left: © CDC/James Archer, right: © PeskyMonkey/iStockphoto

# Last Reserves

**Antibiotics help to combat bacterial infections. More and more often, however, the drugs have no effect. Their wide-ranging use stimulates bacteria to build up counter strategies and become increasingly resistant – even to reserve drugs. The development is being carefully monitored at the BfR.**

Veterinarian Annemarie Käsbohrer sucks a cloudy, watery liquid from a thin tube with a pipette. She spreads it onto a gelatinous substrate in a plastic dish. Routine in a microbiological laboratory. But it's tricky work nonetheless because the tubes contain foodborne bacteria that antibiotics have no effect on – potentially dangerous pathogens. They originate from regional state laboratories which have sent the microorganisms to the National Reference Laboratory for Antimicrobial Resistance for further testing. Professor Annemarie Käsbohrer and her team examine here how pronounced the resistance is. Her laboratory is an important player in the struggle against a medical scourge of our times – durable pathogens that resist medication.

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## 2,400 deaths every year

Just how dangerous antimicrobially resistant pathogens are can be seen from a glance at the statistics: according to the Robert Koch Institute, every year roughly 54,500 people in Germany become infected with pathogens that are resistant to several antibiotics, i.e. multi-resistant. Almost two thirds of them take ill in hospital. Approximately 2,400 people die every year after becoming infected with multi-resistant bacteria. The topic has also taken root in public awareness in the meantime. According to the BfR Consumer Monitor, 89 percent of respondents have heard of antimicrobial resistance. Two out of three are concerned about it.

Antimicrobial resistant bacteria propagate above all where drugs are frequently administered – to patients in hospitals and to housed livestock. Whereas methicillin-resistant *Staphylococcus-aureus* (MRSA), which are dreaded in hospitals, tend to be insignificant as foodborne bacteria, other antimicrobial resistant pathogens – intestinal bacteria such as Salmonella, *Campylobacter* and *E. coli* – deserve more attention. They are regularly detected on raw turkey breast and chicken legs. Although they are killed off by sufficient boiling, frying and roasting, they can cause illnesses in the digestive tract or pass on their resistance to other bacteria if they spread to other foods such as salads or bread before cooking. As soon as pathogens of this kind enter the world they become a problem – because several antibiotics have no effect on them.

## Focus on resistance to reserve drugs

Back to the BfR labs. Special methods are developed here to recognise antimicrobial resistant pathogens. Professor Annemarie Käsbohrer is the head of the reference laboratory for antimicrobial resistance and one of the experts on pathogens that can be transferred via food. She and her laboratory team examine bacteria such as Salmonella and *E. coli*, a basically harmless intestinal inhabitant which can, however, pass on resistance to pathogens. They also test bacteria which form the enzyme ESBL which destroys a range of antibiotics. Certain resistances are of particular interest to Annemarie Käsbohrer and her team: the resistance to colistin and to carbapenems. "Bacteria on which these active substances have no effect are a big problem. Medications with colistin or carbapenems are the last weapon against bacterial infections when other drugs no longer have any effect." They are the last reserve.

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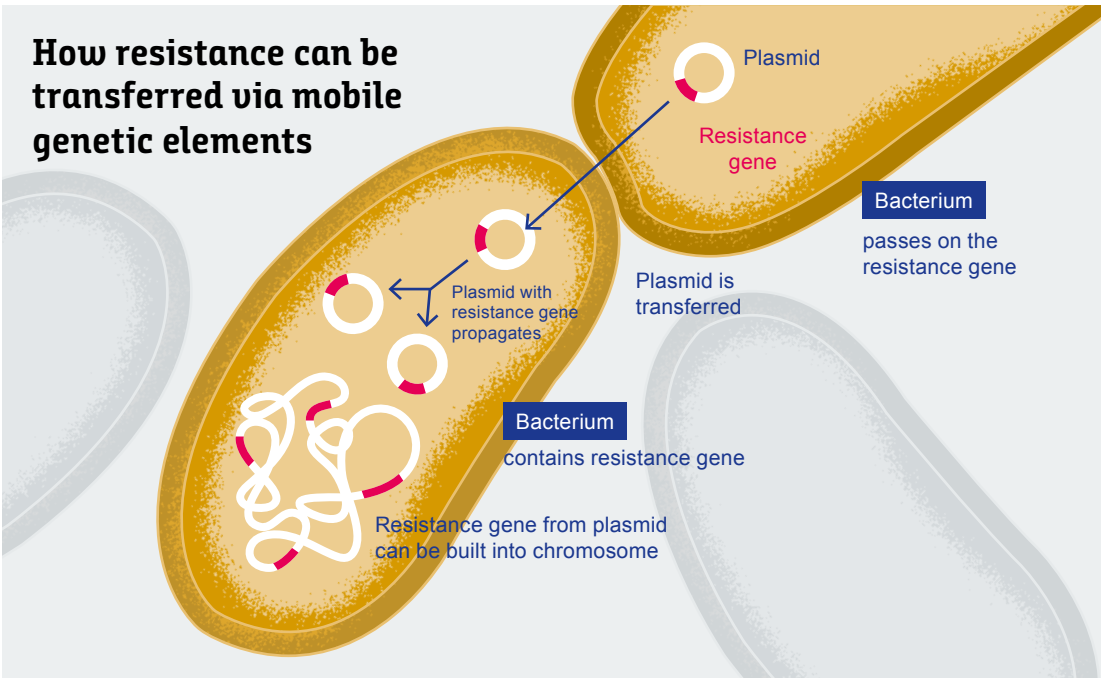
**Bacteria with antimicrobial resistance can survive easily and propagate on turkey and chicken meat.**




## Ingenious defence

Colistin dissolves the outer cell membrane of certain "gram-negative" bacteria. The microbes succeed in warding off this attack with the help of the resistance gene *mcr*. The "defence gene" contains the assembly instructions for a protein which makes the attachment of colistin to the cell membrane more difficult. The colistin attack is repelled. Research in recent years has shown that the *mcr* gene occurs above all on transferrable genetic elements. These plasmids are independent of normal bacterial genetic information. It is thus comparatively easy to transfer resistance to other bacterial species (see chart), including those that occur in humans. The problem here is that the antibiotic is used increasingly for the treatment of infections in humans when no others work anymore. If these resistant bacteria therefore find their way from livestock to humans via food, it is feared that all therapeutic options will be exhausted.

The second problematic resistance Käsbohrer and her team are after is the one to carbapenems, which are also reserve antibiotics in human medicine. "In recent years, we have sporadically been detecting carbapenem-resistant bacteria," says Käsbohrer. "They are Salmonella and *E. coli* that occur in pig farming." This is happening even though carbapenems are not used in livestock. The bacteria form a protein which chemically alters the carbapenem, thus inactivating it. This resistance is also easily transferrable between bacteria. New findings indicate that pathogens which have not been monitored up to now, such as *Vibrio*, can also be the carriers and distributors of carbapenem-resistance.

### Reserve antibiotics

Antibiotics can be classified into various classes according to their structure and mechanism of action. Active substances from the carbapenem class, for instance, cause bacteria to burst. There are further developments of every class of antibiotics in order to have effective drugs on hand despite the occurrence of resistance. If antibiotics used up to now fail to take effect, the medical profession has reserve antibiotics which are only used when no other antibiotics have any effect on someone with an infection. Resistance to these "last reserves" must be monitored particularly closely.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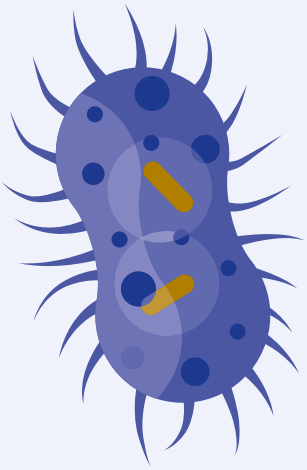




# Curb antimicrobial resistance

The BfR works in numerous research projects on the goal of reducing the risk of the transfer of antimicrobial resistant bacteria to humans via food. To do so requires more precise detection methods, for example. Here is an overview of several projects:

## Europe conducting research on transferrable bacteria

The funding program "One Health EJP" (Promoting One Health in Europe through joint actions on foodborne zoonoses, antimicrobial resistance and emerging microbiological hazards) focuses on pathogens which can be transferred from animals to humans. With this European Joint Programme set to run for five years, the European Commission and involved member states are jointly sponsoring projects from the Horizon 2020 framework research programme. Joint research projects and other integrative projects and training measures deal with foodborne zoonoses, antimicrobial resistance and new infection hazards.

**https://onehealthejp.eu/**

## More precise detection in the laboratory

Recording and observing the occurrence and spread of bacteria with antimicrobial resistance in animals and foods is the goal of the IMPART (IMproving Phenotypic Antimicrobial Resistance Testing) research project which is part of the One Health EJP. The methods form the basis for epidemiological monitoring.

**https://onehealthejp.eu/projects/jrp1-impart/**

## Expansion of resistance in Europe

In the ARDIG (Antibiotic Resistance Dynamics) research project, a comparative examination of the spread of antimicrobial resistance is made using the example of six European countries. Humans, animals, foods and the environment are observed as part of the One Health EJP. It is recorded what influence the use of antibiotics has on the development of antimicrobial resistant bacteria in addition to climatic influences.

**https://onehealthejp.eu/projects/jrp2-ardig/**

## Resistant Staphylococci and food

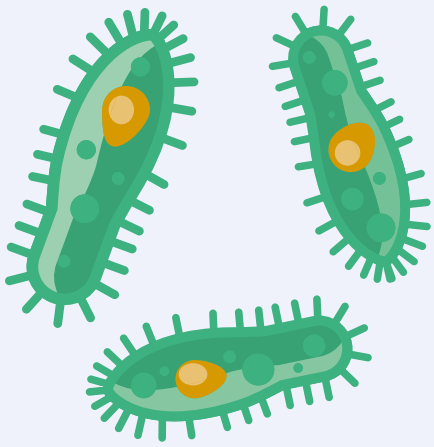
The MedVetStaph research project examined the significance of methicillin-resistant *Staphylococcus aureus* bacteria of animal origin on infections in humans. The Federal Ministry of Education and Research sponsored the interdisciplinary project from 2010 to 2018. The projects carried out at the BfR show that although the transfer of MRSA via food is possible, it is of no great significance.

**http://medvetstaph.net/**

## Antibiotics in livestock holdings

The use of antibiotics in food-producing animals is being recorded in selected, representative holdings within the scope of the VetCAb project and placed in connection with information on the treated livestock. The risk assessment of the use of drugs and the derivation of preventive strategies are enabled by this continuous and systematic data collection method. The BfR is sponsoring the project and conducting it jointly with the Institute for Biometry, Epidemiology and Information Processing at the University of Veterinary Medicine Hannover, Foundation (IBEI-TiHo).

**https://ibei.tiho-hannover.de/vetcab/**

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## They are everywhere

In his role as an epidemiologist at the BfR, adjunct professor (Privatdozent) Dr. Bernd-Alois Tenhagen has been monitoring for years where resistant bacteria occur in food and how they spread. He compiles the data he receives from the laboratory into trends and reports. "We regularly find bacteria with easily transferrable colistin resistance in poultry samples," says Tenhagen. "Poultry meat should therefore only be put on the plate once it has been cooked thoroughly." Tenhagen's expertise is needed. For example during the annual preparation of the sampling plan for the authorities of the federal states. Based on this plan, they examine specific animals and foods for resistant bacteria. The monitoring programmes are adapted to trends every year. In addition to meat, mussels and plant-based foods like tomatoes and sprouted seeds are also examined, because resistant bacteria are popping up here too. That antimicrobial resistance can also be transferred across bacterial species is a significant finding for epidemiological research. It shows resistance is spreading – and has already spread – in a seemingly unstoppable manner.

The National Reference Laboratory discovered bacteria with mobile colistin resistance in archived samples that were taken years ago. They were not tested for it at that time because colistin resistance was regarded as non-transferrable.

## Joint countermeasures

It has long been clear to experts that the effectiveness of antibiotics can only be maintained for humans and animals through close cooperation in line with the "One Health" concept. This means that the health of humans, animals and the environment is interlinked. Fundamental findings on the spread of antimicrobial resistance and pathogens between humans and animals have been made in recent years in the RESET (see BfR2GO 1/2017) and MedVet-Staph (see BfR2GO 2/2018) research networks in which the BfR was involved. Building on this, the BfR is working in European projects (see Page 10) to improve detection methods, for example. It is being examined how bacteria continue to build resistance to antimicrobial


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### How to protect?

Bacteria with antimicrobial resistance are also transferred via food. Only one thing helps here: hygiene in the kitchen, i.e. hand washing before and during cooking, using different chopping boards for meat and vegetables and always cooking meat thoroughly.

**More information:**
BfR brochure "Protection against food infections in private households"
www.bfr.bund.de/en > Publications > Brochures


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substances, including reserve antibiotics. Within the German One Health Initiative for instance (see box), the BfR compares resistant bacteria that occur in humans with those from livestock and pets.

A glance at the numbers shows that the use of antibiotics in livestock farming in Germany is on the decline from 1,706 tonnes in 2011 to 733 tonnes in 2017. Bernd-Alois Tenhagen has also determined a slight decrease in resistance in the bacteria tested at the BfR. To continue this trend, he is demanding "further improvements in livestock farming so that fewer animals take ill and fewer antibiotics have to be used to treat them." Another approach to inhibit bacteria on food, no matter whether resistant or not, is to further improve slaughter hygiene, above all with poultry. Bacteria from the animal gut often spread to the poultry meat in the highly automated slaughter process and still pose a great challenge to many abattoirs. ◘

More information:
**www.bfr.bund.de/en > A-Z-index> antimicrobial resistance**

## Together for health: The German One Health Initiative (GOHI)

Several federal institutions joined together in 2017 to come to terms with global challenges such as antimicrobial resistance. In addition to the BfR and Robert Koch Institute, the Friedrich Loeffler-Institute and Paul Ehrlich Institute are funding research projects on One Health, which are being conducted jointly by the institutes. One of the goals is to develop compatible databases to enable direct access to monitoring data on antimicrobial resistance in human and veterinary medicine and the environmental sciences in future.

**More information:**
www.gohi.online

**Investigations are carried out in the BfR laboratory to establish which resistant bacteria occur in foods.**


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# "Antibiotics are more valuable than gold for us"

**Modern medicine needs antibiotics. Every time they are used, however, there is a risk of resistance – a dilemma. One Health pioneer Professor Lothar H. Wieler on the question of how valuable antibiotics can be sustained in the long term.**

**Professor Wieler, will there soon be no effective antibiotic for the treatment of infections like pneumonia and meningitis?**
There is not so much concern in Germany and Central Europe at the moment, but antimicrobial resistant pathogens must be viewed from a local, regional and global perspective. Healthy people also carry antimicrobial resistant pathogens in their intestines, for example. They can be shed and transported. Pathogens can be carried over long distances thanks to globalisation and widespread travel. It is important to view the situation separately in each region, but to compare the monitoring data with one another. Substance classes that are important for human therapy are not authorised for use with livestock. These include reserve antibiotics for the treatment of MRSA infections in humans.

**The One Health strategy processes the occurrence of resistance in both human and veterinary medicine. What have we learnt in the meantime?**
That the majority of resistant bacteria – roughly 90 percent – detected in human infections originate from human medical treatment. The quantity of antibiotics used in Germany has remained roughly the same in recent years, but worldwide use is rising continuously. It's not only animals and humans that belong to One Health, by the way, pathogens with antimicrobial resistance are also transferred via the environment, especially water. That's why the waste water from hospitals in particular has to be closely watched, along with areas of intense livestock farming. The interlinked research of all federal institutions, including those from the environmental and pharmaceutical sector, is therefore important.

**Where can humans get infected?**
The most common source of infection with resistant bacteria is in a hospital, but infection through contaminated food is also common in Germany.

**And what can be done to prevent it?**
The most important form of protection against infection is hygiene – washing hands thoroughly and disinfecting them too, when necessary. And keeping away from sick, infected persons if possible. Getting vaccinated helps to reduce the use of antibiotics. Above all elderly and immunosuppressed people should get themselves vaccinated against Pneumococci, for example, to prevent pneumonia. An annual flu vaccination provides protection too, because flu is often followed up by bacterial infections.


© Andrea Schnartendorff, RKI

**Professor Dr. Lothar H. Wieler**
As President of the Robert Koch Institute, he has an overview of the problems caused by antimicrobial resistance in the field of human medicine. Because Wieler is a veterinarian and a microbiologist, he also knows that pathogens with antimicrobial resistance are a complex phenomenon. For this reason, he helped to launch the German One Health Initiative (GOHI – see Page 12) in order to initiate research projects on the specific use of antibiotics with partners like the BfR.

**What can be done to reduce the use of antibiotics?**
There are many areas. The hygiene aspect in hospitals should be given more emphasis through more, highly trained and specialised personnel. Committees at the Robert Koch Institute are recording gaps and making suggestions and recommendations. Physicians and the general public can also be given more assistance through research and specific information on how to administer antibiotic drugs as efficiently as possible. That is the essence of the problem that we have to solve: only using antibiotics in specific instances, i.e. when it is absolutely essential to do so. ◘