

15 studies for the entire continent

While scientific studies shed some light on the consumption of antibiotics and the problem of resistance in human medicine, the field of veterinary medicine remains largely in the dark. There is an even greater lack of data for the environmental sector. Only a few scientific studies have so far focused on water pollution caused by antibiotic agents. Ten substances have been detected in the environment – while only two of the nine South African provinces have been examined. For the entire African continent there are only 15 studies that have dealt with the environmental pollution caused by antibiotics.[3]

Ambitious plans

The South African Antimicrobial Resistance Strategy Framework came into force in 2014, and shall remain effective until 2024. The ambitious program follows an interdisciplinary approach and involves various ministries as well as laboratories, clinics, professional associations of human physicians, veterinarians or civil society organizations. Step by step, reporting systems are to be expanded and the monitoring of resistance improved. But investments are also to be made in research and disease prevention. Since 2016, South Africa has been feeding nationwide resistance data from the public and private health sector into the WHO GLASS database.[4] In addition, the government is planning to improve the legislation so that the consumption of antibiotics, e.g. in veterinary medicine, can be better monitored – there are still gaps in the regulation, many drugs are freely available for sale.[5]

Communication and teamwork play a crucial role in combating ABR. Photo:© Health-e

Communication and teamwork

The South African action plan attaches great importance to education, information and communication. In hospitals, for example, so-called Antimicrobial Stewardship (AMS) committees have been set up to ensure that antibiotics are used in accordance with the guidelines and to provide appropriate training and exchange in interdisciplinary teams.[6] Direct and problem-oriented communication between pharmacists, specialists and nursing staff is seen as a key element in achieving behavioral changes.[7,8] This approach is clearly successful, as a case study by our South African partner, Health-E, impressively demonstrates: the AMS committees are improving therapy and leading to a more rational choice of antibiotics. The coming years will show how this affects consumption and also the nationwide resistance rates.[9]

But that alone is not enough. Dr. Jeannette Wadula, professor of clinical microbiology and infectious diseases clarifies: “There is no way to talk about an effective Antibiotic Stewardship Program without talking about infection control and prevention. These two things are actually intertwined together.”[1]

Every year in South Africa, around 300,000 people contract tuberculosis. Photo:© Health-e

Blood cultures of TB patients show whether the standard therapy is effective or whether the pathogen is resistant. Photo:© Health-e

THE TRIPLE BURDEN

Around 5,500 tons of antibiotics are imported into South Africa every year. About three quarters of these are used in human medicine – per capita this is more than in most other countries.[2] Diseases such as HIV/AIDS and tuberculosis are widespread, which contributes to the high consumption. At the same time, the spread of resistant germs poses deadly dangers, especially for these patients.

"Most people feel that an antibiotic is there to make them feel better and they are not really aware of the consequences of using antibiotics inappropriately or using them when they shouldn´t be used at all. In a low-resource setting we tend to fall back on this because we have limited access to other forms of treatment. We feel that antibiotics are a safe measure and patients are recovering if we put them on antibiotics."

Dr. Denasha Reddy, internist, Chairman of the Antimicrobial Stewardship Committee, Baragwanath Hospital in Soweto, Johannesburg [1]

Although antibiotics are only available on prescription in South Africa, misuse, abuse and self-medication are common. Patients save unused antibiotics for later illnesses, exchange the drugs among themselves or do not take them as prescribed.[10] And the number of prescriptions is also high: a few years ago, a study by the Nelson Mandela University examined the prescription trends among 660,500 patients. They received over 1.5 million antibiotic prescriptions in one year. On average, this means more than two treatments per patient in twelve months.[11]

Public hospitals chronically overburdened

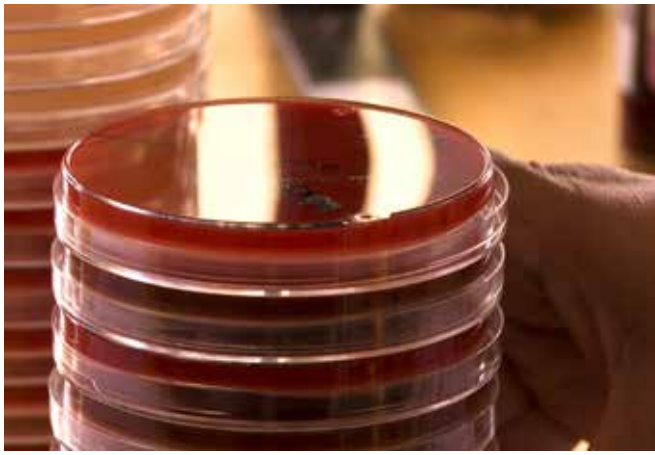
The health system in South Africa is divided into a public and a private sector. Private clinics, pharmacies and doctor's offices exist alongside state institutions. This two-tiered system of care makes data collection difficult, both for resistance and for antibiotic use. The majority of the population (84 %) is covered by the public health care system, while only a few are privately insured.

The drug orders of public and private hospitals are currently used as a basis to estimate the nationwide consumption of antibiotics. The available data are imprecise, however, and do not allow a clear statement on actual consumption.[12] This is because most antibiotics are not used in larger institutions or clinics, but in primary health care.[13] Here in particular, data collection is patchy, and the use of antibiotics is poorly documented.[10]

Patients with a cough often get antibiotics

However, a study by Witwatersrand University suggests that the number of prescriptions is high, particularly in basic care, and often does not meet treatment standards. Patients who went to a public institution and complained of a cold and cough were given an antibiotic in 78 % of cases, although this was not indicated. Private doctors prescribed antibiotics in 67 % of such cases. However, when patients emphasized that they would only take antibiotics when absolutely necessary, prescriptions fell by 20 % in both groups.[14]

Antibiotics are usually prescribed by doctors. However, in the field of HIV and TB therapy, nurses and other health care workers may also prescribe and dispense antibiotics. Pharmacists are also allowed to dispense antibiotics directly to patients in the area of primary care for a whole range of diseases.[12]



Germ diagnostics is crucial for chosing the right treatment. Photo:© Health-e

HIV stirs up consumption

In the public sector, Cotrimoxazole is the most commonly prescribed antibiotic drug – it accounts for half of the total amount of antibiotics used. The drug is used to treat a form of pneumonia that is very common in HIV patients. The high HIV infection rate in the country creates a huge need: almost one in five adults is infected with the HIV virus. South Africa has the world's largest HIV treatment program and for some years now an improved therapy has been strengthening the immune system of those infected. This is gradually reflected in a slightly decreasing consumption of Cotrimoxazole. The demand could therefore decrease in the coming years.[2]

In the public sector, antibiotics of the first and second line of treatment are mainly prescribed. A good 80 % of the antibiotics used are broad-spectrum penicillins. The rare prescription of antibiotics with a narrow spectrum of action is at least partly due to the supply difficulties of these preparations worldwide. The South African government has already taken measures to improve availability. As a result, the consumption of broad-spectrum antibiotics has been slightly reduced in recent years.[2] Nevertheless, shortages of essential drugs remain a challenge in the South African health care system and also affect the guideline-compliant antibiotic treatment.[15]

Most South Africans are cared for in the public system. Only 16 % have private insurance. Photo:© Health-e

Data on resistance

Data on resistance in human medicine is collected by the National Institute for Communicable Diseases and also fed into the WHO GLASS system. All major public hospitals and most private hospitals are connected to the national reporting system. The laboratory values thus provide a good overview of the current situation regarding resistant pathogens – at least as far as the situation in the

Germ diagnostics in a hospital laboratory.
Photo:© Health-e

inpatient sector is concerned:[2] Klebsiella pneumoniae is the most common problem germ in both the public and private sector. The rate of ESBL-producing bacteria has been around 70 % for years and makes cephalosporins ineffective in most cases. The pathogen is also increasingly resistant to the reserve antibiotic carbapenem. Currently the resistance rate is 8 %.[2]

Dangerous hospital germs

Reserve antibiotics (third-generation cephalosporins) are now ineffective in a quarter of the cases in E. coli, a pathogen that frequently causes urinary tract infections.

The situation has improved slightly in recent years for the hospital germs P. aeruginosa and A. baumannii. However, resistance rates remain high, and there are great differences between individual provinces.[2,16] A. baumannii, which is one of the most feared hospital germs worldwide, is over 80 % resistant to carbapenem, a reserve agent. In P. aeruginosa, these drugs are no longer effective in a quarter of the cases. Colistin, which is then used as a last option, is not registered in South Africa. It can only be used in hospitals with highly differentiated diagnostic and therapeutic options, and a special official permit is required for each individual treatment. Resistances are also reported time and again.[17]

In the case of the enterococci, E. faecium in particular is causing problems with resistance rates of over 90 % to the broad-spectrum antibiotic ampicillin. An additional concern is the increasing resistance to the reserve antibiotic vancomycin.

Streptococci, which can cause pneumonia, but also meningitis or inflammation of the middle ear, are often resistant to penicillin.

Former TB patient Bongekile: "I thought I was going to die." Photo: © Health-e

The burden of disease from bacterial pneumonia is particularly high in the province of KwaZulu-Natal and mortality is high – especially among young children.[3] HIV and TB are also particularly common in this region, and infection with resistant pathogens is a major problem.[18]

Faster and better treatment

Especially in the case of tuberculosis, the urgency of the resistance problem is evident. TB breaks out above all in people whose immune defenses are weakened – through malnutrition, poor living conditions or even AIDS. Due to the high HIV rate, there are also many TB patients in South Africa. And the resistance rate is among the highest in the world: of the 300,000 new TB cases that appeared in 2019, 11,000 were multi-resistant (MDR-TB).[19] The protracted and costly therapies required as a result not only place an enormous burden on the health system, but are also an immense burden for those affected and their families.

South Africa is still in a good position in a global comparison: Drugs of the second line of therapy have been available since 2001, and since then new strategies have been developed to improve the success of treatment. Instead of isolating patients in hospitals for months on end, they began to treat them at home wherever possible. In this way, many more patients could be cared for and they received treatment much more quickly. In addition, infections were prevented, because an early start of therapy reduces the risk of infection. But also the diagnostics were significantly improved by faster resistance testing.

The treatment of resistant TB is lengthy and has many side effects. Photo:© Health-e

"I thought I was going to die."

"When we first started (...) the treatment options were very poor," reports the South African TB researcher Helen Cox in conversation with our partner, the journalist team Health-E. "You know, we used old drugs and we used a lot of them and they were often toxic for individuals. The patients had an injection in their buttocks every day for 6 months or more. So it was really hard and the outcomes were not good. So a lot of patients did not finish their treatment and a lot of patients died."[20] A former patient remembers: "I was so weak and I lost so much weight. I thought I was going to die and there was nothing they could do about it. It didn't make sense to go back to the clinic."[21]

In many cases, TB is still diagnosed too late or not discovered at all, complains Helen Cox. As a result, the disease, and with it resistant forms of the disease, continues to spread. "We have so much TB in South Africa that it should be the first thing that healthcare-workers do (...) to ask questions about TB symptoms. But unfortunately it´s not really done." This is also confirmed by statements from patients: "After a month they told me that I had been given the wrong medication. The results now showed that I had MDR-TB and needed to be treated for 2 years instead of 6 months."[21]

NEW HOPE IN HIGHLY RESISTANT TB

In August 2019, a new TB drug was approved in the USA. The antibiotic Pretomanid was developed by the non-profit TB Alliance and clinically tested in South Africa and 13 other countries. It is effective against extremely resistant forms of the disease and could shorten the duration of treatment by many months.[21] After almost four decades of inactivity in TB research, Pretomanid has now become the third new drug to be approved within a few years. However, it may still take years before the drug is approved and readily available in countries of the global south.

Nothing new in sight?

The treatment of multidrug-resistant TB is costly. Especially the newer drugs are very expensive and poorly available in many countries. Helen Cox: "But certainly within South Africa, access has improved a lot and that's part of our decentralized care as well. So that you don't just provide treatment in specialized hospitals in the big cities like Durban, Cape Town and Johannesburg. You can actually provide this treatment at clinics in more district hospitals." However, the fight against tuberculosis still requires international commitment, political will and also more investment in research: "We still need even better diagnostics that can tell us not just resistance to one drug, but resistance to all of the drugs that we currently use. And of course we will always (...) need new drugs because resistance will always develop. If we don´t tackle the problem then transmission will just continue and more and more people will get drug-resistance TB. This is certainly not what we want."

With over-the-counter medicines, farmers in South Africa can treat many diseases in their animals themselves. Photo: CC South African Tourism

A LOT OF DRUGS FREELY AVAILABLE

Many veterinary medicines – including antibiotics – are freely available in South Africa. This leads to high consumption and makes resistance control more difficult. The government wants to change this, but meets with resistance.

The two-part system under which veterinary medicinal products are registered in South Africa is problematic: on the one hand there is Act 101 on the Control of Medicines and Similar Substances of 1965, which covers all veterinary medicines listed in South Africa, including prescription antibiotics. There are also many over-the-counter products and feed additives. They fall under the Fertilizers, Farm Feeds, Agricultural Remedies and Stock Remedies Act 1947, as do other agricultural production and fertilizer products.[23]

This law arose from the need to provide access to medicines for livestock farmers in remote areas without veterinary care. This enabled farmers to treat common diseases in their animals themselves. A whole range of antibiotics, such as tetracyclines, macrolides or polypeptides, are also covered by this law. They serve to prevent and treat diseases, or are used as growth promoters. The substances are freely available, and farmers can buy them from the cooperative or in shops.[24]

Recently, the Ministry of Health has been pushing for all over-the-counter antibiotics to be registered under Act 101/1965, making them prescription-only. However, the South African Animal Health Association, an association of manufacturers of veterinary medicines, wants to prevent this. The restriction could have a negative impact on animal health if farmers are unable to treat their animals promptly for tick-borne diseases and other health problems. The manufacturers therefore want to make a separate proposal to better control the sale of these antibiotics. Among other things, sales staff should be trained better.[23]

No one knows the exact quantity of antibiotic substances used in cattle in South Africa. Photo: CC Lollie-Pop

Reporting system with weaknesses

The Ministry of Agriculture calculates the consumption of antibiotics in animals from the sales volumes of pharmaceutical manufacturers. The majority of the antibiotics used are therefore growth promoters (62 %). Tetracyclines accounted for 17 % and macrolides for 11 %. However, the data situation is still unsatisfactory because antibiotics are not categorized uniformly. For example, manufacturers currently report individual antibiotics registered in South Africa as parasiticides or growth promoters. The government is currently working on improving the reporting system.[2]

No one knows exactly

Antibiotic residues and resistant pathogens on carcasses are monitored in a state monitoring program. There is also a control system for farms and meat producers who supply goods to the EU. The data collection as well as the set limits are based on the EU requirements. This also applies to prohibited substances such as steroids and growth promoters.

According to the report of the Ministry of Health, antibiotic residues were found in 2 % of the samples. Meat produced in South Africa therefore appeared to be low in antibiotic residues. It was quite possible, however, "that this result underestimates the national situation and is due to the low number of samples taken (...)."[2]

A notice at this sausage counter in Cape Town informs that products of the Enterprise and Rainbow Chicken brands have been recalled. The background was a listeriosis outbreak in 2018. The bacterial pathogen is transmitted by contaminated food. Photo: CC Discott

Poultry

The poultry industry has long since become a significant economic factor in South Africa: 80 % of the broilers produced throughout southern Africa come from South Africa – around 990 million animals per year. Industrial fattening cannot do without antibiotics. Tetracyclines, for example, are widely used because they are cheap and easy to obtain. For a long time, antibiotics were regarded as a kind of "insurance" against possible disease outbreaks. This has now changed and awareness of the problem has grown. However, to this day – just as in Germany – prophylactic administration of antibiotics in poultry farming is quite common.[24]

This is also reflected in the development of resistance: between 2009 and 2015, a team of researchers examined thousands of E. coli isolates that came from commercially produced broilers on farms with 15,000-40,000 animals. The pathogens were tested against twelve common antibiotics from eight drug classes. Overall, a good 80 % of the E coli. samples were multi-resistant. Since 2013, however, a decreasing trend has been observed.[24]

Another study detected the resistance gene mcr-1 in South African broilers, and the scientists suspected a wide distribution of the gene. It is now found worldwide and makes pathogens resistant to colistin.

Even wild animals can carry resistant germs.
Photo: Ⓒ Charles J. Sharp

Colistin largely banned in animals

Since the end of 2016, colistin has been largely banned in animals in South Africa. Veterinarians are now only allowed to prescribe it in special cases, and must prove by means of a pathogen test that no other drug is effective.[17] Carbapenems are also not authorized as veterinary medicinal products in South Africa.[2]

Resistant germs and resistance genes that have been detected on farms are also widespread in South African health facilities. This is shown in a survey by Ekwanzala and his team. The scientists conclude that livestock farming plays a serious role in the spread of resistance in health care.[25]

Wild animals are also a transmission path of resistant bacteria that has so far received little attention. The meat of blesbok, kudu or wildebeest is an expensive delicacy in South Africa and the demand for such organic meat is growing steadily – both domestically and abroad. However, even wild animals can carry resistant germs even though they are not given any medication. They get infected, for example, by pets and grazing animals – through direct contact or via shared grazing land.[26]

Active substances that are frequently used in human medicine can also be found in water. Photo:© Health-e

RISK UNKNOWN

For the entire African continent there are only about 15 studies that have investigated the environmental impact of antibiotics. One third of these originate from South Africa.

" The continuous introduction of antibiotics into the aquatic environment from wastewater treatment plant discharges is of major public health concern relating to antibiotic-resistant microbes."[27]

Rodriguez-Mozaz et al. in a study on the entry of antibiotics into the environment

Antibiotic substances enter the environment with wastewater, through agriculture, domestic waste or even through leaks in the sewage system. This is indicated by the locations and concentrations of the substances detected in South Africa. However, the available investigations only focus on two of the nine South African provinces. They detect ten different antibiotics in effluents from sewage treatment plants, in surface water, in river water and in sediments.[3,28]

The active ingredients found reflect consumption in human medicine: drugs used for common diseases such as multidrug-resistant TB, pneumonia or to treat infections in HIV-infected people were also found particularly frequently in the environment.[29]

For example the drug cotrimoxazole. Cotrimoxazole is a combination of two antibiotic active ingredients and is very often used in South Africa to treat concomitant diseases in HIV/AIDS. It is therefore not surprising that one component of the drug was found in high concentrations in the environment. Fluoquinolones and macrolides, which are frequently used to treat bacterial infections, have also been detected in surface water or in river sediments.[3]

In untreated wastewater in Durban, particularly high concentrations of drugs were found which play a major role in the treatment of pneumonia – but also of veterinary medicines. The authors assume that they came from the numerous animal breeding farms

in the province of KwaZulu-Natal. However, the proven concentrations after clarification and discharge into the river are too low to represent an environmental risk.

The remains end up in the drain

Nevertheless, the entries from agriculture are likely to be significant. After all, many provinces in South Africa have large livestock populations that are treated prophylactically against parasites and other diseases. In addition, the high consumption in human medicine suggests that in many places antibiotic substances are released into the environment. This is because a large proportion of the active ingredient ingested is excreted again. It is not uncommon for antibiotic residues to be disposed of directly into the drain or to end up in landfills. This is likely to be a problem, especially in poor districts where many households do not have sewerage systems or sanitary facilities. Scientists consider it likely that such circumstances play a decisive role in the development of extremely resistant tuberculosis pathogens and other multi-resistant germs.[3]

Hospital germs in the reservoir

A team of researchers examined 1,287 meat and water samples for resistant A. baumanii germs over a period of one year. The researchers regularly took samples both from a slaughterhouse in Mthata, Eastern Cape, and from a nearby reservoir that serves to supply the city with water. Their conclusion: the multi-resistant germ, which causes problems in hospitals, is also omnipresent in the environment. The isolates found were resistant to numerous antibiotics. This could further increase the resistance problem in hospitals and also within the population.[30]

Carried on wings

An investigation in KwaZulu-Natal examined the concentration of drugs in the river water of the Msunduzi. Not only were a large number of antibiotics detected, but also the painkiller aspirin. It was the most commonly found drug.[28]

Such drug residues and also resistant germs which enter rivers with treated wastewater are absorbed not least by animals. For example, the colonization of seagulls with resistant E. coli pathogens has been repeatedly proven.[31] Due to their habitat and feeding habits, water birds play a special role in the spread of resistant germs.

Picturesque landscape along the Crocodile River. Its catchment area also includes densely populated areas and large cities like Johannesburg.
Photo: CC JMK

Where the infrastructure is poor, it is likely that a particularly large number of antibiotics end up in the environment.
Photo:© Health-e

Waterfowl play a special role in the spread of resistant germs Photo: © Amada 44

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The summit of Kibo in north-eastern Tanzania is covered with ice and snow. At almost 6,000 m, it is the highest point of the Kilimanjaro massif and the highest mountain in Africa.
Photo: CC Hazie Kapfumvuti

TANZANIA: JUST THE TIP OF THE ICEBERG

Treatment problems due to resistance to antibiotics are becoming more acute. The available studies leave no doubt about this.[2] But exact figures on the extent of the problem are lacking. The greatest challenge in the area of ABR is therefore the collection of reliable data.

"The threat of antibiotic resistance facing us today will be catastrophic for the future generation – unless together we address this problem. Our children and grandchildren have a vested interest in seeing that we address ABR since it's in their lifetimes that the full impact will be experienced."[1]

Eva M. A. Ombaka Professor of Pharmacy at St John's University, Tanzania

It is undisputed that antibiotic resistance is causing massive problems in Tanzania. But little is known about either the consumption of antibiotics or the resistance situation in the country. There is no national monitoring system that collects data on antibiotic use from human and veterinary medicine.[3,4] Targeted approaches require reliable data material.
At the political level, the problem has been well recognized. The Ministry of Health has prepared a national action plan. It is based on the global action plan of the World Health Organization (WHO) and also takes into account the One-Health approach.[3] Although Tanzania is a member of the GLASS network and has thus committed itself to action, no resistance data are currently being fed into the WHO database.[5]

Creating public awareness

The best action plans are ineffective when implementation is lacking. The public perception of ABR in Tanzania has been very low so far and this provides a good breeding ground for growing resistance rates. There is a lack of financial and human resources, and the pharmaceutical market is hardly monitored at all. Nelson

Farmers in Tanzania know little about the issue of antibiotic resistance. The government is working on solutions. Photo: CC Michaelgoima

Faustin, senior pharmacist at the Tanzanian Pharmacy Council in the Pharmaceutical Practice and Inspection Department, sees this as the biggest problem.[6] As a state authority, the Pharmacy Council is not only responsible for the registration of pharmacies, but also issues licenses for pharmaceutical staff and monitors training standards. According to Faustin, work is currently underway to improve the control of medicines in order to improve compliance with prescription requirements. However, it is particularly important to create greater awareness of the problem among healthcare personnel and also among the general population.[6]

People are still dying in Tanzania because they simply do not have access to essential medicines. So the solution cannot be to stop giving antibiotics but to choose the right one.

A self-evaluation by the Tanzanian government in the course of GLASS revealed that employees in agriculture, the food industry and environmental enterprises have so far been poorly informed on the subject of antibiotic resistance, and that training courses are urgently needed.[5] Furthermore, the use of antibiotics in animals and the introduction of these substances into the environment must be better controlled.

Almost half of the population of Tanzania are children. Resistance to antibiotics threatens their future. Photo: CC Rasheedhrasheed

KNOWLEDGE IS THE KEY

Effective control of antibiotic resistance has so far failed mainly due to a lack of money and of qualified personnel. Rapid action is urgently required. In Tanzania, the fact that many antibiotics are already no longer effective affects the youngest in particular. Almost half of the population is under 14. It is about their future and ultimately also about the future of the country.

In Tanzania there are less than three pharmacists for every 100,000 inhabitants – in Germany the figure is over 70.[7] But it is not only qualified pharmaceutical personnel that is in short supply. The same applies to diagnostics and laboratory technology. However, these are necessary in order to prepare an antibiogram before therapy, and to be able to select the right active substance.[2] Because an exact determination of the pathogen is not possible in most health facilities, doctors often prescribe several antibiotics, which increases the resistance problem.[6]

"Antibiotics are easily accessible, anyone who wants to use antibiotics can just go to the drug shop and access them – even without a prescription".[6]

Nelson Faustin, chief pharmacist of the Pharmacy Council, Department of Pharmacy Practice and Inspection

Antibiotics are prescription drugs in Tanzania. But the black market is flourishing. In addition to the state-registered pharmacies, there are numerous unauthorized outlets selling medicines. Especially there, many antibiotics are sold over the counter without a prescription. But even regular pharmacies often issue these drugs without the necessary prescription, sometimes in fewer daily doses than necessary because patients cannot afford the complete treatment cycle.[3] Mboya and colleagues investigated the distribution of antibiotics in 12 registered sales outlets and pharmacies in

Good advice is rare. In Tanzania there are only three pharmacists for every 100,000 inhabitants. Photo: © Erick Venant

Tanzania has public and private health facilities. Although care in the public sector is cheaper, patients have to pay for examinations and treatment here too. Only a small part of the population has health insurance. Photo: CC Riccardo Gangale/VectorWorks/ Courtesy of Photoshare

the community of Moshi in northern Tanzania. They interviewed 152 adults after they had bought an antibiotic. About 80 % of the sales were without a prescription. 23 % of the respondents did not buy the complete treatment cycle, but only individual tablets. In addition, antibiotics were often sold for non-bacterial diseases.[8] About half of the patients received antibiotics for flu symptoms or coughing, 10 % for diarrhea. Irrational use was twice as frequent among patients without health insurance as among those insured.

Many people treat themselves

Penicillin is most often sold without rational indication and used incorrectly. These drugs are inexpensive, but they hardly show any effect due to high resistance rates.[8] A key problem is the lack of awareness among the general population and also among health care workers. Those who are poorly informed and know little about the correct use of antibiotics are also particularly likely to take these drugs incorrectly. The pediatric nurse Pendo Masanja experiences this problem every day and describes it in an interview with our partner Erick Venant: "Few people are aware of antibiotic resistance. It is a common practice in our society to take a five-day antibiotic according to prescription but stop when the symptoms subside." [9] Many people treat themselves – without medical advice and without knowing the cause of their illness or how to use the medicine correctly.[3]

This combination of insufficient knowledge and lack of qualified personnel is driving the resistance problem. Rural areas are most severely affected. This is where the lack of personnel is particularly noticeable. There is a lack of doctors and pharmacists in health care facilities and important drugs are often not in stock. Patients then have to procure the drugs themselves, but there are only a few pharmacies and often supply bottlenecks.[2]

Things are starting to happen

The government has been tackling this problem since 2003. In addition to licensed pharmacies, state-approved dispensing outlets for medicines have been set up – Accredited Drug Dispensing Outlets, or ADDOs for short.[2] These small shops are allowed to sell certain medicines, but their employees must first undergo training. The training also includes the rational use of antibiotics. The ADDOs have significantly improved the supply of medicines in rural areas, and they are achieving "positive results on fighting ABR,"[6] concludes Nelson Faustin. The pharmacist has been working for the Pharmacy Council, which is responsible for the ADDO program, for over 10 years. The success of the ADDOs is also confirmed by Dr.

Suleiman Kimatta, who is involved in the implementation of the program as Senior Technical Director: "We have seen the ADDO dispensers insisting on the proper use of antibiotics to the clients, on the right use of the medicines for the right illness, and the correct dose and duration."[10]

Children in need

Resistance to antibiotics endangers especially the smallest ones. Resistance rates are particularly worryingly high in the case of pneumonia.[4] The pathogen Streptococcus pneumoniae, for example, shows resistance to cotrimoxazole in more than 80 % of the cases in children.[2] But resistant E. coli pathogens also cause problems. Msaki and colleagues found in their study that the germ in febrile children was 100 % resistant to ampicillin, 97 % resistant to cotrimoxazole and 85 % resistant to amoxicillin.[11]
The situation becomes particularly critical when co-infections with malaria or HIV/AIDS occur or poor living conditions prevail. Then the immune system of those affected is weakened and they are more susceptible to bacterial infections, which are increasingly difficult to treat.[2]

Antibiotics against diarrhea

In particular, the widespread assumption that antibiotics are a panacea exacerbates the resistance problem, according to our project partner Erick Venant from the Roll Back Antimicrobial Resistance Initiative (RBA): "For example, patients demand antibiotics for watery diarrhea and the common cold."[12] Diarrhea is especially widespread in Tanzania, and in most cases an oral rehydration solution would be the best treatment. Nevertheless, regardless of the pathogen, an antibiotic is usually given. This has led to high resistance rates in diarrheal pathogens such as Salmonella, Cholera, Shigella or E. coli. In recent years, for example, outbreaks of cholera have repeatedly shown resistance to standard antibiotics. Other problem areas where standard therapies are increasingly failing are urinary tract infections, blood poisoning and sexually transmitted diseases such as gonorrhea.[2]

Gonorrhea

With 78 million cases annually, gonorrhea is the second most common sexually transmitted disease worldwide. The highest infection rates are found in Africa, and Tanzania is also severely affected. Especially in women, gonorrhea can lead to dangerous complications such as pelvic inflammatory disease and ectopic pregnancies, and it increases the risk of HIV infection. Resistant

Many small children in Tanzania die of pneumonia because antibiotics no longer work.
Photo: CC Guojun Yang

Poor people like this street vendor have poor chances for a healthy life. Photo: CC Inbera

Sufficient personnel and good training are central to the fight against antibiotic resistance.
Photo: CC USN

forms of the disease now make therapy extremely difficult. WHO reports worldwide resistance rates of up to 97 % to ciprofloxacin and 81 % to azithromycin.[13] In Tanzania this is a serious problem: here ciprofloxacin is still the drug of choice for sexually transmitted diseases, although it is usually no longer effective. In a study by Buhalata and colleagues, 77.7 % of Neisseria gonorrhoeae isolates were resistant to ciprofloxacin. A revision of the treatment guidelines is therefore urgently required.[14] However, the lack of laboratory capacity to determine the pathogen in individual cases and to demonstrate resistance remains a problem.[15]

Poultry meat usually comes from very small farms – but even there, antibiotics are common.
Photo: © Erick Venant

MANY ANIMALS, FEW VETERINARIANS

In Tanzania, the lack of veterinarians, but also ignorance on the part of farmers and consumers, has led to the careless use of antibiotics in animal husbandry. Especially in poultry fattening on small farms, far too many antibiotics are used in an uncontrolled manner.

The sale and consumption of veterinary medicines is hardly recorded and monitored in Tanzania. The responsibility lies with the TADs and ZIS (Transboundary Animal Diseases and Zoosanitary Inspectorate Services), which also carry out controls on imports and exports. Feed is not controlled at all. There are many small feed manufacturers who add antibiotics to their products and sell the feed illegally at the kiosk.[2]

"In Tanzania we have regulations that you cannot buy antibiotics or other drugs if you are not a veterinarian. But it is difficult to observe that in the absence of professionals in rural areas."[16]

Prof. Robinson Mdegela, veterinarian, Sokoine University of Agriculture

Shady deals

The few studies on the use of antibiotics in animals in Tanzania indicate a high consumption – especially in poultry farming.[2,3,17] The drugs are used as growth promoters or also for the prevention of a variety of diseases. Cattle, goats and pigs are also often treated with antibiotics – for example to cure diarrhea, tick-borne diseases or udder inflammation in cows.[2]

Up to now, most of the veterinary medicinal products used come from Europe, although imports from Asian countries such as China, India and Indonesia are on the increase.[2] Small shops sell the drugs. There are indeed laws that are intended to restrict the use

Chicken meat is popular in Tanzania, and is sold at small markets everywhere.
Photo: CC Sarumakame

Antibiotic for oral administration as an admixture for drinking water. Especially in poultry, antibiotics are also used as growth promoters.
Photo: © Erick Venant

of antibiotics in animal husbandry. For example, only veterinarians are allowed to buy antibiotics and give them to animal owners. In practice, however, such legal requirements play hardly any role because controls are rare and there is a severe shortage of veterinarians.

Serious danger

Resistance in poultry and pigs is particularly widespread regarding E. coli.[18] A study found resistance to amoxicillin in 82 % of chicken E. coli isolates.[3] The pathogen is also often insensitive to other frequently used agents such as tetracyclines, sulfonamides and ampicillin.[19] In addition, resistant Campylobacter infections are widespread in poultry, and also frequently lead to infections in humans. Dairy cows with mastitis have been found to be highly resistant to penicillin, chloramphenicol, streptomycin and oxytetracycline – all the drugs most commonly used against this disease.[2]
There are little data available on resistant germs on food, but the available results indicate high antibiotic residues in milk and meat.[2]

Chicken straight from the farmer

Poultry production in Tanzania is a matter for micro-enterprises. There are just under 1.7 million small farms that breed chickens and market the meat directly. 80 % of the poultry produced in the country is consumed by the local population.[2]
Small farmers in particular often use antibiotics as growth promoters or for mass prophylaxis, and are not aware of the harmful consequences.[2]

250 veterinary surgeons throughout the country

"In Tanzania you have large numbers of animals and yet you don't have enough professionals," criticizes Professor Mdegela.[16] There are about 250 practicing veterinarians nationwide with a stock of 40 million farm animals, not including poultry.[20] In addition, veterinarians mainly tend to live in the cities. Especially the rural regions are undersupplied. In order to remedy this situation, there are so-called paravets in many places. On behalf of state veterinarians, for example, they run small practices in the villages so that the farmers there can get the most necessary things to treat their animals. There are around 1,700 paravets in Tanzania. They have completed a training comparable to that of veterinary assistants in Germany. The government plans that there should be at least one paravet in every village.[2]
But that alone will hardly be enough to remedy the situation. Professor Mdegela emphasizes that the excessive use of antibiotics is not least due to profit interests: "We should not forget that in Tanzania, most of the veterinary services have been under the private

sector. Now in the private sector we speak about maximization of profits. As a result of that [...] you find the selling of drugs going to people that are unauthorized. That's a challenge."[16]

Therapy according to hearsay

A survey of 160 farmers showed that only 30 % had ever heard of antibiotic resistance. A good half did not know which diseases to use antibiotics for, and 40 % were unaware that their use in animals can also have an impact on human health.[19] Professor Mdegela: "Some of the drugs being used, the farmers don't even read the instructions. They just go by experience or what they hear from their colleagues. As a result you have the consequence that humans, through consumption of animal products, are also consuming the drug residues. That is the biggest challenge and contributes to antimicrobial resistances."[16]

Poultry production in Tanzania is a matter for micro-enterprises. Photo: CC Ed Hawkesworth

The way of life is also decisive

But it is not only the frequent use of antibiotics that plays a role. Especially in poor countries, living conditions are a decisive factor in the spread and transmission of resistant germs. This was shown in a research study by Subbiah and his team.[21] The scientists investigated antibiotic-resistant enterobacteria in humans, domestic animals, wildlife and in waters of Northern Tanzania. Over half of the approximately 50,000 isolates showed resistance to at least one antibiotic. In addition, the species of the pathogens were largely identical. The bacteria are thus exchanged between humans, animals and the environment. Certain lifestyles and behavioral patterns such as shared water points, intensive livestock trade, frequent visits to cattle markets or the consumption of unboiled milk are closely linked to the frequency of antibiotic resistance. The conclusion of the researchers: more interdisciplinary scientific studies would be urgently needed to investigate the complex relationships between human habits and the spread of resistant germs.

Nomadic lifestyles, such as intensive livestock trade and frequent livestock exchanges, also contribute to the spread of resistant germs. Photo: CC Nicor

Inadequate wastewater and waste management is a major cause of the resistance problem. Photo: CC SuSanA Secretariat

NEGLECTED: THE ENVIRONMENT

Even if Tanzania's national resistance strategy is oriented towards the one-health approach – the environmental aspect has so far been neglected. There is hardly any information available on the use of antibiotics and resistant germs in the environment.

The spread of antibiotic resistance in the environment is a sensitive issue, and ultimately also threatens the effectiveness of antibiotics in human diseases, summarizes Erick Venant. As founder and managing director of the Roll Back Antimicrobial Resistance Initiative, he campaigns for this issue in Tanzania and calls for more research commitment. "We need to find out what effective solutions are to stop the spread of resistance in the environment."[12] So far, there are not many studies that investigate antibiotic residues and resistance in the Tanzanian environment. However, the available results indicate a serious risk.

Waste disposal and sewage systems play an important role in the development of resistant germs. Worldwide, 80 % of wastewater is discharged untreated into the environment.[22] The World Water Report of the United Nations makes it clear that poor countries in particular are in a poor state of wastewater treatment: in countries with low per capita income, only 8 % of municipal and industrial wastewater is treated. In countries with high per capita income, by contrast, the figure is 70 %.
Analyses of a global study showed that Tanzania, together with Vietnam and Nigeria, had the highest resistance rates to germs in untreated wastewater out of 259 investigated areas worldwide.[23] Even where there are sewage treatment plants, they do not necessarily remove the antibiotic residues and resistant germs. Mohameda and colleagues investigated a sewage treatment plant in

Tanzania and found a high contamination with tetracyclines and quinolone antibiotics at the entrance point to the plant which were still present after treatment of the wastewater.[24]

Flushed down the sink

Another aspect that is relevant for the spread of resistance is the incorrect disposal of drugs. Mwita and colleagues investigated the waste management of private hospitals and drug shops in Tanzania. The scientists concluded that there is hardly any awareness of possible environmental problems or of the necessary professional disposal of drugs. Accordingly, people behave carelessly. Expired medicines, for example, are not regularly disposed of, often not documented, and improperly disposed of. More than 40 % of the facilities investigated flush the drugs down the sink or throw them in the household waste. 64 % of the drugs disposed of were antibiotics. As an obstacle to proper disposal, 40 % of the pharmacists cited the cumbersome procedures.[25]

For Erick Venant in Tanzania, awareness raising, but also reliable information is therefore a top priority: "We need more data in order to be able to take evidence-based action."[12]

"I see that the environment sector is still lagging behind. It should be given more attention than it is getting currently."[12]

Erick Venant, pharmacist, Roll Back Antimicrobial Resistance Initiative Tanzania

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Educational work with young people can make a big difference! The RBA initiative also focuses on educational opportunities in the classroom. Photo: CC Seemannaufland

"YOUNG PEOPLE HAVE POWER"

The RBA Initiative is dedicated to the fight against antimicrobial resistance in Tanzania. This non-governmental organization is recently gaining international recognition. We spoke to its founder Erick Venant. He studied pharmacy and already received numerous awards for his commitment.

"The society needs our contribution, and some of the health challenges can be alleviated by simple measures like raising awareness."[1]

Erick Venant, General Manager of the Roll Back Antimicrobial Resistance Initiative, Tanzania

Where are the biggest problems at present?

In my opinion, the biggest challenge is the lack of awareness. This leads to the misuse and overuse of antibiotics, both among health personnel and among the general population. I see this as the top priority. We must raise awareness of the problems so that the population can act accordingly to prevent the spread of resistance. The same applies to us as healthcare workers.

But there is also a backlog in other areas. These include infection prevention and control, waste disposal and hygiene, and the strengthening of regulations concerning the use of antibiotics.

What needs to be done?

Countries like Tanzania need to accelerate the implementation of their national action plans. I believe we need to give the one-health approach greater consideration and involve all stakeholders.

Antibiotic resistance is now receiving global attention. I am glad to see that the UN, other international organizations and experts are working together to minimize the growing threat of resistance.

What motivated you to found the RBA?

I have always had a burning desire to be involved in solving a wide variety of public health problems. Therefore, I started to organize various events at the university to raise awareness for more hygiene and rational use of medication. In 2017 I became president of

the Association of Pharmacy Students in Tanzania (TAPSA). I wanted to show what contribution young people can make to improve public health.

At that time I realized that antibiotic resistance is a major threat and that 700,000 people die every year worldwide as a result. If we do nothing more, that number could rise to ten million deaths a year by 2050. I saw how much the problem was underestimated in Tanzania, and how little attention it received here. I thought that a simple but very important step in the fight against resistance was to raise awareness and educate people. I decided to run a nationwide campaign in secondary schools during the semester break. We managed to reach over 100 schools. Many of the students did not even know what antibiotic resistance meant. But they were happy to learn something about it, to understand its effects, and to learn what they can do themselves.

What is the RBA initiative doing?

The RBA Initiative is a registered non-governmental organization with the aim of combating antibiotic resistance in Tanzania. Its headquarters are in Dodoma, in the center of the country. We promote the rational use of antibiotics, spread knowledge about resistance, advocate behavioral change and effective hygiene. Through our work, we also promote awareness of the need to take action against antibiotic resistance in our country as quickly as possible.

In the past year we have carried out a number of awareness-raising activities, addressing different target groups. Among other things, we organized workshops for people from the health sector. We also visited secondary schools and offered information events. In addition, we wanted to address the broad mass of the population. So we used local radio stations. This enabled us to reach three million people with our message last year.

This year we are putting a special focus on schoolchildren. We will establish school clubs on antibiotic resistance in Dodoma and the surrounding area, and inform the younger generation on the topic. Because we believe that they can be good ambassadors for the rest of their community.

What is your advice for young people who want to change things?

Young people have the power to initiate positive changes in their society. They should start with small things and use the available resources. Through commitment, self-motivation and esprit they can achieve greater goals. Especially in the health sector there are many challenges. Young people can be part of the solution.

Erick Venant (25 years old) received the Legacy Award from the Diana Award Charity in 2019 and met Prince William at Kensington Palace.
Photo: © The Citizen Reporter

Endnotes

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60,000 landless Indian farmers began their protest march from Gwalior to Delhi on 3 October 2012. When they arrived in Agra, the government gave in and signed an agreement that was the prelude to land reform. Photo: CC Yann Forget

TIME FOR A TURNAROUND

Resistance to antibiotics concerns us all

When it comes to ABR, the onus is as much on governments as it is on consumers, healthcare workers or farmers. Every individual has a role to play. And time is pressing.

Our country reports on the resistance situation in Germany, India, South Africa and Tanzania clearly show that the problem is global, and that bacterial super pathogens have fatal consequences, especially in poor countries. The international interactions in the spread of resistant germs are considerable, and are probably still underestimated due to a lack of systematic recording. Although approaches to solutions are obvious, there is a lack of political will to implement them consistently.

"Of course we have to combat antibiotic resistance in the future! If we don't do that, it's a time-bomb. We need to invest more and we need to do more – the global effort pays!"[1]

Richard Valimba, pharmacist and consultant to the ADDO programme in Tanzania

Eradication of poverty

Fighting poverty worldwide is the top priority. Because it is also a driving force in the field of antibiotic resistance. Poor living conditions and lack of hygiene are, on the one hand, the breeding ground for high infection rates, more severe courses of disease and the associated high consumption of antibiotics, which accelerates resistance. On the other hand, especially in poor countries, the exchange of resistant pathogens between humans, animals and the environment is a blatant problem – so far largely neglected by researchers and governments alike. The close coexistence of humans and animals, shared water points, lack of toilets, inadequate wastewater disposal and treatment – all these are decisive factors in the transmission and spread of resistant bacteria.

Strengthening the health systems is the order of the day. Photo: © Health-e

Strengthening health systems

The strengthening of health systems is also important. This applies equally to North and South. After all, a lack of personnel in health care facilities is just as fatal when it comes to ABR as a lack of laboratory technology or gaps in the stock of medicines. Supply bottlenecks for antibiotics occur again and again worldwide and also in Germany, because production is concentrated in a few countries. Doctors often have to resort to antibiotics with an unnecessarily broad spectrum of activity or even reserve agents.[2]

Setting the course

Worldwide, the majority of antibiotics are used in animal husbandry. Especially in the global south, meat production is growing rapidly. Since 2000, it has increased by 68 % in Asia and 64 % in Africa.[3] The window of opportunity to set the course for sustainable agriculture and livestock farming is narrow. Rich countries like Germany should support this transition. After all, antimicrobial agents have been used here since the 1950s. This enabled factory farming and thus an enormous expansion of meat production. The price for this is the worldwide spread of resistant germs. It is time for a turnaround – for the benefit of humans, animals and the environment!

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OUR PROJECT PARTNERS

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Erick Venant is founder and managing director of the Roll Back Antimicrobial Resistance Initiative (RBA Initiative) in Tanzania. The organization supports projects and measures to combat the resistance problem. Among other things, it conducted an education campaign in 23 government districts of Tanzania, which reached 49,000 students and teachers in secondary schools.
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https://health-e.org.za/

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Resistant pathogens: a danger for humans, animals and the environment.

The World Health Organization (WHO) ist sounding the alarm: without swift, coordinated action, the world is heading for a postantibiotic age. Not only widespread infections, even minor injuries could become a deadly danger. This is true for patients in Germany, and even more so for those affected in India, Tanzania or South Africa, where people fall ill more frequently, and the necessary specialists, diagnostics or therapies for the treatment of multi-resitant infections are available at best in large cities.

Together with partner organizations in India, Tanzania, South Africa and Germany, we have investigated the causes and consequences of the increasing development of resistance worldwide. This Pharma-Brief Special presents the results. It highlights threats and problems of multidrug-resistant pathogens for humans, animals and the environment. Local problems and approaches to action are just as much in focus as international interactions or the responsibility of doctors, farmers and consumers.

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