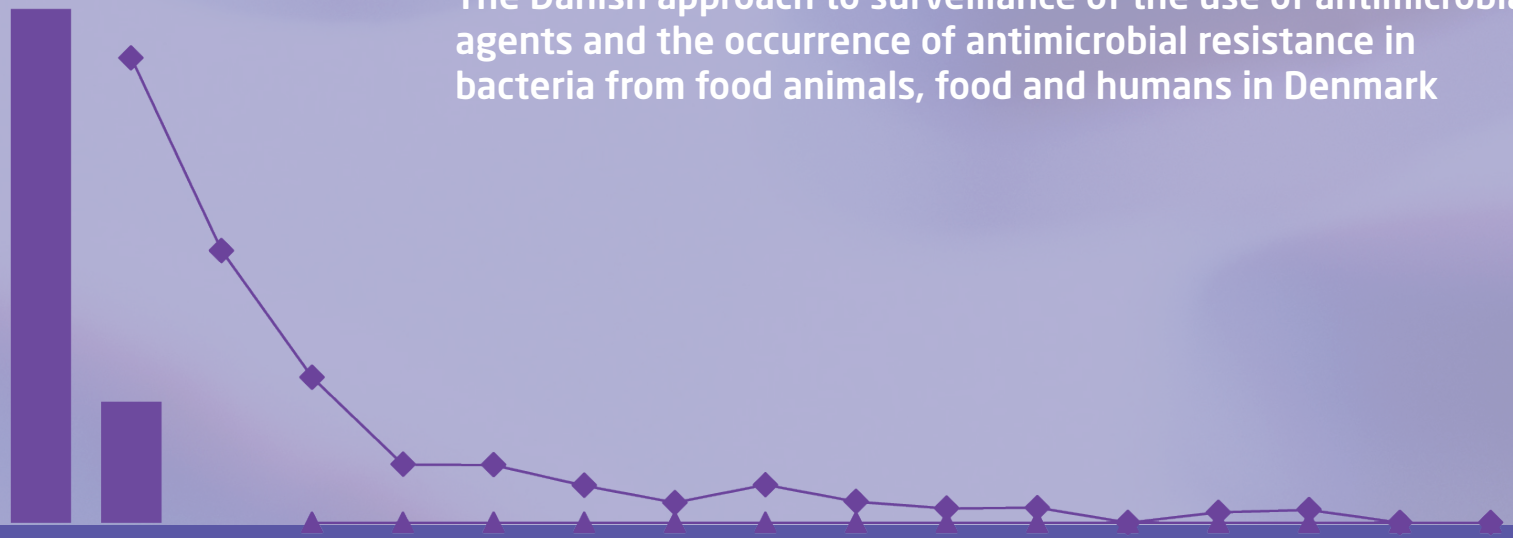
Data for action

The Danish approach to surveillance of the use of antimicrobial agents and the occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark



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Frontpage: Resistance to avoparcin in Enterococcus faecium and Enterococcus faecalis from broilers and the consumption of avoparcin in Denmark

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Integrated surveillance in the fight against antimicrobial resistance

Antimicrobial agents are essential drugs for human and animal health. Infectious diseases that a person would typically die from before 1940 are now considered relatively harmless and receive standard treatment with a good recovery in most countries.

However, we now run the risk that antimicrobial agents will become ineffective. The continuing emergence, development and spread of pathogenic organisms that are resistant to antimicrobial agents are a cause of increasing concern. Antimicrobial resistance is today a serious global public health issue that is impacted by use of antimicrobial agents for both humans and animals.

The Danish surveillance programme, DANMAP, has existed since 1995, covering the entire chain from farm to fork to sickbed. The DANMAP programme provides scientific data on the use of antimicrobial agents in animals and humans and monitors the occurrence of antimicrobial resistance in bacteria isolated from food animals, food and humans.

The success of the Danish approach is based on unique methods, where scientific data creates the basis for action and cross-sector collaboration between scientists and authorities. Other countries, including the USA, are now looking to the Danish experience, and world-leading scientists on food safety recommend adopting the Danish approach on surveillance of the consumption of antimicrobial agents and the occurrence of resistant bacteria in food animals, food and humans.

On the following pages, you can read about the Danish surveillance programme and the results we have achieved in our 15-year existence. However, we are continuously challenged by new emerging antimicrobial resistant bacteria that cross borders, and to prevent further spread of antimicrobial resistance global initiatives are needed.

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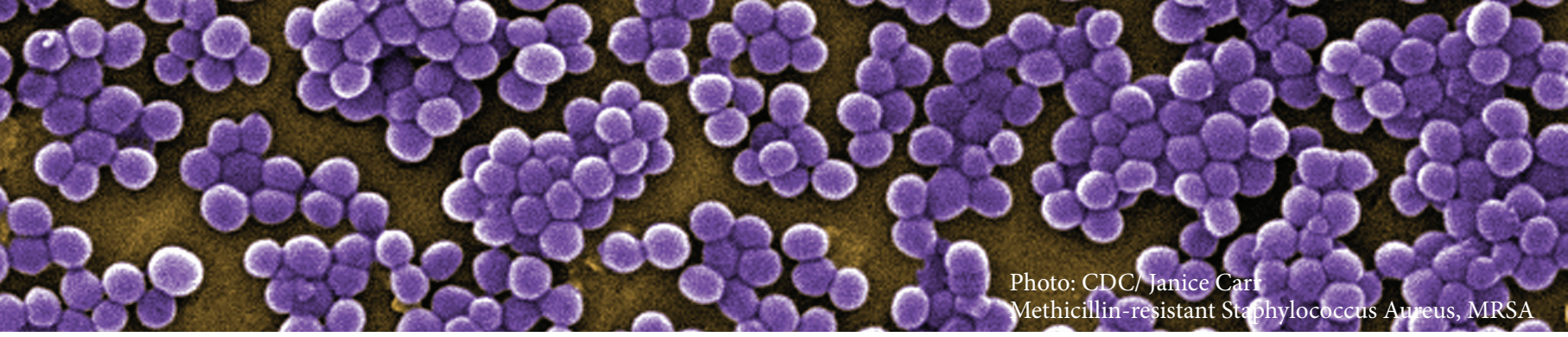


Photo: CDC/ Janice Carr
Methicillin-resistant Staphylococcus Aureus, MRSA

Facing the problem of antimicrobial resistance

The World Health Organization, WHO, has named resistance to antimicrobial agents one of the most significant threats to public health – a treat that can be combated by reducing the use of antimicrobial agents. If bacteria causing infectious diseases in humans can withstand treatment with antimicrobial agents, we are facing a dark future.

Antimicrobial resistance is considered one of the major risks to human health. The use of antimicrobial agents is the main factor for selection and spread of antimicrobial resistance, although the relationship may be complex.

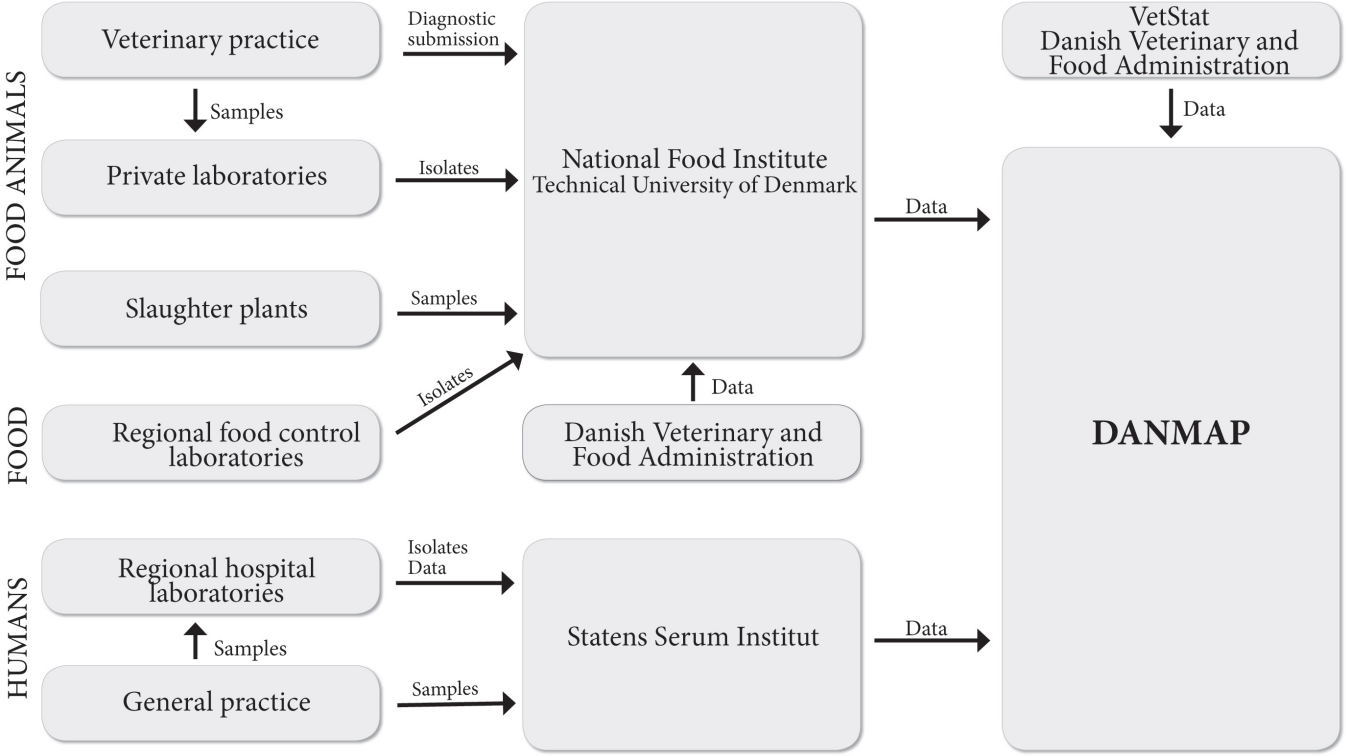
The resistance threat is a common problem of serious concern in industrialised as well as developing countries. There is now increasing awareness of the potential human health problems caused by antimicrobial resistance originating in food-producing animals, as well as problems due to the transmission of resistant bacteria between patients. Resistant bacteria spread across borders via trade and travel and antimicrobial resistance is therefore a global problem.

Use of antimicrobial agents creating resistance

In order to limit the development and global emergence of resistant bacteria, it is important to monitor trends and

Organisation of DANMAP

DANMAP, the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme, collects data from a variety of sources and is part of cross-sector collaboration between scientists and authorities where risk assessment and risk management are separated.



to identify the microbial and epidemiological risk factors contributing to the emergence and spread of antimicrobial resistance, as well as their interactions. Animal and human consumption of antimicrobial agents selects for antimicrobial resistant bacteria that can spread to humans through the food production chain. An integrated approach that takes this into account is therefore needed.

When bacteria are exposed to antimicrobial agents they can develop resistance either by mutation or by taking up resistance genes from other bacteria. Resistant bacteria from animals can be transferred to humans either through direct contact or consumption of meat or animal products. Resistant bacteria can also be transmitted between patients. Antimicrobial treatment failure may occur if the resistant bacteria are causing infections, or if resistance mechanisms are transferred to other pathogenic bacteria.

Global solutions needed

Resistant bacteria can spread through many routes – from animal to animal, between animals and humans, between humans and through the environment. The modern way of life also includes travelling around the world, importing food and livestock from other countries and continents – and the resistant bacteria are travelling along.

Therefore, antimicrobial resistance calls for global solutions.

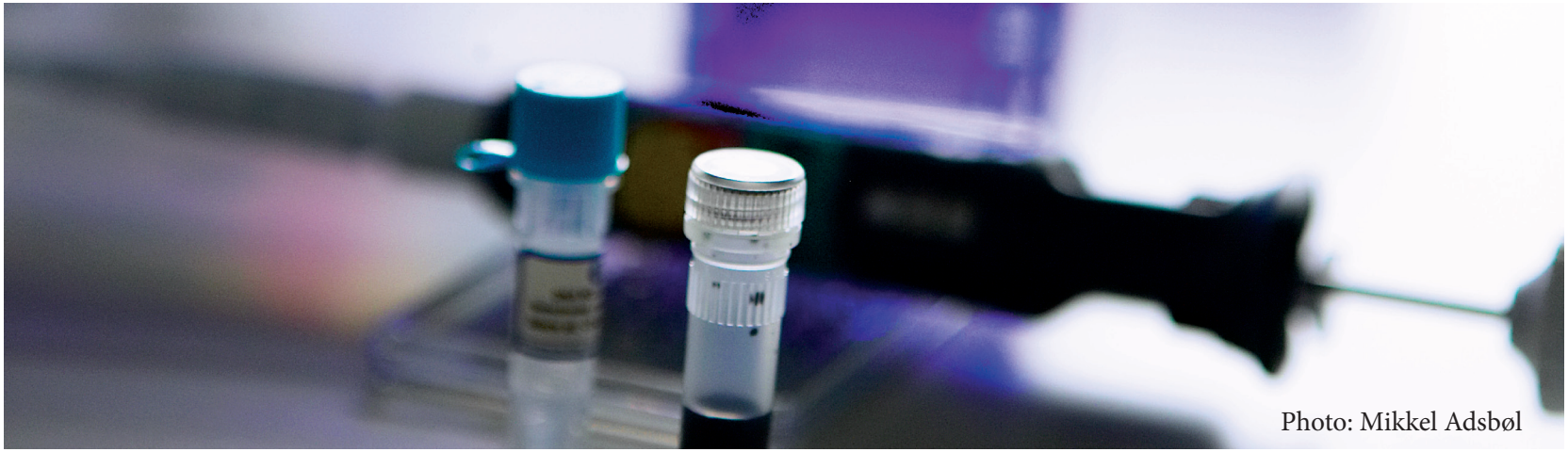
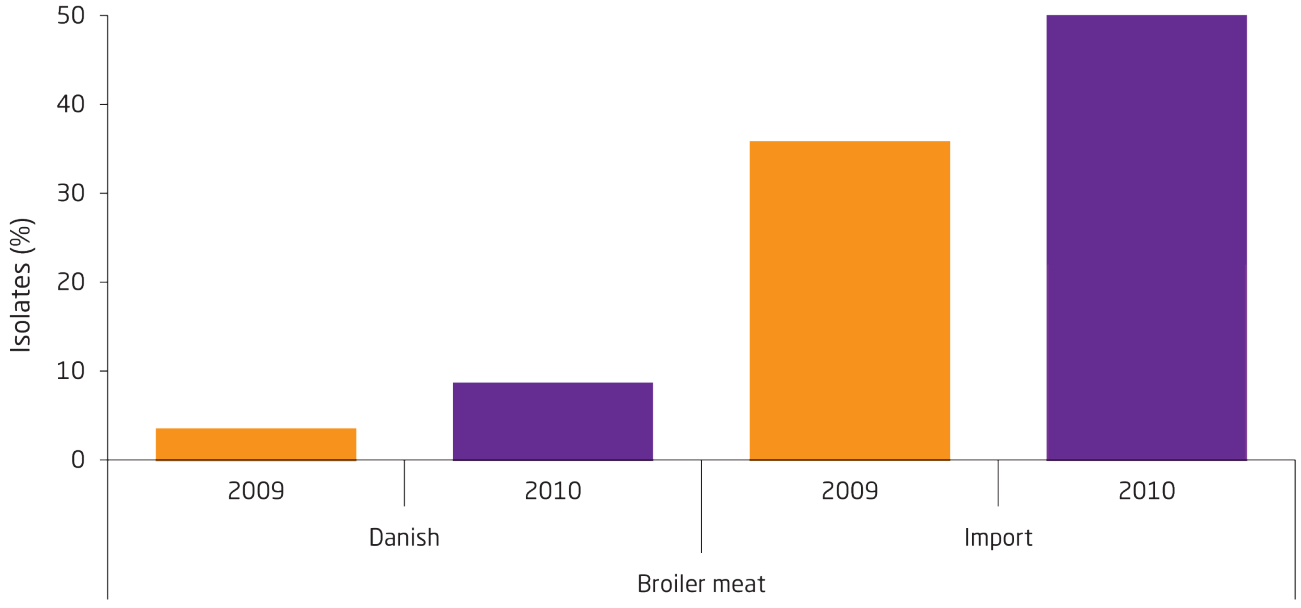


Photo: Mikkel Adsbøl

Occurrence of ESBL E. coli in broiler meat

During the past decade, the Danish surveillance programme, DANMAP, has reported a much higher level of resistance in bacteria like ESBL E. coli from imported meat than from domestically produced meat. This type of resistance seems to be related to food producing animals and may spread to humans via food.



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The Danish approach – DANMAP

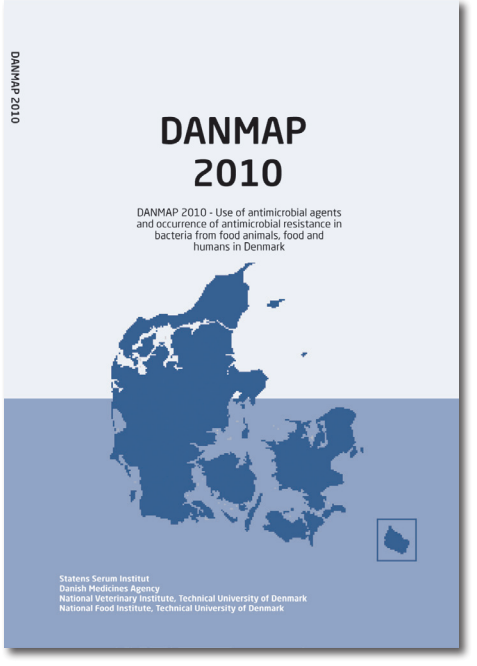
Since 1995, Denmark has maintained an integrated, cross-sector surveillance of the consumption of antimicrobial agents and occurrence of resistant bacteria in food animals, food and humans, named DANMAP, to safeguard human health.

In the 1990s, Danish scientists discovered a link between antimicrobial agents used as growth promoters in food animals, and resistance. They documented that the routine consumption of antimicrobial agents as growth promoters in animals lead to high occurrence of bacteria resistant to important antimicrobial agents used for human therapy in the animals. This was achieved by a systematic approach generating data determining the magnitude of current or potential future public health hazards from nonhuman use of antimicrobial agents. As a consequence, Danish authorities banned the use of the antimicrobial growth promoter avoparcin and established a national surveillance programme.

An increasing part of human infectious diseases originate from animals due to bacteria and viruses transferred from animals or food, for example Salmonellosis. Preventing such diseases thus requires cross-sector collaboration and surveillance.

National, cross-sector surveillance

The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme, DANMAP, was established in 1995 on the initiative of the Danish Ministry of Health and



the Danish Ministry of Food, Agriculture and Fisheries as a coordinated national surveillance and research programme for antimicrobial consumption and antimicrobial resistance in bacteria from food animals, food and humans. Denmark was the first country to establish such a systematic and continuous integrated monitoring programme. Similar surveillance programmes are now established in other countries as well.

To safeguard human health, DANMAP monitors the use of antimicrobial agents and the occurrence of antimicrobial resistance and studies the association between consumption of antimicrobial agents and resistance.

The programme participants are the National Food Institute and the National Veterinary Institute, both at Technical University of Denmark and Statens Serum Institut (SSI). The DANMAP programme is funded jointly by the Ministry of Health, the Ministry of Science, Innovation and Higher Education, and the Ministry of Food, Agriculture and Fisheries.

Part of the DANMAP data on veterinary use of antimicrobial agents derives from an IT monitoring programme called VetStat, which was initiated in 2000 by the Danish Government. VetStat collects data on prescribed medicine used in animals.

Separation of risk assessment and risk management

The strength of the integrated programme derives from collaboration between microbiologists, physicians, veterinarians and epidemiologists, offering a broad range of cross-sectorial expertise. The sampling involves, among others, veterinary practices, slaughterhouses, regional food control laboratories and hospitals. Furthermore, relevant stakeholders have access to all relevant data from animals, food, and humans.

Photo: Mikkel Adsbøl

The objectives of DANMAP are:

- to monitor food animal and human consumption of antimicrobial agents
- to monitor the occurrence of antimicrobial resistance in bacteria isolated from food animals, food and humans
- to study associations between antimicrobial consumption and antimicrobial resistance
- to identify routes of transmission and areas for further research studies.

Another characteristic of the Danish approach is that the surveillance and assessment of risks are separated from the handling of the potential risk. In Denmark, scientists are assessing the risk while the authorities, such as the Danish Veterinary and Food Administration and the Danish National Board of Health are conducting the risk management.

Since 1997, the results covering the three reservoirs food animals, food, and humans have been published in annual reports. The monitoring of antimicrobial resistance is based on three categories of bacteria: Human and animal pathogens, zoonotic bacteria, i.e. bacteria transferred from animals to humans, and indicator bacteria.

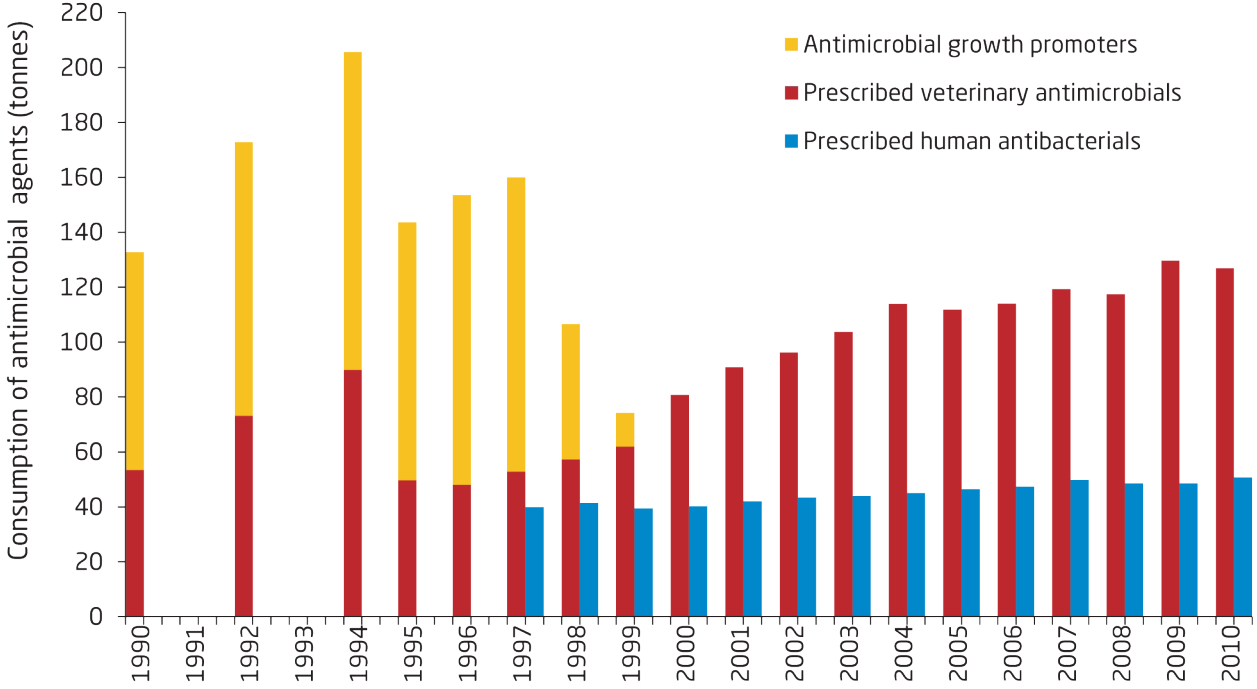
Human and animal pathogens are included because they cause infections and primarily reflect resistance caused by the use of antimicrobial agents in the respective reservoirs.

Zoonotic bacteria are included because they can develop resistance in the animal reservoir, which may subsequently compromise treatment effect when causing infection in humans.

Indicator bacteria (Enterococci and E. coli) are included due to their ubiquitous nature in animals, food and humans, and their ability to readily develop or transfer antimicrobial resistance in response to selective pressure in both reservoirs.

Consumption of antimicrobial agents in animals and humans

The first integrated surveillance report of consumption of antimicrobial agents in Denmark was published in 1996. In 1994, the consumption of antimicrobial growth promoters constituted more than half of the total antimicrobial consumption by animals in Denmark. The consumption of antimicrobial agents in animal production is approximately double the size of that of for humans. The total amount of antimicrobial agents used in animal production decreased in 2010, while the amount of prescribed human antimicrobial agents was the highest in the 15 years the Danish surveillance programme has existed.



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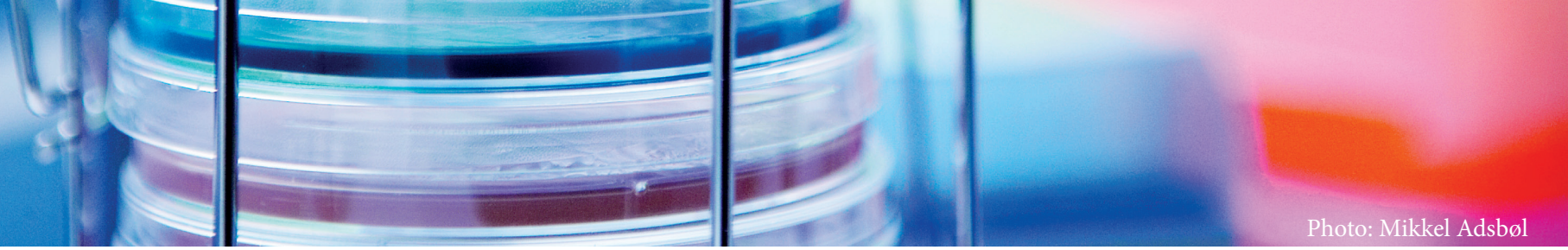


Photo: Mikkel Adsbøl

Results from 15 years of Danish surveillance

Results from the DANMAP programme have helped Danish authorities reduce antimicrobial resistance. In Denmark, based on solid scientific data from DANMAP, the spread of resistant bacteria in food animals, food and humans has been reduced by limiting the use of antimicrobial agents for animals and humans.

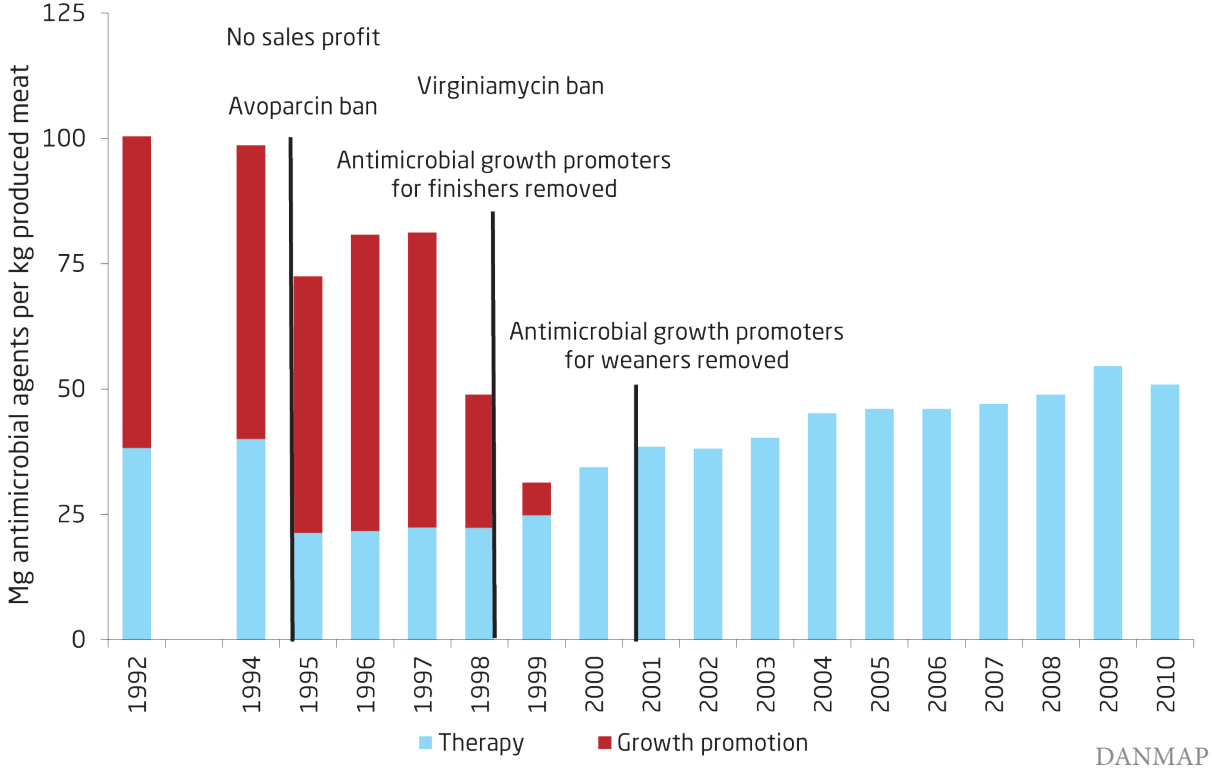
For several decades, antimicrobial agents were used as a feed additive for growth promotion in food animals and no one suspected it would create severe problems later on. In 1993, however, the first report of a nonhuman reservoir of bacteria resistant to the antimicrobial agent vancomycin, a vancomycin-resistant Enterococcus, was published in the United Kingdom. In humans, Enterococci can cause serious hospital infections with a high mortality.

Reports from other European countries in 1994 indicated problems treating patients with infectious diseases due to resistant bacteria. By 1995, vancomycin-resistant Enterococci had been found in animals, humans and sewage in Germany. For the first time, scientists suspected resistance in human pathogens to originate from bacteria transferred from food animals.

In 1994, the consumption of antimicrobial growth promoters constituted more than half of the total antimicrobial consumption by animals in Denmark, the total consumption at

Ban of growth promoters in general reduces use of antibiotics in animal production

Soon after the antimicrobial agents became commercially available, they were used in animal production, not only to treat animals with infections but also as growth promoters. Adding a low dose of antimicrobial agents to the feed made the animals grow faster. In 1995, Denmark banned the use of the antimicrobial growth promoter avoparcin. At the same time, another ban prohibited veterinarians from profiting from selling antibiotics. Five years after, all use of antimicrobial growth promoters was banned in Denmark.



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that time being 206 tons. Growth promoters were used on virtually all broiler chicken and pig farms in Denmark, leading to a high level of resistance to bacteria from food animals.

Scientific evidence led to ban of growth promoters

Danish scientists documented that routine consumption of antimicrobial growth promoters in animals led to resistant bacteria and problems in treating human infectious diseases. In 1995, the Danish Minister of Agriculture and Fisheries imposed a national ban on the use of the antimicrobial growth promoter avoparcin. Despite the ban, the total use of growth promoters increased until the Danish pig and poultry producers voluntarily stopped using all antimicrobial growth promoters in finisher pigs and broiler chickens in 1998.

DANMAP measured and documented the effect of the avoparcin ban, and data showed that the ban had a substantial effect on lowering the occurrence of resistant Enterococci from broiler chickens. The data from DANMAP provided the evidence that led to the EU ban of avoparcin in 1997. As the first country, Denmark banned all antimicrobial growth promoters for animal feed additives in 2000 on a scientific basis. The final step towards terminating the use of antimicrobial agents for growth promotion in the entire EU was taken in 2002 during the Danish EU presidency. The EU Council decided that all use of antimicrobial growth promoters should be terminated starting in 2006.

Critically important antimicrobial agents in focus

Today, the focus has changed from antimicrobial growth promoters to antimicrobials critical for human therapy. In 2007, World Health Organization identified a number of different types of antimicrobial agents critically important for treatment of serious infections in humans. Fluoroquinolones, cephalosporins and macrolides are among the most critically important antimicrobial agents.

Results from DANMAP showed an increase of 230% in the consumption of fluoroquinolones in hospitals from 2001 to 2007, resulting in increased resistance to E. coli from bloodstream infections.

In 2000, DANMAP reported an increase in macrolide resistance of Streptococcus pneumoniae in humans from 0% in 1990 to 3.4% in 1999. Streptococcus pneumoniae is a pathogen causing pneumonia. This increase was related to a relatively high consumption of macrolides in human therapy. These results showed that even if the consumption of an antimicrobial agent generally is low, a small temporary rise in consumption can shift this balance in an unfavourable direction. Today, the level of resistance is approximately 4%, which is similar to the other Nordic countries, but much lower than that reported from other European countries.

During the 1990s, DANMAP reported an increase in the consumption of fluoroquinolones for animal production. In 2002, Danish regulation restricted the use of fluoroquinolones in animal production, and consumption was reduced by 84% from 2001 to 2005.

Farmers stopped using cephalosporins

Pig production accounts for about 80% of the total veterinary consumption of antimicrobial agents in Denmark, and the consumption of antimicrobial agents in pigs thus primarily determines the overall development in consumption. From 2002 to 2004, antimicrobial use increased by 27% in pig production. To reduce the use of the critically important antimicrobial agents, fluoroquinolones and cephalosporins, new guidelines for pig production were introduced by the Danish Veterinary and Food Administration in 2005. DANMAP documented that the consumption continued to increase, also the use of cephalosporins.

In 2010, the guidelines were therefore supplemented by the so-called 'yellow card'. The farmers and the veterinarians that have the highest consumption of antimicrobial agents get a 'yellow card'. The farmers and the veterinarians must together develop a plan for reducing the consumption of antimicrobial agents. DANMAP has documented that consumption of antimicrobials for pig production has been reduced significantly after the introduction of the 'yellow card'.

In June 2010, the Danish Meat Association launched a voluntary programme discontinuing the use of cephalosporin for a two-year period in pigs. As a result, cephalosporin consumption saw a 50% reduction from 2009 to 2010.

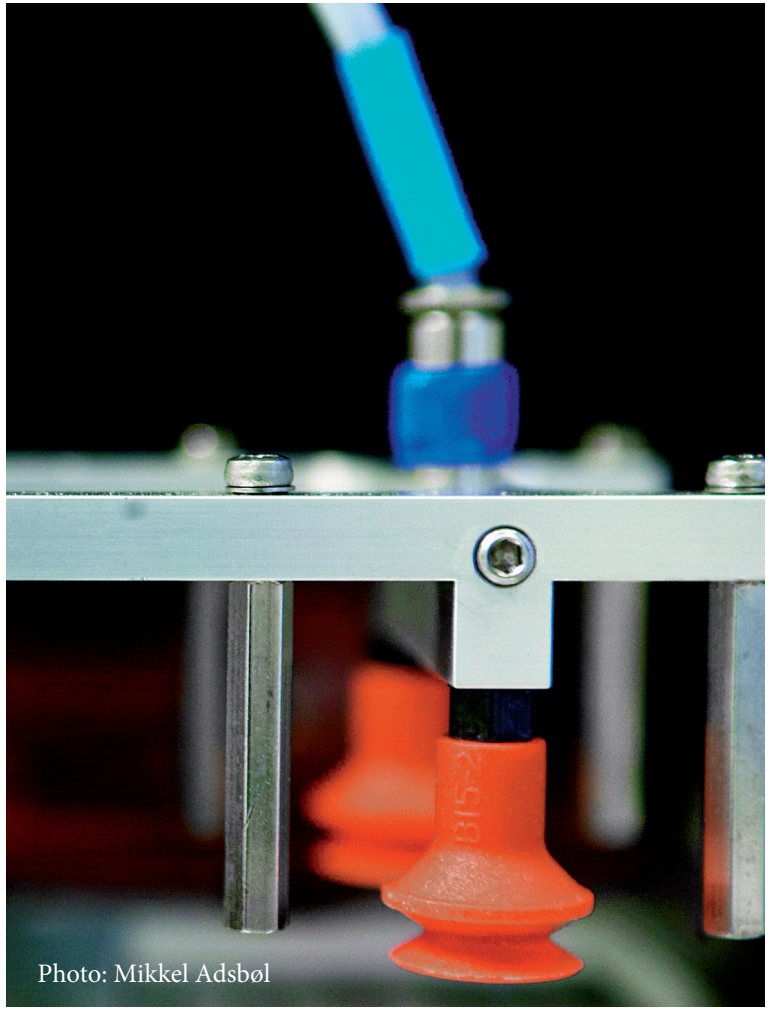
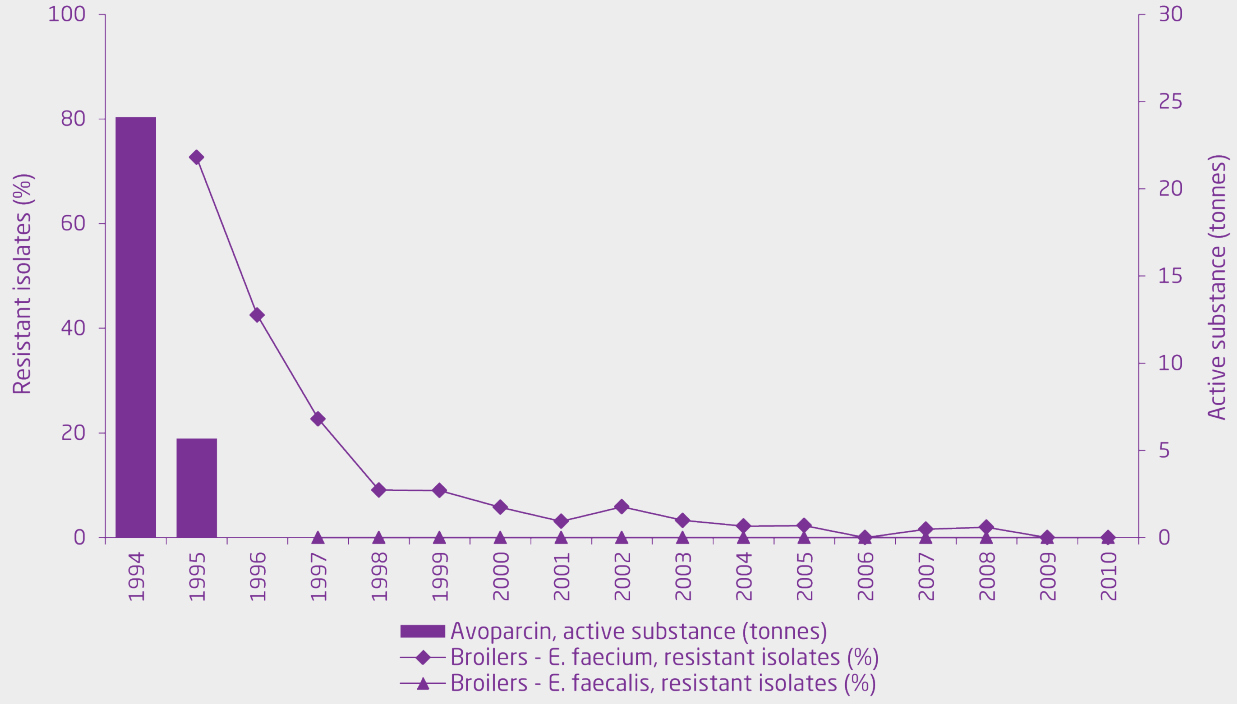


Photo: Mikkel Adsbøl

Resistance to avoparcin decreases after ban

In 1995, Denmark banned the use of the antimicrobial growth promoter avoparcin. Results from DANMAP show that the ban had a substantial effect on lowering the occurrence of resistance to avoparcin in broilers.



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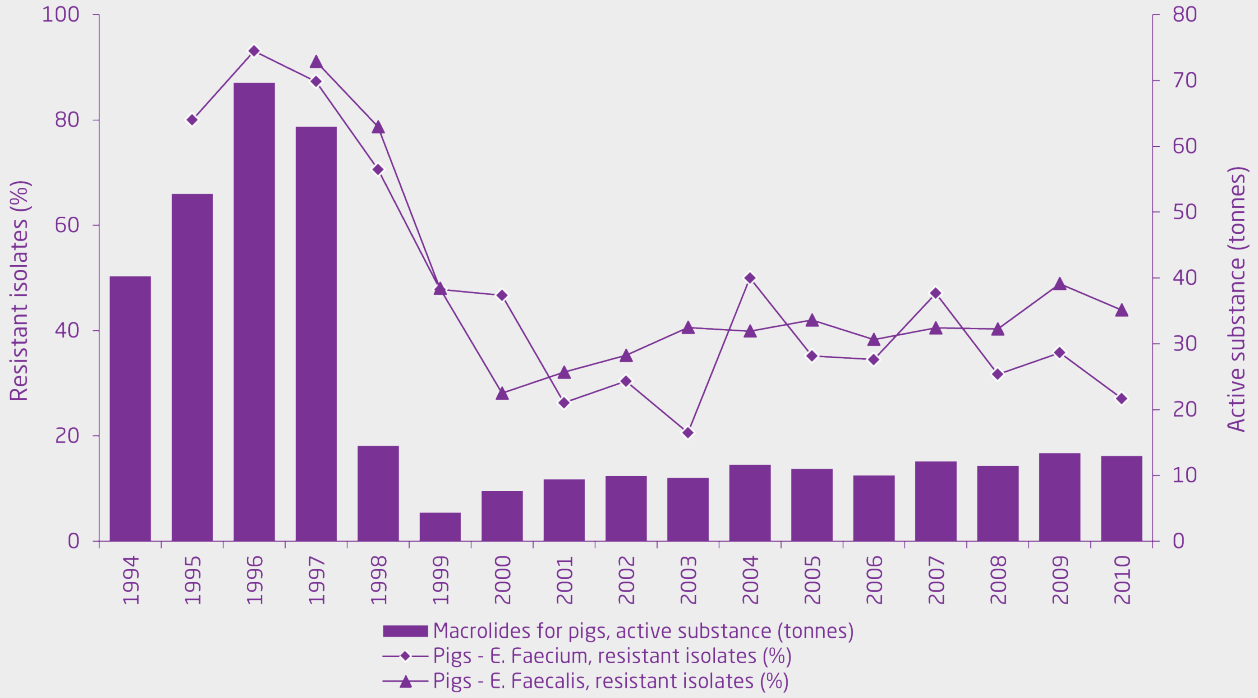
Resistance to erythromycin follows the consumption

Macrolides are one group of antimicrobial agents that the World Health Organization has indicated as critically important antimicrobial agents for human therapy. The consumption of macrolides in pigs has decreased over the past 15 years, but it is still used. The resistance to one of the macrolides, erythromycin, has followed the decrease in the total consumption of macrolides, showing an association between consumption and resistance.



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A new era in the fight against antimicrobial resistance

The fight against antimicrobial resistance is far from over. New multiresistant bacteria are spreading, threatening public health. Meanwhile, DANMAP is heading in new directions, testing new technological tools in the fight against antimicrobial resistance.

One of the fastest growing antimicrobial resistance problems in the world are the so-called ESBL-producing bacteria which are multiresistant not only to penicillins, but also to the critically important antimicrobial agents, cephalosporins. Different kinds of bacteria can be ESBL-producing, e.g. E. coli, Salmonella and Klebsiella. These bacteria can cause life-threatening infections in humans and treatment options against these infections are limited. Furthermore, infections with ESBL-producing bacteria often lead to prolonged hospitalisation and convalescence and are thus associated with significant human and economic costs.

ESBL E. coli bacteria from food animals and meat

Results from DANMAP show that nearly half of the broiler meat imported to Denmark in 2010 contained ESBL E. coli bacteria. In Danish broiler meat, the prevalence was five times lower. But surprisingly more than every fourth broiler contained ESBL at slaughter despite no usage of cephalosporins in the Danish broiler production for at least ten years. DANMAP scientists are currently studying the association. The higher prevalence in imported broiler meat is probably due to a higher consumption of antimicrobial agents in the broiler production in other countries.

Also in public health care, an increase in incidences of ESBL E. coli bacteria in patients has been reported in DANMAP. The occurrence of the same type of ESBL in both animals and humans suggest that ESBL E. coli bacteria from food can cause infections in humans, but more research is needed to further investigate the human hazard in relation to the findings of ESBL-producing E. coli in meat and animals.

Reduction in use of cephalosporins can reduce resistant bacteria in hospitals

In the recent years, DANMAP has reported an increasing prevalence of ESBL-producing Klebsiella bacteria that can lead to septicemia in humans. A recent initiative at Bispebjerg Hospital in Copenhagen shows that a 76% reduction in the consumption of cephalosporins resulted in a decrease of resistant Klebsiella bacteria from 43% to 16%.

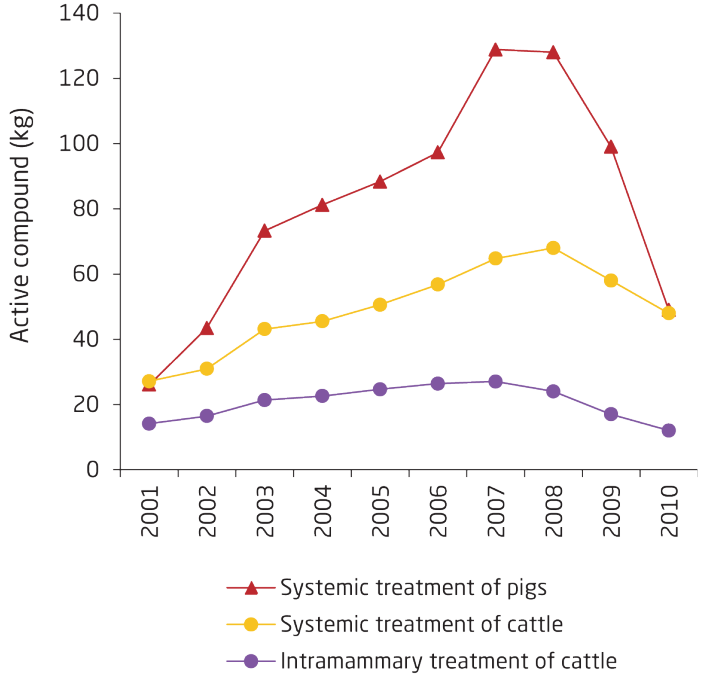
Increasing number of MRSA cases

MRSA, methicillin-resistant Staphylococcus aureus, is another emerging antimicrobial problem. Surveillance of MRSA in production animals, meat and humans has in the recent years been part of the DANMAP programme.

MRSA is a significant human pathogen that can cause a wide range of infections such as skin and soft tissue infections and bloodstream infections. MRSA is resistant to all beta-lactam antibiotics, including penicillins and cephalosporins. At hospitals, Staphylococcus aureus is the most common cause of post-surgery infections. As a response to the increasing number of cases of MRSA in humans, the Danish National Board of Health in 2006 issued new national MRSA guidelines focused on hospitals.

Farmers stopped using cephalosporins

Cephalosporins belong to the group of antimicrobial agents that the World Health Organization has indicated as critically important antimicrobial agents for human therapy. After an increase in the consumption of veterinary antimicrobial agents throughout the 2000s, the Danish authorities introduced the so-called "yellow card" to reduce the consumption in animal production. In mid-2010, the Danish farmers voluntarily stopped using cephalosporins in the pig production.



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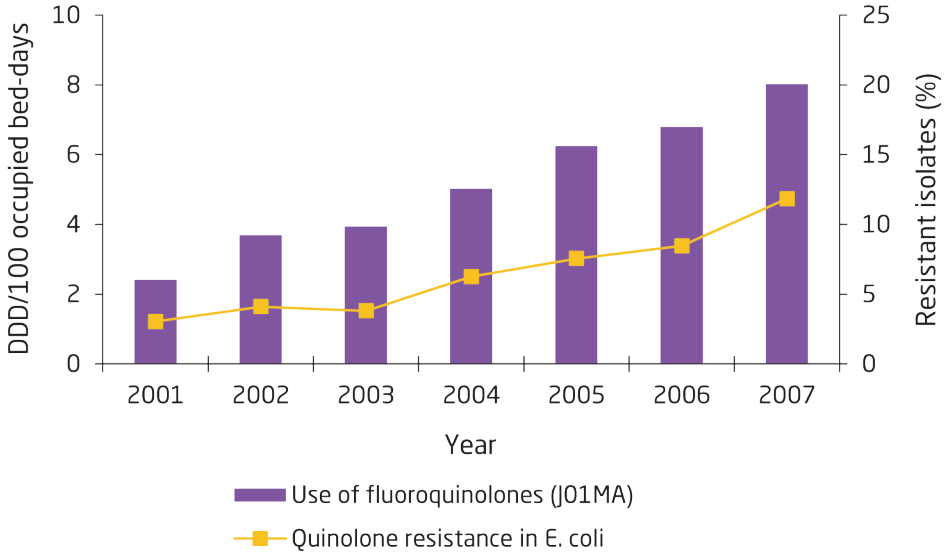
Resistance to fluoroquinolones in humans is increasing

DANMAP results showed an increase of 230% in the consumption of fluoroquinolones from 2001 to 2007 in humans, resulting in increased resistance in E. coli from bloodstream infections. Fluoroquinolones belong to the group of antimicrobial agents that the World Health Organization has indicated as critically important antimicrobial agents for human therapy.



DDD is the Defined Daily Dose, indicating the assumed average maintenance dose per day in adults.

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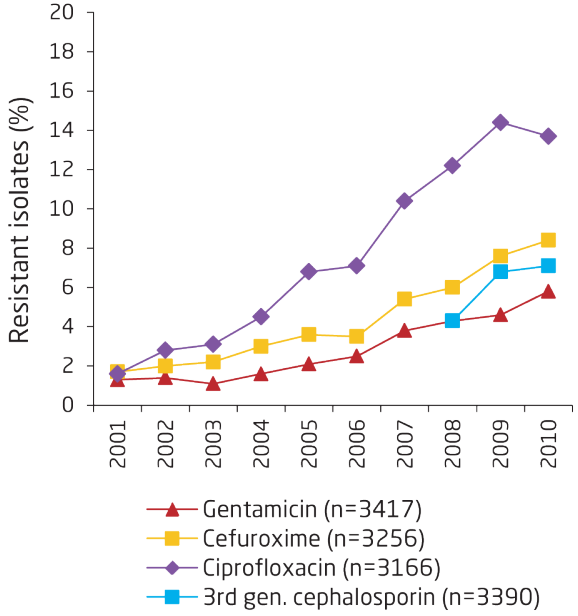
Increasing resistance in E. coli from human blood

Over the past decade, resistance to a variety of antimicrobial agents in E. coli has increased significantly in blood samples from patients in Danish hospitals. The level of resistance to third-generation cephalosporins in blood samples from patients reported in Denmark is now above the level in the other Nordic countries.



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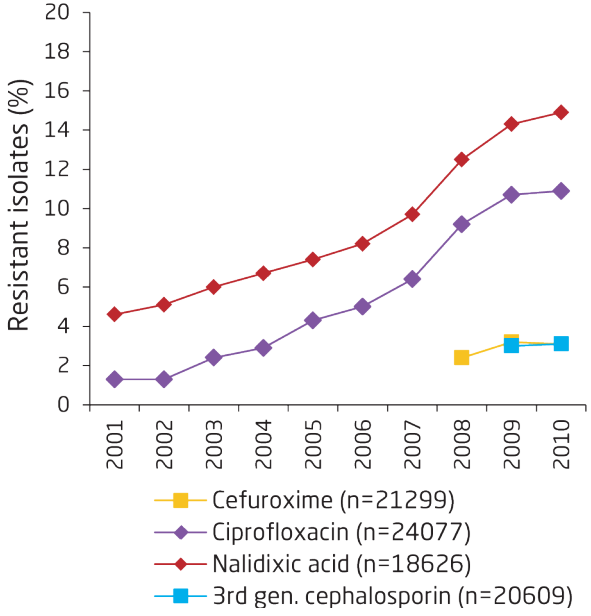
Increasing resistance in E. coli from human urine

The past decade has seen an increase in the occurrence of resistance to ciprofloxacin and nalidixic acid in E. coli from urine samples from the Danish primary health care. Both ciprofloxacin and nalidixic acid belong to the group of antimicrobial agents called fluoroquinolones.



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Results from DANMAP showed that the number of new cases of humans with MRSA increased by 25% from 2009 to 2010 – the highest level in 25 years. The increase in cases is seen especially outside hospitals, while the number of in-hospital cases remains low, indicating that the MRSA guidelines from 2006 work.

Many of the new cases of MRSA were seen in connection with foreign travel or family visits from abroad. The increasing use of antimicrobial agents in primarily the Danish healthcare sector has probably also contributed to the development.

In recent years, the same types of MRSA are found in humans and in production animals, including pigs and cows. MRSA from swine is currently one of the major reservoirs for new MRSA cases in humans with an increase in the number of new cases from 40 in 2009 to 163 in 2011.

Swine MRSA originates from humans

New results from DANMAP scientists using a complete analysis of genetic material of bacteria have recently shed new light on the evolution of MRSA from swine, also known as MRSA-CC398. The data show that MRSA-CC398 most probably originate from susceptible bacteria in humans. After the host jump it developed resistance.

As a resistant bacterium, MRSA-CC398 has adapted to pigs and has had difficulties spreading to people who did not have direct contact with infected pigs. Since the original antibiotic-sensitive Staphylococcus originates from humans, it is possible that the newly emerging resistant bacteria will eventually adapt to people again, potentially leading to the bacteria spreading more easily between humans.

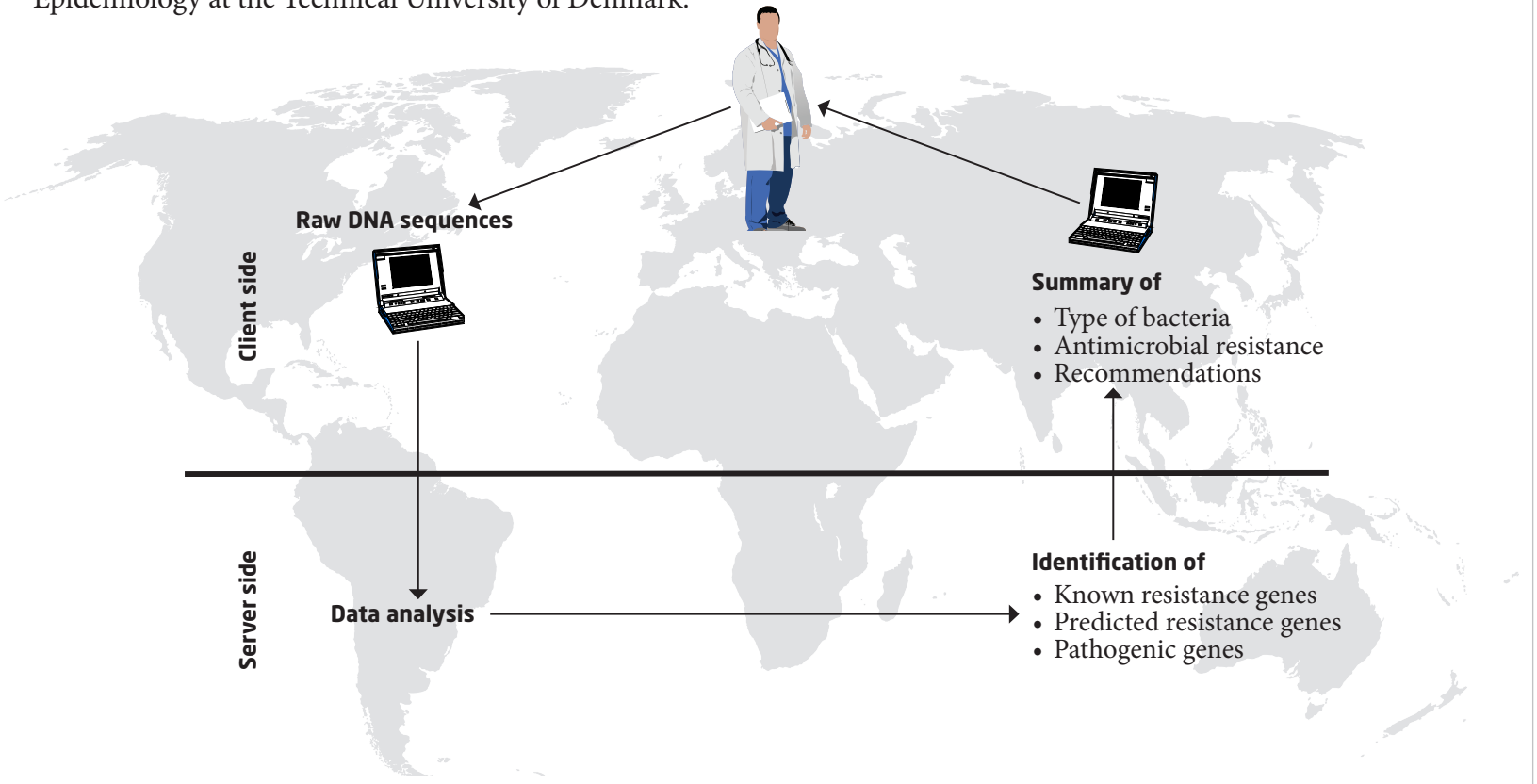
New technologies expecting to impact surveillance of antimicrobial resistance

Today, it can take days to determine the species, strain and resistance to antimicrobial agents of most pathogenic bacteria. However, using whole genome sequencing of bacterial genomes could potentially reduce this time to hours. This in turn opens up the possibility of doctors being able to treat patients with the right medicine while at the same time improving the chances of preventing infectious diseases from spreading.

DANMAP scientists have initiated validation projects that investigate the possibilities of using analysis of the complete genetic material of pathogenic bacteria in the surveillance of antimicrobial resistance, and these methods could become part of the surveillance programme in the future.

Integrated global detection of infectious diseases

In the future, complete analysis of genetic material of pathogenic bacteria in the surveillance of antimicrobial resistance might potentially be a fast, inexpensive, and simple global technology. Using genome sequencing can make it possible to identify pathogenic bacteria anywhere in the world and at the same time share and show the results online on, for example, web-based world maps. The technology is based on tools currently being developed at the Center for Genomic Epidemiology at the Technical University of Denmark.



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