Questions and answers on ESBL and/or AmpC-producing antimicrobial resistant bacteria

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Bacteria can be resistant to certain antibiotics. When this happens with pathogenic bacteria, these antibiotics remain ineffective if they are used to treat an illness caused by the bacteria.

Important antimicrobials towards which increasing resistance has been observed include the group of aminopenicillins and cephalosporins. One of the causes of this antimicrobial resistance are enzymes designated as”extended-spectrum beta-lactamases” (ESBL) and “ampC beta-lactamases“ (AmpC). Bacteria require a certain “resistance gene” in order to produce these enzymes. This genetic property can be passed on from one bacteria generation to the next through cell division during propagation. During the lifetime of a bacterium, however, it can also be passed on from one bacteria cell to another on transmissible gene sections such as plasmids. These two cells can also belong to different bacteria types.

The use of antibiotics in humans and animals promotes the spread of ESBL and/or AmpC-producing bacteria because antimicrobial resistance means an advantage in the competition with other bacteria (types).

In recent years, there have been more and more reports about the expansive spread of ESBL and/or AmpC-producing bacteria among animals and in foods. A possible connection with human diseases is under discussion. In the following paragraphs, the BfR has compiled selected questions and answers on this subject.

What are ESBL?
ESBL stands for “extended-spectrum beta-lactamases” and designates enzymes which alter a broad spectrum of beta-lactam antibiotics, thus making them ineffective. Bacteria which produce these enzymes become insensitive (resistant) to important active substances such as aminopenicillins (e.g. ampicillin), cephalosporins (including those of the third and fourth generation) and monobactams. This resistance can be detected in various bacteria species, in particular enterobacteria which include Salmonella, Klebsiella and *Escherichia coli* among others. The genes for these enzymes lie on transmissible gene sections and can be exchanged between bacteria of the same type or of different types (horizontal gene transfer).

What are AmpC?
AmpC beta-lactamases (AmpC) are enzymes which convey resistance to penicillins, second and third generation cephalosporins and cephamycins. They also result in resistance to combinations of these antibiotics and substances which are actually intended to inhibit the effect of beta-lactamases. They do not convey resistance to fourth generation cephalosporins. The genes for these enzymes occur naturally in some bacteria species as so-called chromosomal AmpC (e.g. in *E. coli*, but not in Salmonella up to now). The enzymes are only actually formed and only become effective under certain conditions. The important thing is the increasing number of AmpC genes localised outside the chromosome on so-called plasmids, which is why they are often referred to as ”plasmidic AmpC” (pAmpC). They ensure the constant formation of the enzyme and lie on transmissible gene sections. These can be exchanged between bacteria of the same type or of different types (horizontal gene transfer).

What causes the bacteria that carry ESBLand/or AmpC and how are they spread?
To enable bacteria to produce ESBLand/or AmpC, they must carry the necessary genetic information (resistance genes). The origin of these genes is not known. As they are passed on from one bacteria generation to the next during cell division (so-called vertical transfer), the propagation and distribution of these bacteria also contribute towards the spread of the resistance genes. Poor hygiene in hospitals, animal sheds and in the home too plays a role in the carryover of the bacteria.

Because the resistance genes very often lie on transmissible gene sections, they can also be exchanged between bacteria of the same type or of different types (so-called horizontal gene transfer). The big problem here is that harmless intestinal bacteria can pass on the genes for ESBL and/or AmpC to pathogenic bacteria, such as Salmonella.

The use of antibiotics with animals and humans promotes the spread of ESBL and/or AmpC-producing bacteria and their genes because resistances to certain antibiotics results in a selective advantage over competing bacteria. The exchange of genes between the bacteria is also promoted under the selection pressure that builds up on the bacteria when antibiotics are used.

How frequently do ESBL and/or AmpC-producing bacteria occur in foods and domestic animals?
ESBL and/or AmpC-producing bacteria occur in all livestock species as well as in many animals kept as pets (dogs, cats etc). In foods, they are detected particularly often in broiler meat, but they can also occur in turkey meat, beef and pork as well as plant-based foods.

In examinations on the occurrence of cephalosporin-resistant Salmonella in foods, it was shown that in particular the resistance rate to cephalosporins has increased in recent years in the Salmonella from broiler meat. Most of the bacteria detected on foods originate from agricultural livestock farming and are transmitted to the food in the course of food production (slaughtering, milking).

With isolates from animals, the highest proportion of cephalosporin-resistant *E. coli* was found in the isolates of calves that had contracted diarrhoea. In examinations of healthy animals, the proportion of cephalosporin-resistant *E. coli* was highest among broilers. The highest detection rate of 13.5% was observed in zoonosis monitoring in 2010. Cephalosporin-resistant *E. coli* was not detected as often in turkeys.

Tests using selective methods with which cephalosporin-resistant bacteria are looked for specifically have shown that germs of this kind are very widely spread and can be detected in the vast majority of cattle, pig and broiler farming businesses. Most of the animals in businesses of this kind carry these resistant bacteria too, but in small quantities.

Details of the spread of ESBL and/or AmpC-producing cacteria can be found in the BfR Opinion “ESBL-forming bacteria in foods and their transfer to humans”:
http://www.bfr.bund.de/cm/349/esbl-forming-bacteria-in-foods-and-their-potential-transfer-to-humans.pdf

How significant is the detection of ESBL and/or AmpC-producing bacteria in domestic animals and food?
The occurrence of ESBL and/or AmpC-producing bacteria in domestic animals and in food is significant for several reasons. On the one hand, the resistant bacteria can find their way to the consumer via food (e.g. meat). As some of these bacteria are pathogenic (e.g. Salmonella), the possibility exists of resistant pathogenic bacteria being transferred to humans via food.

A second important aspect is the possibility of giving additional antimicrobial resistance genes to other bacteria that are already pathogenic for humans. This method of exchanging genetic properties among bacteria is referred to as horizontal gene transfer.

To what extent ESBL and/or AmpC-producing bacteria from livestock and food contribute to the occurrence of infections with ESBL and/or AmpC-producing bacteria in human medicine cannot currently be quantified with certainty. However, it is regarded as certain that this transfer takes place. Current studies prove that the same ESBL genes can often be detected with *E. coli* isolates from livestock, pets and humans. In most cases, however, these genes are localised on various *E. coli* isolates which once again emphasises the significance of horizontal gene transfer.

Which routes of infection are of significance to humans?
The risk of infection via food depends among other things on the quantity of pathogens in the food. Contributing factors to the quantity of pathogens are the extent to which the germ is transferred from the animal to the food during food production and whether or not the pathogen can propagate in the food. The hygienic conditions under which foods are prepared are also important as resistant bacteria can also be transferred from one food to another during preparation.

ESBL and/or AmpC-producing bacteria can also be transferred to people who work in livestock farming businesses by way of direct contact and through them into healthcare facilities, for example. Direct contact with pets such as dogs and cats can also lead to an exchange of germs between humans and animals. It has been known for quite some time that an exchange of germs takes place to a considerable extent between domestic animals and the people who handle them. This also applies to germ flora in the gastro-intestinal tract.

As humans can also be carriers of these bacteria, transfer from person to person is possible. This occurs particularly in hospitals and other healthcare facilities. Research is currently being conducted to establish the extent to which the various routes of infection are responsible for cases of human illness. The results currently available indicate that the transfer routes are complex.

How frequently do human infections with ESBL and/or AmpC-producing bacteria occur?
In recent years, various studies have been conducted on the occurrence of ESBL and/or AmpC-producing bacteria in humans. It is being observed more and more often that ESBL-producing bacteria play a major role in healthcare facilities as the pathogen that causes so-called nosocomial, or hospital-acquired, infections. However, most of the bacteria that produce ESBL are harmless intestinal inhabitants (“commensals”) which do not cause any disease and go unnoticed for this reason. A study conducted in southern Germany showed that approx. 5 % of the healthy general public are inhabited by bacteria of this kind.

It is not yet known how often contact or colonisation with ESBL and/or AmpC-producing bacteria results in illness in humans, nor is it known to what extent the resistance per se influences the course of the disease. It is known though that if a person is ill, treatment is more difficult. Third and fourth generation cephalosporins are among the most important active substances in the treatment of infections of this kind in humans. ESBL-forming bacteria are resistant to this group of substances, which means that they have no effect.

Does contact with ESBL and/or AmpC-producing bacteria always result in illness?
In most cases, people will not notice colonisation with ESBL and/or AmpC-producing bacteria because most of these bacteria are harmless intestinal inhabitants. Among the ESBL and/or AmpC-producing bacteria, however, there are types, e.g. Salmonella, Klebsiella and enterohaemorrhagic *Escherichia coli* (EHEC), which can cause disease in humans. Several of these bacteria result in illness, especially among risk groups, such as infants, pregnant women, the elderly and people with a weakened immune system. If these illnesses have to be treated with antibiotics, the success of the treatment can be impaired due to the resistance of the pathogens. The illness can last for longer and be more severe, thus making hospitalisation necessary and increasing the risk of permanent health damage. In the worst cases, the illness can be fatal.

Can consumers recognise whether a food is contaminated with ESBL and/or AmpC-producing bacteria?
Consumers cannot recognise contamination of this kind. Only by means of specific laboratory tests can it be established whether foods are contaminated with ESBL and/or AmpC-producing bacteria.

How can the occurrence of ESBL and/or AmpC-producing bacteria in German broiler stocks be explained considering the fact that the corresponding antibiotics (3rd and 4th generation cephalosporins) are not authorised for poultry in Germany?
ESBL and/or AmpC-forming bacteria can make their way into poultry flocks in several ways, each of which has to be checked separately from one another. There is no fundamental difference between ESBL and/or AmpC-producing bacteria and other bacteria (e.g. Salmonella). This means that it is possible for the chicks to have acquired the pathogen in the hatchery so that they already carry the bacteria when they are released into the production area.

It is also possible for staff members, as well as animate and inanimate vectors (e.g. rodents, tools) to carry the bacteria into the flocks. The bacteria could also have been carried over from other livestock populations. Once ESBL and/or AmpC-producing bacteria are established in a population, they do not only benefit from the use of 3rd and 4th generation cephalosporins but also from other antimicrobials, in particular beta-lactam antibiotics, which means that the use of cephalosporins is not necessarily the prerequisite for the occurrence of these specific bacteria.

What can consumers do to protect themselves from infections with ESBL and/or AmpC-producing bacteria?
Consumers can considerably reduce the risk of colonisation or infection with the ESBL and/or AmpC-producing bacteria present on the meat by carefully observing the rules of kitchen hygiene. The still frequent occurrence of infections with Salmonella and Campylobacter indicates, however, that the transfer of these bacteria to humans is also to be expected.

To protect themselves against ESBL and/or AmpC-producing bacteria, consumers should observe the same hygiene rules that apply to other pathogens that can be transmitted to humans from animals or food, which include:

- Wash hands with warm water and soap after every contact with animals, including household pets.
- Cook foods thoroughly before eating them, especially meat and eggs.
- Thoroughly wash raw foods, such as lettuce, sprouts, vegetables and fruit, with drinking water prior to consumption and peel fruit and vegetables.
- Avoid the direct or indirect contact of raw meat and raw eggs with raw vegetables and ready-to-eat foods which are not to be subsequently heated. Ensure strict compliance with the relevant hygiene rules for the storage and preparation of foods in order to keep the bacteria count as low as possible.

The BfR has published consumer tips on this "Protection against food infections in private households" (available in German).
http://www.bfr.bund.de/cm/350/verbrauchertipps_schutz_vor_lebensmittelinfektionen_im_privathaushalt.pdf

What measures does the BfR recommend to prevent antimicrobial resistance?
To prevent the development and spread of antimicrobial resistance, including ESBL and/or AmpC-producing bacteria, the use of antibiotics in human and veterinary medicine should be kept to an absolute minimum in the opinion of the BfR. To this end, measures have to be taken which serve the preservation of the animals' health, thus dispensing with the necessity for treatment with antibiotics. Improved management of businesses, hygiene measures to prevent the introduction and spread of pathogens, and measures to improve the state of health through better husbandry and feeding, as well as vaccination against common diseases are regarded as important measures. In addition to this, it should be ensured that resistant pathogens are not released into the environment where they can be transmitted to consumers in various ways.

What measures have been taken to minimise the occurrence of ESBL and/or AmpC-producing bacteria in agricultural businesses?
The use of antibiotics in veterinary medicine is regulated in the German Drug Act (AMG) and other regulations based on this law which were revised in 2013. The new regulations stipulate that the use of antibiotics with production animals has to be recorded and reported to a national database, thus enabling a comparison of treatment frequencies. Businesses in which antibiotics are used above the average level must take effective measures to reduce use.

In addition to this, the Federal Chamber of Veterinarians has prepared "Guidelines for the safe use of antimicrobially effective veterinary medicines" which are intended to help veterinarians to use antimicrobial substances properly (available in German).
http://www.bundestieraerztekammer.de/downloads/btk/antibiotika/Antibiotika-Leitlinien.pdf

Apart from using antimicrobially effective veterinary medicines in a responsible manner, what can livestock farmers do to minimise the occurrence of ESBL and AmpC-producing bacteria on their premises?
The occurrence of ESBL and/or AmpC-producing bacteria in livestock farming is determined by the carryover of the bacteria into populations and the spread of these bacteria within the population. It has to be assumed that the selection pressure in the direction of resistant pathogens can be reduced through the restricted use of antimicrobially effective veterinary medicines. In addition to this, control of the animals prior to confining them to closed stalls, thorough cleaning and disinfection between fattening cycles and the prevention of the infiltration

of the bacteria from the vicinity of the sheds and stalls (e.g. from neighbouring sheds and stalls) are also helpful.

What is the German Antimicrobial Resistance Strategy?
In November 2008, the federal ministries of Health, Food, Agriculture, Education and Research presented a common strategy to contain antimicrobial resistance (Deutsche Antibiotika Resistenzstrategie, DART – available in German):
http://www.bmelv.de/SharedDocs/Downloads/Broschueren/DART.pdf?__blob=publicationFile

Within the scope of DART, additional measures to contain antimicrobial resistance were identified. These included:

- The recording of the quantities of antibiotics issued and consumed
- The expansion of resistance monitoring, including the conducting of standardised resistance determination and the monitoring of the effectiveness of antibiotics.

These measures are accompanied by research in the course of which the microbiological and molecular biological relationships of resistance formation are to be investigated. Resistance testing is to be standardised and alternatives to the administration of antibiotics identified.

The results of these studies are published at regular intervals. Accordingly, the BfR reports on the examination results of the National Reference Laboratory for Antimicrobial Resistance at the BfR on its homepage and to the European Food Safety Authority (EFSA).

How does the European Food Safety Authority (EFSA) assess ESBL and/or AmpC-producing bacteria?
Studies conducted by the European Food Safety Authority (EFSA) show that ESBL and/or AmpC-producing bacteria were detected in animals and in foods in several European countries. In its latest EFSA report on antimicrobial resistance, special attention is placed on the resistance of intestinal bacteria to third and fourth generation cephalosporins.
http://www.efsa.europa.eu/en/efsajournal/doc/2154.pdf

In its “Scientific opinion on the public health risks of bacterial strains producing extended-spectrum β-lactamases and/or AmpC β-lactamases in food and food-producing animals” http://www.efsa.europa.eu/de/efsajournal/pub/2322.htm, the EFSA recommends that the use of antibiotics with food-producing animals be reduced within the European Union (EU) in order to reduce the risk to public health that emanates from resistances in the food chain. According to the EFSA, an effective measure would be to restrict or completely stop the use of cephalosporins with food-producing animals.

How does the European Commission deal with the topic of ESBL and/or AmpC-producing bacteria?
The monitoring of the resistance situation of zoonosis pathogens in cattle, pigs and poultry, as well as foods made from them, has been obligatory throughout the EU since 2003. This legislation was extended in 2013 by prescribing that commensal bacteria now have to be included in resistance monitoring too. Since 2014, the isolates have been examined more and more for resistances to cephalosporins and carbapenems and suspect isolates have largely been characterised. From 2015, new detection methods are to be used throughout the EU in order to estimate the spread of ESBL and/or AmpC-producing bacteria. These tests will lead to better understanding and form an important basis for the introduction of countermeasures.

How does the BfR assess the risks from the occurrence of ESBL-producing bacteria in the food chain and their transmission to humans?
How significant the contribution of food, domestic animals, pets and livestock populations is as sources for the ESBL problem regarding illness in humans is currently being assessed. Even now, though, it can be derived from the available epidemiological and molecular biological findings that ESBL-producing bacteria from livestock farming and on foods constitute a risk to human health.

First analyses aimed at quantifying the significance of domestic animals as a reservoir for ESBL-producing *E. coli* in Germany show not only that the most common ESBL genes occur both in isolates of humans and animals but also that there are big differences in the proportions of ESBL-producing *E. coli* isolates of animals and humans. This supports previous findings which indicate that animals play a role as a source of bacteria of this kind and/or their resistance genes. At the same time, the studies make it clear that identical resistance genes occur in all observed domestic animal groups, which means that not only poultry plays a role as a reservoir. At present, the vast majority of cases of colonisation of humans with ESBL-producing *E. coli* cannot be explained by the vertical transfer of the bacteria with their properties via exposure through animals that deliver it through livestock farming and food. In addition to the direct transfer of the bacteria, the possibility also exists that these merely serve as a vehicle which can then transfer the resistance genes to other bacteria inside the human body. In this case, the transfer route can often not be fully understood because the infection bacteria and resistance gene have different sources. The results also substantiate that the transfer routes are complex and that the role of other reservoirs and infection sources will have to be observed in future.

In light of the wide distribution of ESBL-producing bacteria in domestic animal stocks and on foods, measures should be taken to curb this development.

Additional details can be found in BfR Opinion 002/2012 “ESBL-forming bacteria in foods and their transfer to humans”:
http://www.bfr.bund.de/cm/349/esbl-forming-bacteria-in-foods-and-their-potential-transfer-to-humans.pdf