“Only a joint strategy can be effective”

Bacteria that are resistant to antibiotics pose a public health risk. Professor Dr. Annemarie Käsbohrer is tasked with addressing this challenge at the BfR. In this interview, she explains which factors play a role in the spread of antimicrobial resistance.

Ms. Käsbohrer, one of your major research interests is antimicrobial resistance. In the public debate, a connection is often made between the frequent use of antibiotics in livestock management and the occurrence of resistant bacteria in the field of human medicine. But aren’t animals given different antibiotics than humans?

To explain the differences, we need to distinguish between the drugs themselves and the antibiotic substance groups. When treating animals, veterinarians use different drugs than those used by doctors treating human patients – but the active ingredient, the antibiotic, can be the same. Antibiotics can in turn be divided into active substance groups. In terms of these substance groups, the fact is that most of the antibiotics we use in humans belong to the active substance groups that are also used in veterinary medicine. There are only very few antibiotic groups that are used solely in the one or other field. These include carbapenems, for example, which may not be used for livestock. In the field of human medicine, carbapenems are above all used when other antibiotics are no longer effective.


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If they can’t be used in livestock, how is that you have found carbapenemase-producing bacteria in samples from livestock at the BfR during the RESET research project?

The emergence of antimicrobial resistance is a natural process with bacteria, and the use of antibiotics accelerates this process. Resistance to a certain active substance can also spread although the active substance group in question has not been used. Due to the selection process, the general rule is that if I use an active substance, then I favour those bacteria that are resistant to the substance. But carbapenemases, in other words the enzymes that are formed by carbapenem-resistant bacteria, can inactivate not just carbapenems but also almost all other β-lactam antibiotics. It is therefore theoretically possible that resistance to

> **If an infection pathogen collects multiple resistance mechanisms over time, it may be the case that there is no therapy at all that is ultimately effective.**

Professor Dr. Annemarie Käsbohrer heads the „Epidemiology, Zoonoses and Antimicrobial Resistance“ Unit at the BfR, and this unit also comprises the National Reference Laboratory for Antimicrobial Resistance. In April 2016, she was also appointed to the position of Professor at the Vetmeduni Vienna, where she heads the „Public Veterinary Health Institute“.

carbapenems can spread although the veterinarian used a different active substance group in the livestock. Once a resistance to bacteria is present, there are many routes via which it can spread. A shed is not a sterile room but a living environment. Possible entry routes for resistant bacteria in a shed include live vectors such as newly introduced animals, mice, flies or birds as well as non-live vectors like feed, water, dust or equipment.

How has your work at the BfR changed since you found carbapenemase-producing enterobacteria in samples from livestock?

This finding had a wide range of consequences. Above all, we strengthened our targeted investigation activities. Since 2014, bacterial isolates from livestock and food have been routinely tested for carbapenem resistance within the framework of resistance monitoring at the BfR. In addition, we have also been able to draw on a further targeted detection method for carbapenemase-producing bacteria since 2015. This is an area in which there is a need for training in the laboratories. Moreover, the National Reference Laboratory for Antimicrobial Resistance at the BfR is testing bacteria suspected of producing carbapenemase for the characteristic resistance genes. To this end, various methods have been established at the BfR for analysis of *E. coli* and *Salmonella*. These kinds of resistance genes have only been detected very rarely to date – the case of the gene $bla_{\text{VIM-1}}$ in livestock, and the gene $bla_{\text{NDM-1}}$ in a wild bird.

It is often the case that genes encoding resistance to carbapenems are localised together with other resistance genes on mobile genetic elements. Why is particular caution advised in these cases?

First of all, the probability for selection is higher if multiple resistance genes are on one genetic element. In other words, the use of different antibiotics can create a "selection advantage". The localisation of resistance genes on mobile genetic elements plays a key role in the transmission of resistance, because these resistance genes can be transferred to entirely different bacteria groups via horizontal gene transfer. This realisation triggered a kind of revolution. For a long time, a pathogen with all its properties was viewed as a single entity. But if resistance can be transferred back and forth between bacteria groups, then this possibly falsifies our perspective on a group. As a result, the detection methods had to be adapted accordingly and the transferability of resistance also analysed. This is further complicated by the fact that a resistance gene can become a problem on an otherwise harmless bacterium. Some bacteria, such as *E. coli* are part of the normal intestinal flora. If a bacterium of this kind possesses a resistance property, this is not dangerous in itself. But it can potentially pass this property on to a pathogen.

> **Resistance to a specific active agent can also spread even if this substance group has not been administered.**

What are the specific potential consequences of this kind of transferal of resistance properties?

If a pathogen collects multiple resistance mechanisms over time, the final result may be that there is no effective therapy at all. Doctors are already resorting to active substance groups that had long been frowned upon in human medicine. This is the case with colistin, for example. It is not well tolerated by humans, and possible side effects include damage to the kidneys or the nervous system. Colistin has played a major role in veterinary medicine for decades, above all for the treatment of gastrointestinal infections in livestock and in order to avoid the use of other active substance groups.

Does the mobility of the resistance gene also play a central role in the case of colistin?

In the meantime yes. Up to the end of 2015, scientists agreed that colistin resistance is not transferable. In other words: if this kind of resistance occurs in a pathogen in livestock, it is not automatically transferrable to a human pathogen bacterium. Then, however, the transferable *mcr-1* gene was described for the first time at the end of 2015 in China. Studies in Belgium subsequently led to the description of a further mobile gene for colistin resistance in livestock, namely *mcr-2*. This means that transmission of the resistance conferred by this gene to a human pathogen bacterium is theoretically possible. To date, however, this appears to happen only rarely.


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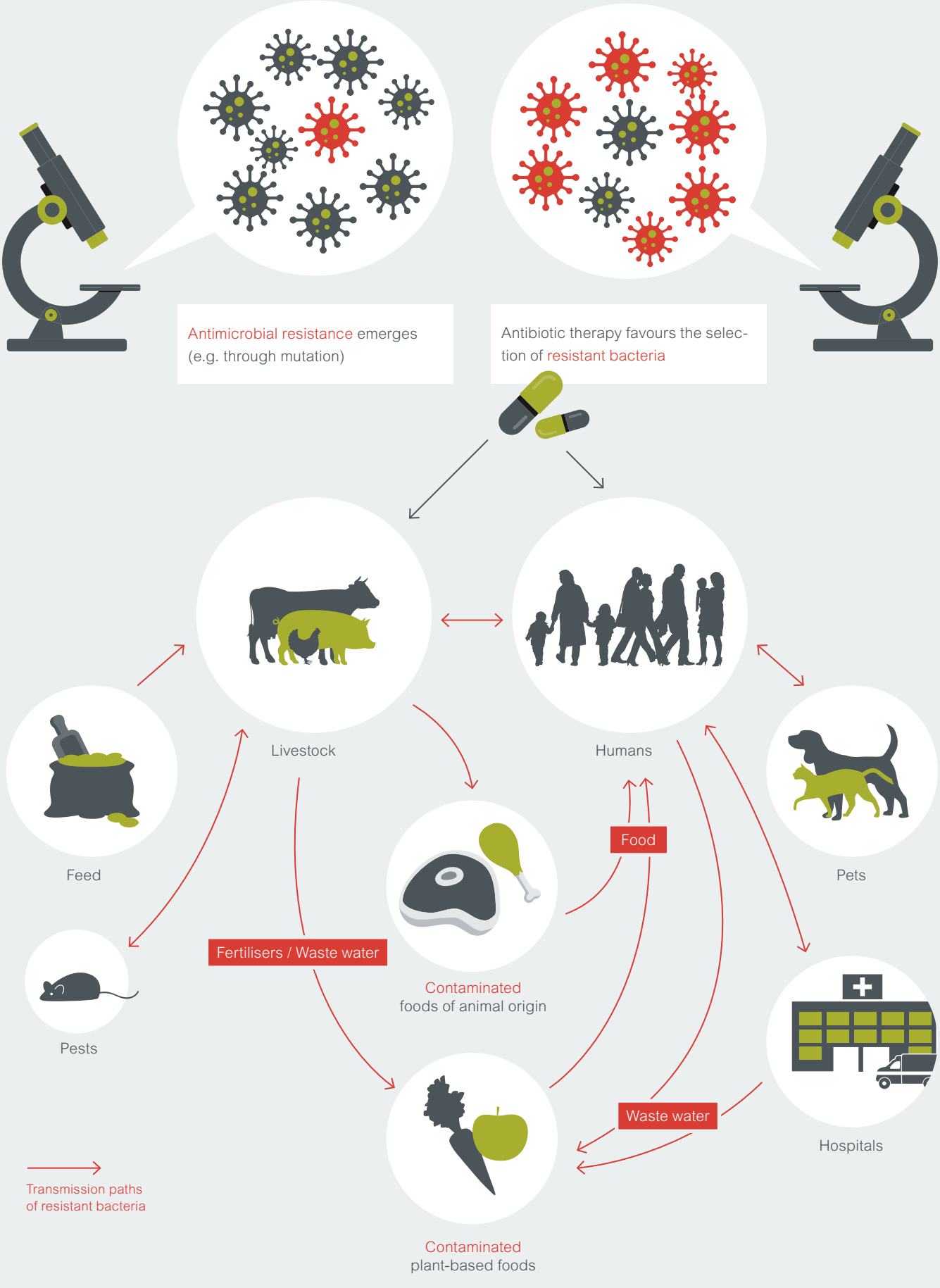
Spread of antimicrobial resistance



These insights underline the major need for more research. What do you do in the "Biological Safety" Department to assess the risk?
When it became clear in 2015 that there is a transferable colistin resistance, we naturally addressed this problem right away in our ongoing projects. In the RESET research project, for example, we analysed the existing bacterial material and the whole genome information from our cooperation partners for the occurrence of this new resistance gene. We soon realised that this gene was present in the sequences. And the analysis of colistin-resistant isolates from our strain collection confirmed that this resistance gene is already widespread.

Is it now necessary to initiate new research projects on this topic?
Yes, because there are still many unanswered questions: how often is the resistance actually transfered? What triggers this? There are also diagnostic problems. The standard method used in human medicine to test resistance does not generally cover resistance to colistin. There is a lot to do, in other words. We need to develop new diagnostic and typing techniques, expand our resistance monitoring activities, and routinely test phenotypically resistant isolates for the gene. We must then conduct a holistic assessment of the findings in order to pave the way for potential courses of action.

Which transmission paths play a role in colistin resistance for humans?
Actually, we can't say this with certainty. The Chinese working group has identified colistin resistance in both pork and humans, and this supports the hypothesis that this resistance is transmitted via foods. At the same time, what we are generally seeing is the nosocomial spread of resistant bacteria, in other words the spread of antimicrobial resistance in the hospital environment.

Resistances are spreading, the "silver bullets" are losing their effect, and we're not even safe in hospitals. Is there any effective strategy at all that can counter the spread of antimicrobial resistance? And who needs to step up?
If we are to prevent the spread of antimicrobial resistance, we need a joint strategy. At the end of the day, we are dealing with complex interrelationships between humans, animals and the environment. This is why we at the BfR advocate close cooperation with all the actors in the public health and veterinary system. This "one health approach" calls on both veterinarians and physicians to contribute their expertise. Consumers can also minimise their risk of infection with a resistant bacterium.

What do consumers need to be aware of?
They need to observe the same hygiene rules that apply to other disease pathogens that can be transmitted to humans by animals or food. People should wash their hands with hot water and soap after they have had contact with animals, for example. They should also wash their hands thoroughly after handling raw meat. Meat, eggs and raw milk must be heated prior to consumption, while raw vegetables and fruit should be washed thoroughly with drinking water or peeled before they are eaten. What is also important is to avoid direct or indirect contact between raw meat or raw eggs and ready-to-eat meals that will not be subsequently heated. By observing hygiene rules, people can prevent the transfer of resistant and / or pathogenic bacteria to other foods. ◘

More information:
Irrgang et al. 2017. Recurrent detection of VIM-1-producing *Escherichia coli* clone in German pig production. Journal of Antimicrobial Chemotherapy 72: 3, 944–946.

RESET

From 2010 to 2017, the RESET research network investigating antimicrobial resistance in animals and humans has been concerned with resistance to the particularly important antibiotic classes of β-lactam antibiotics and (fluoro-)quinolones in intestinal bacteria like *Escherichia (E.) coli*. If bacteria are resistant to both active substance classes, this dramatically restricts the range of therapeutic options. This kind of resistance has already been proven in *E. coli* and *Salmonella enterica*. The BfR is involved in the research network with two of its projects. The systematic merging of findings in the various research fields to create a joint database has made it possible to close the gaps in our knowledge and has paved the way for the assessment of risks. RESET was funded by the German Federal Ministry of Education and Research.

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