Textbox 1.1

National action plan on antimicrobial resistance in humans

Minister's foreword

Antimicrobials are essential for the functioning of modern healthcare systems. They allow us to treat commonly occurring infections, perform essential medical procedures and utilize advanced therapies. The emergence of antimicrobial resistance therefore poses a threat to modern healthcare.

Concerted day-to-day efforts by healthcare professionals have successfully reduced the consumption of antibiotics in Denmark. Their work has been supported by national initiatives such as DANMAP, strengthened infectious disease surveillance and preparedness in accordance with the recommendations in the *Joint action plan on antibiotics and resistance* from 2010. In 2017, three goals for antimicrobial consumption followed in the *National action plan for antibiotics for humans*. Yet, resistance rates are rising, nationally and in particular globally. Antimicrobial shortages are increasingly frequent. The situation calls for action and political leadership to curb this worrying development.

Therefore, I am proud to have presented a new Danish *National action plan on antimicrobial resistance in humans* in June 2025. The action plan is the result of an agreement between the Danish Government and all parties of the Danish parliament underlining a broad political commitment to combatting antimicrobial resistance in Denmark and allocating a total of DKK 130 million from 2025-2028 to AMR initiatives.

The national action plan broadens the scope of Danish efforts to combat antimicrobial resistance in humans by strengthening four central priority areas: (1) antimicrobial stewardship, (2) access to antimicrobials, (3) infection prevention and control and (4) international engagement. Each priority area contains an overarching political objective and a number of underlying indicators to monitor overall progress towards reaching the political objective. In total, 21 initiatives provide concrete steps to achieving the political objective of ultimately contributing to combatting the development and spread of antimicrobial resistance.

Sophie Løhde,
Minister of the Interior and Health

Antimicrobial stewardship

Inappropriate use of antimicrobial drugs is a key driver of antimicrobial resistance. Reducing and rationalizing our consumption of antimicrobials must therefore be an integrated part of any effort to hinder the development of antimicrobial resistance. We therefore commit to reducing the use of antimicrobials and prioritising antimicrobials associated with a lower risk of resistance development by:

1) Strengthening cooperation on infection prevention and control and the rational use of antibiotics between hospitals and municipalities, general practitioners and practising specialists.
2) Strengthening diagnostics through a research-based pilot project developed in a public-private partnership to generate knowledge on how rapid point-of-care diagnostics can be implemented in primary care.
3) Assessing the need for prescription requirements for topical antimicrobials currently available over the counter to promote rational use.
4) Adjusting the packaging of antimicrobials to ensure greater alignment with treatment guidelines and updated package leaflets.
5) Improving quality in general practice through a cluster package on the rational use of antimicrobials for within clusters practice.

Access to antimicrobials

Measures to ensure antimicrobial stewardship necessitates access to the appropriate antimicrobials. Limited availability and shortages may lead clinicians to resort to less suitable alternatives and hinder the proliferation of stewardship efforts. We therefore commit to working to ensure a more stable and improved supply of antimicrobials by:

6) Exploring the potential for participating in an innovative joint European procurement model to safeguard access to essential antibiotics.
7) Strengthening Nordic cooperation on the development of a joint procurement model to improve the availability of narrow-spectrum antibiotics that are particularly used in Denmark and the rest of the Nordic region.
8) Exempting antimicrobials from annual fees to the Danish Medicines Agency to remove unnecessary barriers to marketing and keep antimicrobials on the market in Denmark.

Infection prevention and control
Preventing infections reduces the underlying need to prescribe antimicrobials, thereby slowing the development of antimicrobial resistance. We already know that vaccines and basic hygiene are cost-effective infection prevention and control measures. We therefore commit to combating any upward trend and working towards a reduction in the level of infections requiring treatment by:

9) Strengthening training in hygiene and infection prevention and control by developing new educational materials on hygiene and infection prevention
10) Conducting a Health Technology Assessment (HTA) of pneumococcal vaccination to provide a well-founded basis for decisions on a potential public vaccination programme.
11) Introducing antimicrobial resistance as a parameter in the Danish Health Authority's future professional assessments of vaccine effectiveness
12) Simplifying guidance materials to streamline and support staff in their infection prevention and control efforts
13) Improving general practitioners' access to the Danish Vaccination Register (DDV) to enhance citizens' access to vaccines with conditional reimbursement.

International engagement
The fight against antimicrobial is a global issue. The movement of people and goods contribute to cross-border spread of antimicrobial resistance. Denmark have extensive experience in fighting antimicrobial resistance. We therefore commit to strengthening Denmark's international engagement and contribution to global efforts against antimicrobial resistance by:

14) Actively applying Danish knowledge and experience to support initiatives to combat AMR in both bilateral and multilateral partnerships.
15) Appointing a *High-Level Representative* to promote Danish solutions, participate in international forums and influence the global AMR agenda.
16) Providing financial support to the International Centre for Antimicrobial Resistance (ICARS) to sustain its ongoing work with low- and middle- income countries in developing evidence-based and sustainable AMR solutions adapted to local contexts.
17) Supporting the scaling up of the DTU National Food Institute's engagement as a WHO Collaborating Centre to strengthen Danish research-based advisory capacity and global capacity building.

In addition to the four priority areas, the action plan includes a number of cross-cutting initiatives aimed at supporting the national action plan's overall objective of combatting antimicrobial resistance by:

18) Establishing a national AMR advisory group where stakeholders involved in the implementation of the action plan can meet and exchange experiences to support broad societal anchoring.
19) Continuously monitoring the objectives of the action plan to provide the necessary knowledge base for future decision-making in the AMR area.
20) Promoting further research in AMR to generate new knowledge that can form an important foundation for future efforts to combat anti-microbial resistance.
21) Designing awareness and information campaigns on AMR targeting both the public and healthcare professionals.

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Textbox 1.2

National action plan against antimicrobial resistance in animals and food 2024-2027

In September 2024, a new national action plan against antimicrobial resistance (AMR) in animals and food was launched by the Danish Veterinary and Food Administration (DVFA). This is the third national action plan from the DVFA and it continues the efforts against AMR in the period 2024-2027. The vision for the action plan is to prevent the occurrence of resistant microorganisms in animals and food in order to ensure effective treatment of microbial infections in humans and animals. This will be facilitated by a number of initiatives, under four focus areas:

- Strengthened Monitoring with a One Health Perspective
- Healthy Livestock with a Prudent and Low Consumption of Antibiotics
- Targeted Communication in order to Contribute to Informed Choices
- National and International Cooperation as High Priorities

The initiatives relate to antimicrobial consumption, antimicrobial resistance, and biosecurity:
The DVFA will continue to monitor antimicrobial use in animals and resistance in food and animals with a continuous focus on ensuring data of high quality. This will include implementation of new requirements by the EU, to report the use of antimicrobial medicines for animals at species level (Textbox 4.1).

Good biosecurity is important to keep livestock healthy. The DVFA has launched a project on biosecurity, which, amongst other things, will go through legislation in the area and make knowledge more accessible to the public.

In accordance with the Food and Veterinary Agreement, the action plan aims to support reducing the consumption of antibiotics in pigs, by 2027, to a politically agreed target of an 8% reduction based on the 2018 level.

A new focus area in the action plan is targeted communication. One of the first initiatives will be to improve and consolidate information about AMR on the DVFA website.

The DVFA continues to share experiences with other authorities and organisations, while also learning from other countries that have found good solutions in the fight against AMR. This is done through active participation in international forums on AMR.

The full list of initiatives can be found in the official National Action plan, which is available at the DVFA website (www.fvst.dk).

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Textbox 3.1

Understanding the spread of extended-spectrum cephalosporin-resistant *E. coli*: Insights from a dual modelling study

Background
Extended-spectrum cephalosporin-resistant *Escherichia coli* (ESC-EC) is an increasing public health concern, as it is now frequently detected not only in clinical settings but also in healthy individuals and various animal species. This study used two complementary modelling approaches to explore the spread of ESC-EC in Denmark: a compartmental model to simulate the risk of transmission in various sub-populations, and a Bayesian source attribution model to estimate the relative contribution of different sources to human infections based on genetic resistance profiles [1].

Method
The compartmental model
A compartmental model was developed to simulate ESC-EC transmission, capturing four stages of infection: susceptible, colonised, infected, and infected receiving antibiotic treatment. The Danish population was divided into three subpopulations: the general public, farmers, and pet owners, reflecting different patterns of exposure. Transmission pathways included person-to-person spread, foodborne exposure (from both domestic and imported meat), direct contact with animals such as livestock and pets, and colonisation following international travel.

Animal- and food-related exposures were quantified using an exposure indicator, which incorporated the proportion of resistant bacteria in each source, contact frequency, and the likelihood of transmission at the point of exposure, e.g., accounting for risk-reducing factors such as cooking or hygiene practices. The model estimated the total number of ESC-EC infections and evaluated the impact of individual sources by simulating scenarios in which each was removed. The additional burden of infections due to earlier antibiotic use was also assessed.

The Bayesian source attribution model
To complement the dynamic model, a Bayesian source attribution model was applied to estimate the contribution of different reservoirs to human ESC-EC infections, based on the distribution of resistance genes. The model compared the frequency of resistance gene combinations in human clinical isolates with those from isolates from various potential sources, including pets, domestic and imported food, and healthy human carriers. Data from DANMAP Chapter 3 formed the core of the dataset, supplemented with data from Swedish surveillance [2] and published literature.

Results
The compartmental model estimated a total of 61,067 ESC-EC infections annually in Denmark, with 3.2% linked to increased infection risk due to earlier antibiotic use. Human-to-human transmission was identified as the most significant pathway, and removing this route alone led to a 79% reduction in total infections. Excluding livestock sources resulted in a 59% decrease in infections, with cattle being the most influential species, responsible for 27% of the total burden. Foodborne transmission was responsible for 17% of infections; within this category, imported meat contributed more substantially than domestically produced meat. Pets, particularly dogs, accounted for 9% of infections. In contrast, colonisation via returning international travellers had only a modest impact, with their exclusion reducing total infections by just 3%.

In total, 2,696 *E. coli* isolates were included in the source attribution analysis: 1,295 from clinical cases, 265 from healthy colonised individuals, and 1,136 from non-human sources. A total of 101 distinct resistance gene combinations were identified, 21 of which were shared between infected humans and at least one of the different sources.

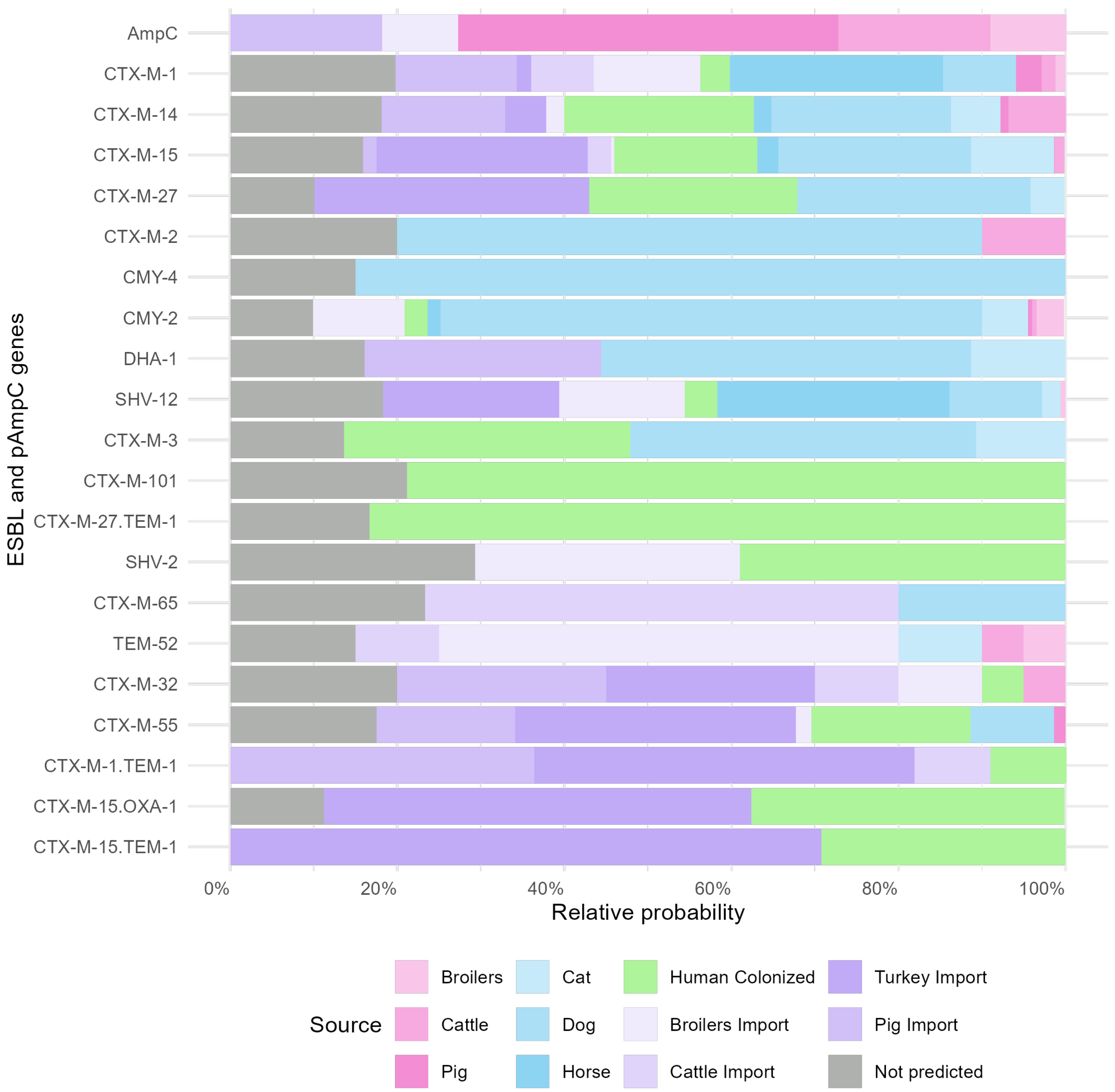
The Bayesian model estimated that dogs were the most significant contributor, accounting for 20.3% of human cases. This was followed by imported turkey meat (18.7%) and colonised humans (16.0%). Gene-specific attribution (Figure 1) revealed that pets (blue shades) and imported meat (purple shades) generally had higher attribution probabilities. For example, CMY-4 was exclusively attributed to dogs, while AmpC promoter mutations were the only resistance determinants present in infected humans and strongly linked to domestic animal sources, particularly pigs. In contrast, CTX-M-101 and CTX-M-27+TEM-1 were found only in colonised and infected humans, and not in any non-human reservoirs, suggesting possible human-adapted lineages.

continued ... Textbox 3.1

Conclusion

The findings of this study underscore the dominant role of human-to-human transmission in the spread of ESC-EC, while also highlighting the significant contributions from livestock, food, and pets. Although the impact of international travel was relatively limited in this model, it may still serve as a route for the introduction of novel resistant strains. Overall, the complexity of transmission dynamics revealed by this study supports the application of a One Health framework—integrating human, animal, and environmental health—to guide future surveillance, intervention, and policy efforts targeting antimicrobial resistance.

Figure 1 ESC gene-specific attribution in individuals infected with *E. coli*, shown as relative probabilities (%) DANMAP 2024



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Textbox 3.2

Antibiotics in wastewater and surface water

A) Current and forthcoming regulation on antibiotics in wastewater.

The Urbane Wastewater Treatment Directive
Antibiotics, as active pharmaceutical ingredients or partly degraded compounds, can be excreted to urban wastewater as a result of human consumption.

In November 2024, a revised Urban Waste Water Treatment Directive (UWWTD) was approved[1]. The directive sets the legal framework for the collection, treatment and discharge of urban wastewater.

The revised UWWTD has determined a requirement for establishment of a quaternary treatment step on wastewater treatment plants to remove micropollutants – including pharmaceuticals and thus antibiotics – from urban wastewater. All urban wastewater treatment plants of 150.000 p.e.[2] and above shall provide quaternary treatment, and for wastewater treatment plants of 10.000 -149.999 p.e. quaternary treatment must be established for wastewater treatment plants discharging effluent to areas identified as sensitive to pollution with micropollutants. The requirement of quaternary treatment shall gradually be implemented at all relevant wastewater treatment plants from 2033 to 2045.

Requirements for the quaternary treatment step is a minimum 80 percent removal of minimum six out of 13 indicator compounds all of which are pharmaceuticals. The list of indicator compounds include one antibiotic.

The additional costs related to installation of new treatment technologies at urban wastewater treatment plants has to be paid through an extended producer responsibility system. An assessment of micropollutants in urban wastewater determined that pharmaceuticals and cosmetic residues contribute to 92% of the total toxic load of untreated wastewater, of this pharmaceuticals account for 66% and cosmetic products for 26%[3]. Thus, producers of compounds from these two product categories will be included in the extended producer responsibility system in accordance with the polluter pays principle.

The UWWTD further requires monitoring of a broad number of compounds in influent and effluent from wastewater treatment plants; - minimum two samples per year for wastewater treatment plants of 150.000 p.e. and above and at least one sample every two years for wastewater treatment plants of between 10.000 p.e. and 150.000 p.e. The monitoring scheme will thus give continuous data on the content of a broad number of micropollutants expected to include antibiotics.

Current Danish regulation on wastewater
In Denmark, discharge of wastewater from wastewater treatment plants to surface water requires a discharge permit issued by the municipalities. The municipalities is also the legal authority to issue permit for discharge of wastewater from hospitals to surface water. The Danish Environmental Protection Agency issues discharge permit for wastewater directly to surface water from pharmaceutical industry. The permit must secure that discharge of micropollutants – including pharmaceuticals – to surface water does not compromise compliance with EU and nationally established environmental quality standards and criteria or other ecotoxicological threshold values (proposed no effect concentration values).

If wastewater from pharmaceutical industry or hospitals is connected to sewers leading to waste water treatment plants, this requires a connection permit issued by the municipalities, which must secure that micropollutants in the effluent does not prevent the wastewater treatment plants from complying with their discharge permits.

B) National surveillance of antibiotics in surface water and wastewater.

The national surveillance program for aquatic environment and nature (NOVANA[4]) monitors the status of the aquatic and terrestrial environments in Denmark and ensures that Denmark meets national legislation, EU directives, and international conventions. Furthermore, NOVANA provides data supporting the national action plans to support fulfillment of the water frame directive. The monitoring is carried out by the Agency for Green Transition and Aquatic Environment in Denmark.

As part of NOVANA, the presence of micropollutants in the aquatic environment is monitored. Thus, a wide range of different substances are measured in samples from streams, lakes, and marine areas. The list of substances monitored includes pharmaceuticals, such as antibiotics, metals, pesticides, plasticizers, and PFAS. The substances are monitored in water, sediment or biota (fish or mussels) depending mainly on their physical-chemical properties. Selected substances are also monitored at point sources such as wastewater treatment plants and storm water overflows, in order to identify which substances are emitted as a direct result of human consumption with wastewater.

Results

In 2017 a total of four antibiotics - trimethoprim, sulfamethiazole, sulfamethoxazole, and sulfadiazine, was included in the NOVANA surveillance program of surface water. The antibiotics are monitored in freshwater from streams as this is where the highest concentrations is expected to be found. Reviewing the collected data from 2017-24, sulfamethiazole has been found most frequently in 20% of the samples in concentrations ranging from 0.005 to 1.1 µg/L. The remaining antibiotics have been found in approximately 5% of the samples (table 1). None of the detected concentrations exceed the national environmental quality standards (EQS) for trimethoprim (100 µg/L) and sulfadiazine (4.6 µg/L).

Table 1 Overview of data from the national surveillance of antibiotics in surface water (streams) DANMAP 2024

	Parameter	CAS	Incl. in NOVANA	Number of samples	Detection frequency (%)	Range of concentrations (µg/L)
1478	Trimethoprim	738-70-5	2017-25	1297	3	0.001-0.45
912	Sulfamethiazole	144-82-1	2017-25	678	19	0.005-1.1
915	Sulfamethoxazole	723-46-6	2017-25	685	4	0.01-0.2
909	Sulfadiazine	68-35-9	2017-25	1080	3	0.0077-0.98

At point sources a total of six antibiotic (azithromycine, clarithromycine, erythromycine, sulfamethiazole, sulfamethoxazole, and trimethoprim) are monitored in samples from wastewater treatment plants and storm water overflows through NOVANA. Based on the results from the surveillance program, national mean concentrations[5] of discharges are estimated for each type of point source[6, 7]. For sulfamethiazole a national mean concentration of 0.58 µg/L is found in effluent from advanced wastewater treatment plants while a national mean concentration of 4.8 µg/L is found in effluent from mechanical treatment plants. It is, at this point, not possible to establish reliable national mean concentrations for the remaining antibiotics. Approximately 95% of the total amount of wastewater in Denmark is treated in advanced treatment plants and the remaining 5% in mechanical treatment plants.

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1 DIRECTIVE (EU) 2024/3019 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 November 2024 concerning urban wastewater treatment
2 One population equivalent' or '(1 p.e.)' means the organic biodegradable load per day, having a five-day biochemical oxygen demand (BOD5) of 60 g of oxygen per day.
3 Feasibility of an EPR system for micropollutants. Final Report (070201/2020/837586/SFRA/ENV.C.2)
4 https://www2.mst.dk/Udgiv/publikationer/2023/09/978-87-7038-556-5.pdf
5 National mean concentrations signify the best estimate of the national Danish annual mean value of the concentration of a substance
6 https://www2.mst.dk/Udgiv/publikationer/2021/03/978-87-7038-287-8.pdf
7 https://www2.mst.dk/Udgiv/publikationer/2022/01/978-87-7038-386-8.pdf

Textbox 3.3

Infection prevention and control and prevention of antimicrobial resistance are interconnected

In Denmark there are numerous activities concerning infection prevention and control (IPC) and antimicrobial resistance (AMR) - both on the national and on the international level. Across Europe as well as globally it is increasingly stressed that controlling AMR in human health must be based on aligning efforts within surveillance, antimicrobial stewardship (AMS) and IPC.

IPC is for the first time in a Danish action plan on AMR specifically mentioned as one out of four central focus areas in the newly issued national action plan (NAP) on AMR as of 11 June 2025[1]. In June 2023, the European Union recommended to step up EU actions to combat antimicrobial resistance with a One Health approach[2]. To support the countries in stepping up the AMR actions the European Commission has invested 50 million Euros in EU-JAMRAI 2 four-year-project (2024-2027)[3] under the EU4health programme[4].

EU-JAMRAI 2 (European Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections) seeks to implement concrete actions to monitor, prevent and effectively tackle AMR across human, animal and environmental health domains through a "One-Health" approach and to make Europe a best practice region. The project focuses on multiple areas, such as AMS, surveillance, awareness raising, capacity building, IPC, behavioral science and updating NAPs on AMR with a focus on both AMR and IPC[5].

The project was launched at a kick-off meeting in Paris in February 2024 and an annual meeting took place in Bilbao in March 2025[6]. The project is progressing well and the first results will be available and presented from autumn 2025 and onwards.

Among the 10 work packages (WP) in EU-JAMRAI 2, Denmark participates in WP5 (National Action Plans), WP6 (Antimicrobial Stewardship), WP7 (Infection Prevention and Control), WP8 (One Health Surveillance) and WP9 (Access to antibiotics).

WP7 is about improving IPC actions within the human, veterinary and environmental sectors and has a general focus on behavior change strategies to support further uptake of IPC recommendations. Several subtasks are described within the human activities: Development of frameworks for implementation of IPC competencies and prioritizing EU standards in IPC programs, support the participating member states and associated countries in the implementation of IPC core components, give access to an IPC toolbox and, finally, organizing peer-to-peer activities and exchanges with IPC experts. Topics which constitute a challenge for IPC of today as e.g. lack of educated workforce, specialized care moving out of the hospitals and replaced by care at home, and IPC in the green transition will be included in the work.

As part of the EU-JAMRAI 2 project the Danish National Center for Infection Control (CEI) in close collaboration with our national IPC partners aim at improving the access to IPC knowledge and tools, strengthening IPC networking and the sharing of knowledge. A general focus is on how to improve and maintain IPC competencies. CEI follows a number of IPC implementation activities from around the country. Both municipalities, regions and projects across sectors are represented. The implementation and behavior change knowledge from these projects will later be shared. In 2025, as a part of the peer-to-peer programme, CEI has organized a national behavior change workshop and mediated a number of IPC webinars in collaboration with EUCIC (European Committee on Infection Control)[7]. CEI has launched a new site for IPC inspiration for the sharing of materials and tools among healthcare professionals working with IPC in Denmark. Read more about the Danish EU-JAMRAI 2 IPC activities at CEI SSI subsite[8].

EU-JAMRAI 2 receives funding from the European Union's EU4Health programme under grant agreement n°101127787.

EU-JAMRAI Joint Action Antimicrobial Resistance and Healthcare-Associated Infections

Funded by the European Union

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The Danish IPC guidelines are in place

All healthcare professionals are expected to be familiar with and act in compliance with the national guidelines for IPC (published by the National Centre for Infection Control at SSI); in Danish "NIR Generelle forholdsregler for sundhedssektoren"[9]. The supplemental national guideline includes specific guidance on VRE, ESBL and other multidrug-resistant microorganisms (MDRO) and should be followed when being in contact with a patient, for which either clinical infection or carriage of MDRO is suspected or known; "NIR Supplerende forholdsregler ved infektioner og bærertilstand i sundhedssektoren"[10].

The Guidance on Preventing the Spread of MRSA by the Danish Health Authority was issued in 2006, the year MRSA became notifiable. The applicable 3rd edition of the guideline is from 2016; Guidance on Preventing the Spread of MRSA - The Danish Health Authority (sst.dk)[11]. The guideline represents the national recommendations and strategic framework for preventing the spread of MRSA at hospitals and in other healthcare settings and nursing homes. A 16-year MRSA surveillance report[12] has shown that the national MRSA strategy has been successful in controlling the spread of MRSA at hospitals as the primary goal of the MRSA guideline and to stabilize the spread of livestock-associated MRSA.

The first national guideline on preventing the spread of CPO by the Danish Health Authority was issued in 2018 (only in Danish); "Vejledning om forebyggelse af spredning af CPO"[13]. The guideline provides a national strategic framework for detection and management of CPO in hospitals. The main purpose of the guideline is to maintain a low prevalence of disease caused by CPO associated with certain high-risk situations. Despite this national guideline CPO is increasing in Denmark (see chapter 8.3.2, carbapenemase-producing organisms, CPO) indicating that more needs to be done in order to combat the outbreaks at hospitals and at long-term care facilities. There are a lot of challenges in controlling these outbreaks as they are long-lasting.

The purpose of both guidelines is to minimize the spread of these often highly resistant bacteria to the ill and weak patients at hospitals and in long-term care facilities, simultaneously keeping the occurrence of these bacteria on a continued low level. The guidelines contain recommendations for active screening of patients on admission to hospital, based on assessment of certain risk situations, e.g. admission to a hospital abroad during the last six months. Both guidelines are free of charge and easy to download from the Danish Health Authority website www.sst.dk.

In hospitals, nursing homes and home care, it is necessary to supplement the general precautions with transmission based (isolation) precautions in the case of an outbreak: "Infektionshygiejniske retningslinjer for MRSA"[14] and "Infektionshygiejniske retningslinjer for CPO"[15].

All IPC guidelines emphasize the importance of all healthcare staff, irrespective of profession, to contribute to the management and prevention of infections and to prescribe antibiotics with care.

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14 https://hygiejne.ssi.dk/retningslinjer/infektionshygiejniske-retningslinjer-for-mrsa
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Textbox 4.1

The effect of the discontinued use of zinc oxide on antimicrobial usage in Danish pig farms

Background

On June 26, 2022, Denmark implemented a ban on veterinary medicinal products containing zinc oxide, generally used for prevention of *E. coli*-related post-weaning diarrhoea in pigs. The decision followed an EU directive issued in 2017 driven by environmental concerns. A five year phase-out period allowed farms the time to gradually discontinue the use of zinc oxide. In the year the ban was enforced, a national increase in antimicrobial usage (AMU) in pigs – primarily driven by an increase in the peroral use of neomycin in weaners – was observed by DANMAP.

Method

In this study, the farm-level effect of the discontinued use of zinc oxide on AMU in weaners and finishers in Denmark was assessed [1]. The study included 4020 conventional, organic, free-range and breeding farms in Denmark supervised by 146 veterinarians from January 2018 to December 2023. Data was extracted from two national databases: farm characteristics from the Central Husbandry Register (CHR) and antimicrobial prescription records from the Danish Veterinary Medicine Statistic Program database (VetStat). Separate datasets were compiled for weaners and finishers, using only data from the longest period under one veterinarian. The monthly within-farm AMU was standardized by converting the amount of antimicrobials prescribed into number of Defined Animal Daily Doses (ADDkg) administered per pig, on the respective farm, per day, in the respective study month (ADDkg/pig-day). The VetStat data showed that each month before the ban, ~75% of farms with weaners used zinc oxide and that a gradual decline in usage began about a year before the ban was enforced (Figure 1). Farms discontinuing zinc oxide use within that year were classified as zinc-using prior to the ban. Additionally, a farm-level time variable marked AMU before, 1-5 months after, or >5 months after zinc discontinuation (for zinc-using weaner farms) or the legal ban (for other farms). The three level data (AMU in a study month, on a farm, supervised by a veterinarian) was analysed using a linear mixed-effect model including time-dependent and farm-specific fixed effects as well as the random effects of the individual farms and veterinarians.

Results

Figure 2 presents the estimated percentage changes in AMU (ADDkg/pig-day) on the individual farms 1-5 and >5 months after the implementation of the ban or the within-farm discontinuation of zinc oxide. The most significant effect was seen in zinc-using farms, where AMU for weaners increased by ~5% on average 1-5 months after the within-farm discontinuation of zinc oxide, followed by a ~17% increase after >5 months. In contrast, the AMU for finishers initially decreased by ~5% on average 1-5 months after the ban – likely a collateral effect of the increased AMU in weaners – but returned to pre-ban levels thereafter. An effect was also seen >5 months after the ban in non-zinc-using farms, where AMU in weaners increased by ~19% on average – however, this increase occurred from a ~14% lower average pre-ban AMU compared to zinc-using farms, indicating that non-zinc-using farms generally had a lower disease frequency. The rise in AMU among non-zinc-using farms may be attributed to a national increased disease frequency or shifts in veterinary prescribing practices in response to the ban.

The effect of the zinc oxide ban resembles that of the antimicrobial growth promoter (AGP) ban in 2000, where antimicrobial treatment for diarrhoea doubled in the first year [2]. However, this increase declined again as producers adapted to the change and the Danish pig production was not negatively impacted long-term [3]. A similar adjustment may follow the zinc oxide ban but has yet to emerge. While the average zinc-using farm increased AMU in weaners following the discontinuation of zinc oxide, some farms faced substantial increases, whereas others had few or no problems maintaining gut health in weaners during the transition – a pattern that was similarly observed after the discontinued use of AGPs. This between-farm variation indicated that the effect of the absence of zinc oxide on the prevalence of post-weaning diarrhoea was significantly influenced by individual farm management practices.

Figure 1 The proportion of farms with weaners using zinc oxide (vertical axis) each study month throughout the study period (horizontal axis), estimated from the extracted VetStat data. Horizontal dashed lines mark the year preceding the enforcement of the ban DANMAP 2024

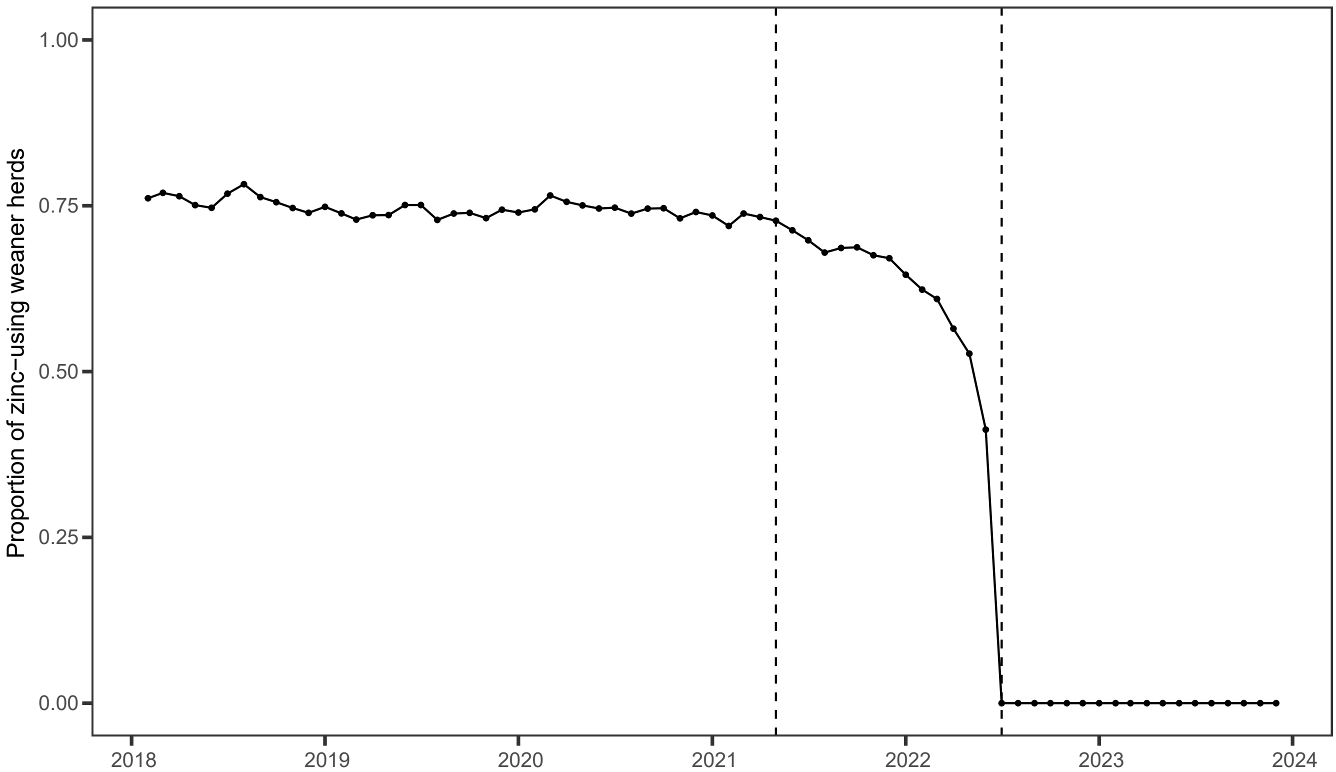
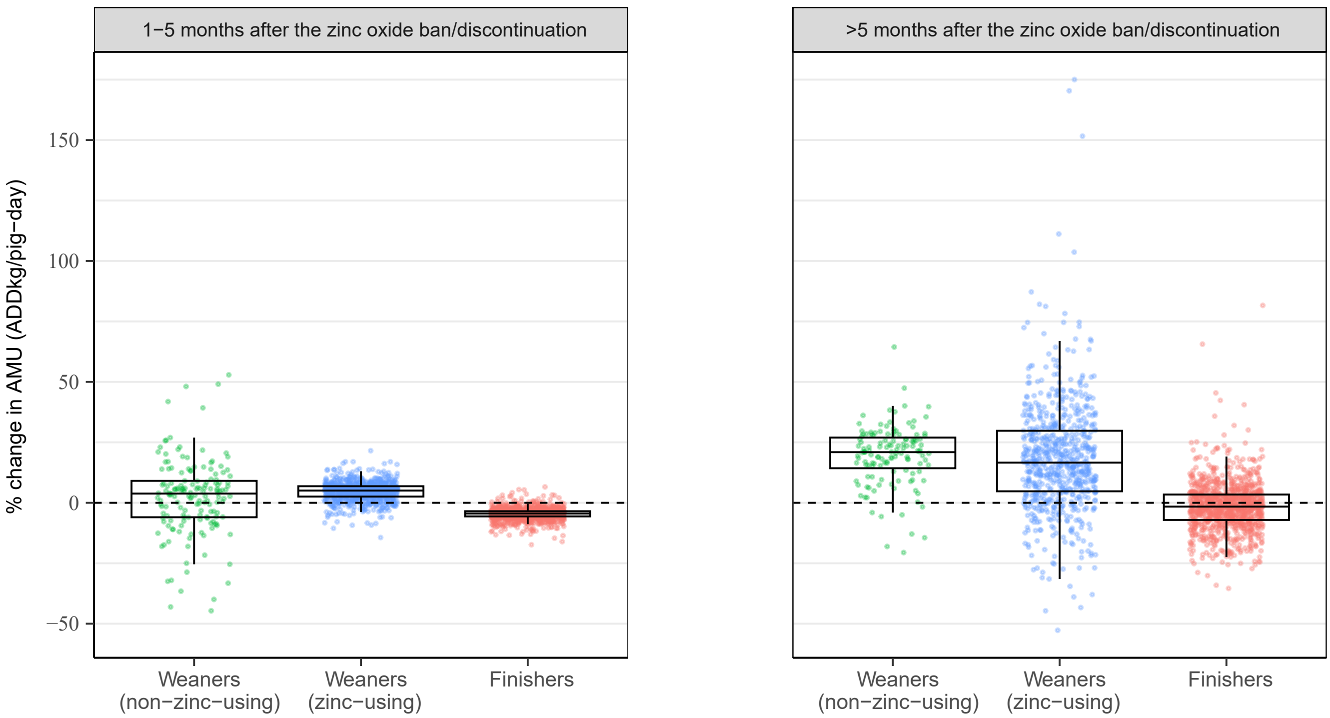


Figure 2 The effect of the zinc oxide ban, estimated as the predicted percentage change in AMU (ADDkg/pig-day) in weaners and finishers in the individual farms *1-5 months* and *>5 months* after the zinc oxide ban/discontinuation, compared to before the zinc oxide ban/discontinuation. The effect was predicted for the individual farms in the study where data was available both before and after the ban/discontinuation (number of farms from left to right: 158, 840, 1268, 131, 689, 1028) DANMAP 2024



continued ... Textbox 4.1

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Textbox 4.2

The european sales and use of antimicrobials for veterinary medicine (ESUAvet): 2023 surveillance report

The European Sales and Use of Antimicrobials for Veterinary Medicine (ESUAvet) annual surveillance report is a new initiative launched by the European Medicines Agency aimed at addressing the critical challenge of antimicrobial resistance in veterinary medicine across the European Union. In March 2025, the first ESUAvet report was published, summarizing data reported from 2023 by all EU member states, as well as Iceland and Norway.

Data is reported by participating countries via the *Antimicrobial Sales and Use* (ASU) Platform, which was strategically developed to support the EU's commitment to mandatory data collection and transparent reporting on the sales and use of antimicrobial medicinal products across all animal sectors throughout the EU and European Economic Area. In this first year of ESUAvet reporting, countries were required to report sales data for all animals and use of antimicrobials for cattle, pigs, chickens, and turkeys. The reporting will be expanded in 2027 to include additional production animal species, such as horses, and in 2030 to encompass companion animals including cats, dogs, and fur animals.

Results of the 2023 ESUAvet Report and data comparisons
According to the 2023 ESUAvet report, 71.1 tonnes of antimicrobial active compounds were sold for treatment of animals in Denmark, corresponding to 20.1 mg/kg animal biomass. This places Denmark in the mid-range compared to the other countries in the report.

Only sales results were presented in the 2023 ESUAvet report, as the data on antimicrobial use across all participating countries was not considered complete and accurate enough for quantitative analysis. Many countries are still in the process of developing or refining systems for collecting data on antimicrobial use.

For Denmark, sales data was reported by the Danish Medicines Agency, based on pharmacy sales records. Use data was reported by the Danish Veterinary and Food Administration (DVFA), using data from *VetStat*, the national database for veterinary prescription medicine use, based on reports from veterinarians, feed mills, and pharmacies. Because sales and use data are derived from different sources and reflect different levels of the supply chain, they should not be directly compared.

It is also important to acknowledge that differences in data processing methods and analytical approaches can impact the results. For this reason, the ESUAvet report includes a disclaimer noting that the country-level results presented may differ from those published in national reports. In Denmark, the DVFA and DANMAP have jointly identified challenges related to data harmonization between the antimicrobial use determined in the reporting process to the ASU platform and DANMAP respectively. The primary discrepancy in methodology concerns classification and quantification of antimicrobial products, including the use of different International Units and derivative conversion factors. These differences highlight the continued strategic importance of thorough methodologies and established national surveillance systems like DANMAP.

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Textbox 5.1

Maintaining access to antimicrobials in a time of increasing product shortages

Access to antimicrobials, especially the narrow spectrum, is crucial to promote rationale use of antimicrobials and thus to combat antimicrobial resistance. In a time of increasing supply issues, antimicrobials risk to disappear from the markets which in turn may push the treatment of infections towards more broad-spectrum antimicrobials.

In Denmark, national stakeholders work to promote and maintain access to antimicrobials in collaboration with national and international experts. We have invited three of them to present their point of views on this matter. Below, you can read the contributions from The Danish Medicines Agency, the pharmaceutical wholesaler Nomeco and the procurement organization for hospital medicines Amgros.

Joint Nordic Initiative to ensure access to critical antibiotics
The consumption of antibiotics in Denmark and other Nordic countries is characterized by a high proportion of older, narrow-spectrum antibiotics[1] – not least due to the focused national efforts in antibiotic stewardship. The national authorities are very aware of the risk of supply failures for these generics and have under the auspices of the Nordic Council of Ministers initiated joint work on the development of common models to ensure access to critical antibiotics to the Nordic countries.

From the Danish side, the initiative is an element of the national action plan for antimicrobial resistance in humans[2], which includes a number of initiatives regarding resistance control with a focus on the use of antibiotics that lead to a lower risk of resistance development, as well as a focus on a more stable and improved supply of antibiotics.

One of the joint Nordic initiatives is to develop and implement a revenue guarantee model for antibiotics in the primary sector. The companies involved will receive a revenue guarantee combined with a fixed participation award, if they commit to having no registered shortages of the product up to a maximum guaranteed package volume.

The model will ideally cover the entire Nordic market for important formulations of narrow-spectrum antibiotics in the primary sector, thereby ensuring larger and more attractive volumes for companies. This may require system and legal changes in all countries, so the initiative starts with a proof of concept (POC) for a single formulation of an antibiotic substance and separate service contracts with the manufacturers for each country. The aim is to test whether a revenue guarantee actually can improve the availability of an important antibiotic and to gain experience on possible adjustments for such a model to possibly be effective.

The proposed antibiotic substance to test in the POC is **phenoxymethylpenicillin 50mg/ml oral suspension**, which is 1st line treatment in most of the Nordic countries primarily for neonates and toddlers. The product is provided to the Nordic market by four companies.

Status: In 2025H2 the medical, legal and commercial challenges and solution options will be identified in each country, along with a preparation of a proposal for a cooperation model and a process plan for implementing the model. This must be approved by the Nordic Council of Ministers in early 2026, after which the POC can be initiated.

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[1] The Nordic countries have the highest proportion of narrow-spectrum consumption in Europe. The consumption of narrow spectrum penicillins, cephalosporins and erythromycin in the Nordic countries was 2.5-10 times the consumption of broad-spectrum penicillins, cephalosporins, macrolides (except erythromycin) and fluoroquinolones in 2023. For the EU as a whole the proportion was only around 0,2 times. Source: *Antimicrobial consumption in the EU/EEA (ESAC-Net) - Annual Epidemiological Report for 2023*

[2] Danmark opruster i kampen mod antibiotikaresistens med ny handlingsplan | Indenrigs- og Sundhedsministeriet

By working with this model, Nordic cooperation in this area will be significantly strengthened on several levels. The experience, the structures and the processes that need to be built up to develop and implement the model will strengthen future joint initiatives in this area. Collaboration on reimbursement models also connects to other Nordic collaborations in the area, such as joint purchasing, joint electronic package leaflets, treatment recommendations, and possibly joint stockpiling.

Danish Medicines Agency
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Nomeco's proposed initiatives for an improved robustness of the supply-chain of narrow-spectrum antibiotics
Nomeco is Denmark's largest pharmaceutical wholesaler handling approximately ¾ of all pharmaceuticals in the pharmacy sector and more than half of the pharmaceuticals used in the hospital sector – including antibiotics. Nomeco is a full-line and product neutral wholesaler meaning, that we keep stock of all registered pharmaceuticals, regardless of manufacturer, brand, type, price etc. Nomeco's stock and purchasing profile and algorithms are based on current pharmacy legislation and advanced forecasting – and obviously product availability from our suppliers

With the aim to improve the availability of all critical pharmaceuticals – not least antibiotics, Nomeco has put forward several concrete proposals on how to strengthen the supply security of narrow-spectrum antibiotics in Denmark.

The first set of proposals concerns a *redistribution model* aimed at better utilization of existing stocks. Often back-orders are short and regional or even local. So, to avoid reaching out for the broad-spectrum antibiotics in cases were the narrow-spectrum products are unavailable locally or temporarily, Nomeco suggest looking into alternative and more dynamic distribution models – including elements like consignment stocks at pharmacy level or models enabling redistribution of individual products between pharmacies facilitated by the wholesalers. Financing of the costs resulting from alternative and dynamic distribution models could be made via a tiny fee on all pharmaceuticals going into a fund controlled by the authorities. Such a fund should of course also cover other costs throughout the pharmaceutical supply chain resulting from increasing shortage, instability and risk in general.

The second set of proposals focuses on economic incentives to ensure stable production and attract new manufactures. This includes elements like attractive pricing and a national tender model with at least two winning suppliers and long-term agreements. Other elements to consider include guaranteed minimum purchase volumes etc.

Nomeco is of course fully aware that the above-mentioned initiatives do not solve the underlying problem concerning lack of sufficient supplies of narrow-spectrum antibiotics. Nevertheless, initiatives like these are crucial to ensuring a more stable supply of critical pharmaceuticals and thus also contributing to the fight against antibiotic resistance.

Nomeco, pharmaceutical wholesaler
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continued ... Textbox 5.1

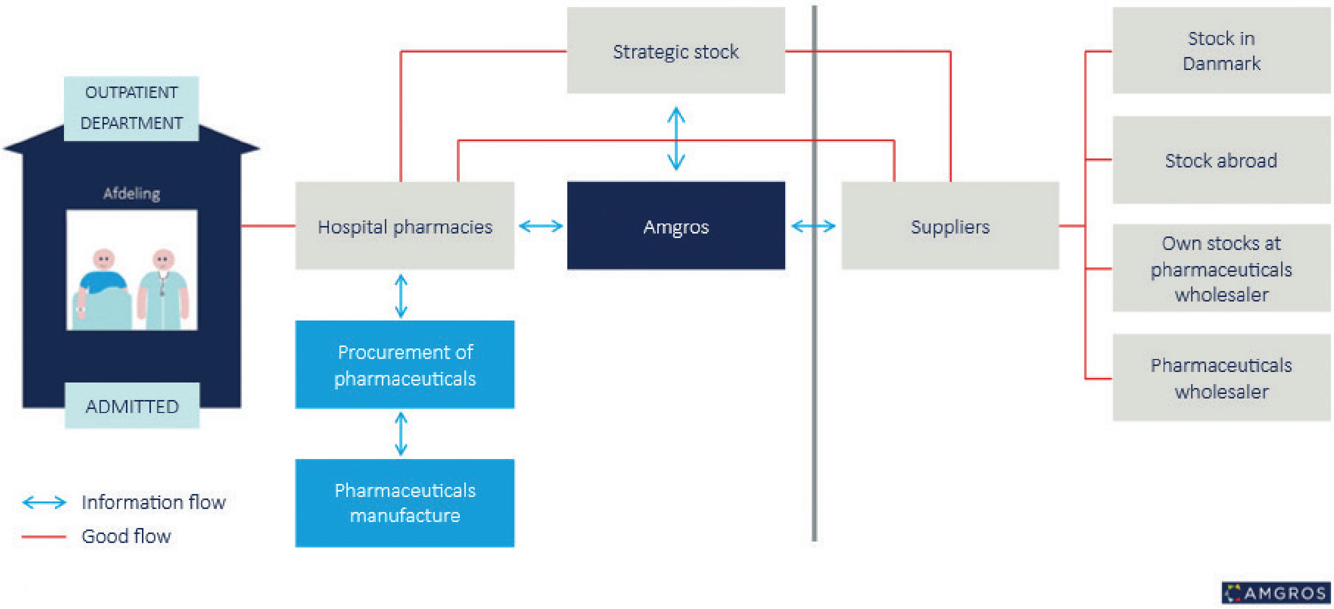
Amgros' Backorder Management of Medicines for Public Hospitals

Amgros is the procurement organization for hospital medicines and hearing aids on behalf of the Danish healthcare regions. Together with the country's hospital pharmacies, Amgros ensures that essential medicines are available to patients in public hospitals - at the right time, in the right place, at the right price - and with environmental considerations in mind. This is achieved through strategic planning and execution of tenders and procurement, ensuring supply security, and systematic follow-up on backorders. In 2024, Amgros achieved savings of DKK 9.9 billion, corresponding to approximately 49% of total expenditure. Around 98% of the medicines used in public hospitals are supplied through Amgros contracts.

National Backorder Management in the Hospital Sector

Amgros and hospital pharmacies continuously monitor orders and registers backorders to manage supply disruptions by standardized escalation model. The model is outlined below.

Figure 1 Amgros': How medicine meets hospital patients in Denmark DANMAP 2024



Escalation Model - Steps 0-5

Step 0: Prevention: In collaboration with hospital pharmacies Amgros is incorporating preventive measures into contracts to ensure supply security

Step 1: Standard Backorder Handling: Amgros' IT system ensures structured and transparent handling of backorders, including registration, monitoring, and coordination with relevant stakeholders. Most backorders are resolved at this stage.

Step 2: Assessment of Compounding: The possibility of in-house compounding at hospital pharmacies is assessed.

Step 3: Procurement of IRS Medicines: Evaluation of the possibility of purchasing alternative medicines without Danish marketing authorization (IRS medicines).

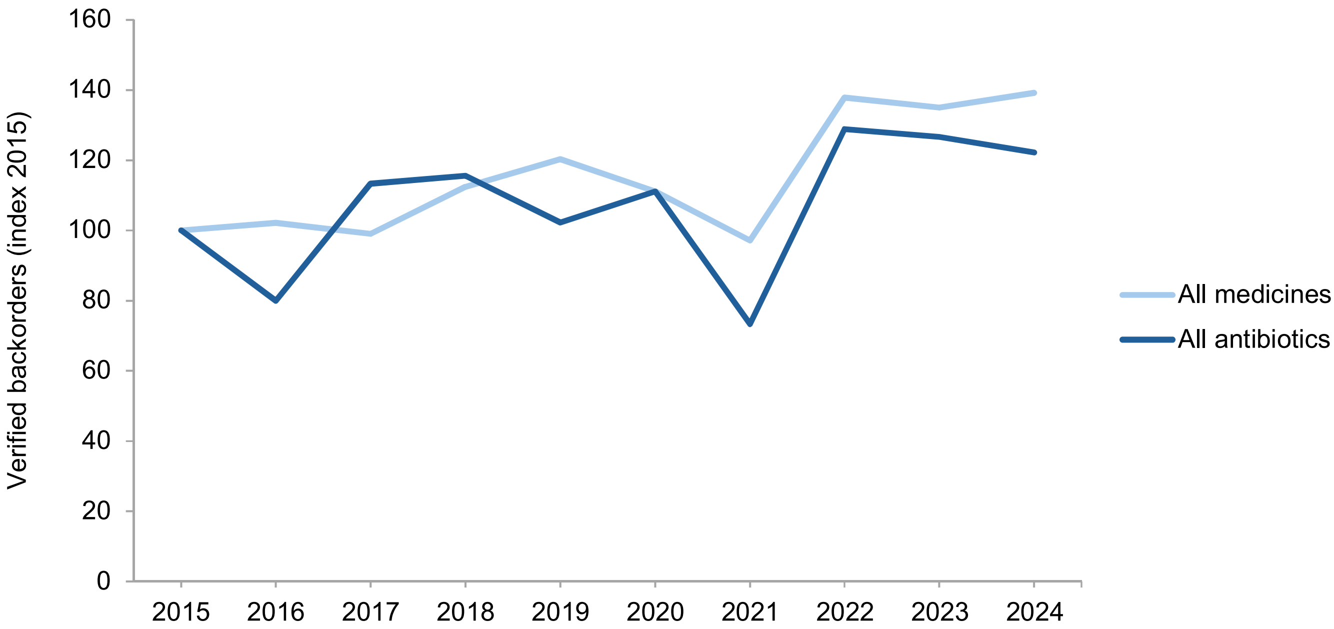
Step 4: Alternative Treatment Regimens: Clinical experts assess analog treatments, patient prioritization, or alternative handling. A cross-regional working group ensures broad implementation of the solution.

Step 5: Initiation of Production: In very rare cases, production is initiated at a hospital pharmacy or an external supplier if APIs, raw materials, and packaging are available.

Supply Situation for Antibiotics in the Hospital Sector

Antibiotics are particularly challenging due to treatment criticality, seasonal variation, and low prices over many years, which have made the market less attractive and reduced the number of suppliers. The backorder index for antibiotics was 120 in 2024 compared to 100 in 2015 meaning a 20% increase in backorders for antibiotics, compared to a 40% increase for all medicines. In almost all cases, alternatives were found based on the backorder management system and flexible procurement options.

Figure 2 Verified backorders of all medicines and of antimicrobials at hospitals, Denmark, 2015-2024 DANMAP 2024



Strategic Measures by Amgros to Improve Supply Security

Creating an Attractive Market: Amgros has a strategic approach to tenders, which includes market analysis, outreach to attract more suppliers to Denmark, and adjustment of tender criteria aimed at supply security.

Strategic Medicine Stock: Amgros and hospital pharmacies operate a national stockpile of treatment-critical medicines and medicines with low supply security. This provides a buffer in case of delivery failures and helps prevent disruptions from affecting patients.

Use of Forecasts: Amgros systematically collects consumption data and prepares forecasts as an integral part of the tender process. Once the contract is signed, the expected consumption is shared with the supplier, enabling them to adjust production and logistics to anticipated demand. Suppliers are also informed in case of significant changes during the contract period, allowing them to adjust production.

International Cooperation: Amgros participates actively in the Nordic Pharmaceutical Forum working for a more attractive Nordic market. Several joint Nordic tenders, including selected antibiotics, have been carried out by Denmark, Norway, and Iceland. In addition, the Nordic Pharmaceutical Forum collaborate with the Nordic medicines agencies to promote registration of joint Nordic packages.

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Textbox 8.1

20 years of fungemia surveillance in Denmark (2004-2023)

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Fungaemia (blood stream infection with fungi) is most commonly caused by species currently or previously classified as *Candida*. Some of these have now formally been reclassified as other genera or species (e.g. *Candida glabrata* as *Nakaseomyces glabratus*, *Candida krusei* as *Pichia kudriavzevii* etc) meaning that only about 50% of "candidaemia" cases are due to *Candida* species if the novel taxonomy is adopted. For easy recognition we maintain the previously used *Candida* names and species groupings. *Candida* are part the human microflora. Most invasive infections are encountered in severely ill hospitalised patients and fungemia is associated with a significant overall mortality of ~40 percent in Denmark, necessitating prompt and correct treatment[1].

Denmark has had an active prospective voluntary surveillance since 2004, which in 2009 became nationwide with retrospective data retrieved from 2004-2009[2,3]. This has enabled a detailed surveillance of incidence rates, species distribution and acquired resistance patterns over 20-years[3]. Here we present new data from 2023 and patterns over the full period.

During 2023, a total of 573 isolates from 551 episodes and 509 individual patients were included. The incidence rate was 9.3 episodes/100,000 inhabitants and stable over the recent four years but consistently higher than other published European national surveys. The highest incidence rate groups are males aged >60 years and the peak incidence age has increased over time to ≥80 years (Figure 1). The reason for this is unclear but may reflect the longer lifetime and that more intensive treatment is offered to higher age groups.

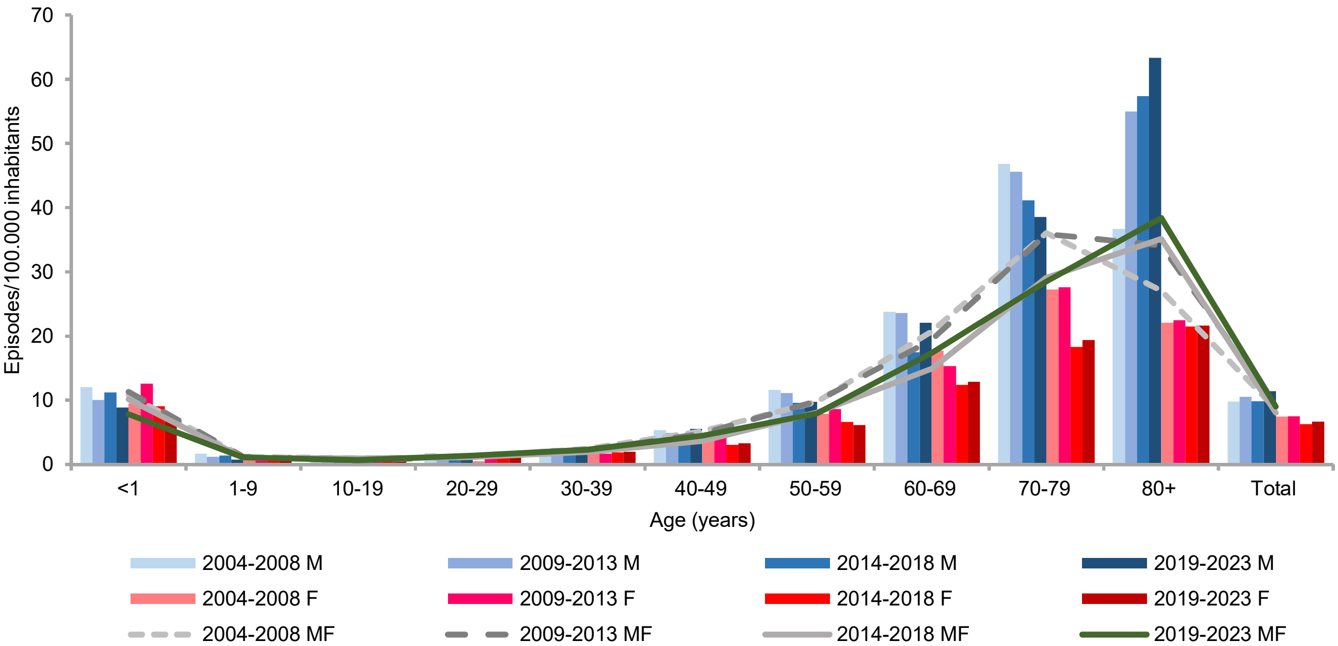
The species distribution followed the pattern from previous years with a marked decrease in the percentage of the intrinsically susceptible species *C. albicans* (36% in 2023) concomitantly with an increase in the less susceptible species *C. glabrata* (33% in 2023) (Figure 2). This has been linked to the increase in azole use until 2014, with a high fluconazole use in the GP sector (figure 3). Furthermore, *C. auris* fungemia has been detected for the second time since 2021.

Mainly due to the increase in *C. glabrata*, the fluconazole susceptibility has decreased from 71% (2004-2009) to 57% (2023)[2]. During the past 3 years (2021-2023), acquired fluconazole resistance has been detected in 0%/2.3%/9%/5.7% in *C. albicans*, *C. dublinensis*, *C. glabrata*, *C. tropicalis*. For *C. parapsilosis* no fluconazole resistance (MIC >4 mg/L) was detected in 2021-2022 but high-level resistance was found in 2 out of 36 (5.6%) susceptibility tested isolates of *C. parapsilosis* in 2023, both harbouring ERG11 alterations associated with clonal hospital outbreaks in e.g. Southern and Middle Europe, Asia, North and South America. [4-6]. The amphotericin B coverage remains high at (1666/1688) 98.7%. Acquired echinocandin resistance remained low among intrinsically susceptible species (C. *albicans/dublinensis/glabrata/krusei/tropicalis*) during the years 2021-2023 (≤1% yearly for all species combined) whereas no acquired resistance was found in *C. parapsilosis*.

Conclusion
The nationwide surveillance has revealed a notable change in the species distribution towards the less susceptible species *C. glabrata*, which today is almost as common as *C. albicans* as cause of fungaemia. This may be linked to azole usage[7]. Despite an increase in echinocandin usage little resistance has emerged, securing our first line treatment for candidemia. It will be interesting to follow the echinocandin resistance rates during the forthcoming years when the once weekly dosed echinocandin rezafungin will allow outpatient use. The new species *C. auris* and azole resistant *C. parapsilosis* have both been detected in Denmark, emphasising the need for continued vigilance and screening of potentially colonized patients from countries with outbreaks or high endemicity to avoid hospital outbreaks.

continued ... Textbox 8.1

Figure 1 Incidence by patient age and gender across four 5-year periods DANMAP 2024



F: Females. M: Males. MF: All

Figure 2 Number of yearly isolates and species distribution in percentage over the years DANMAP 2024

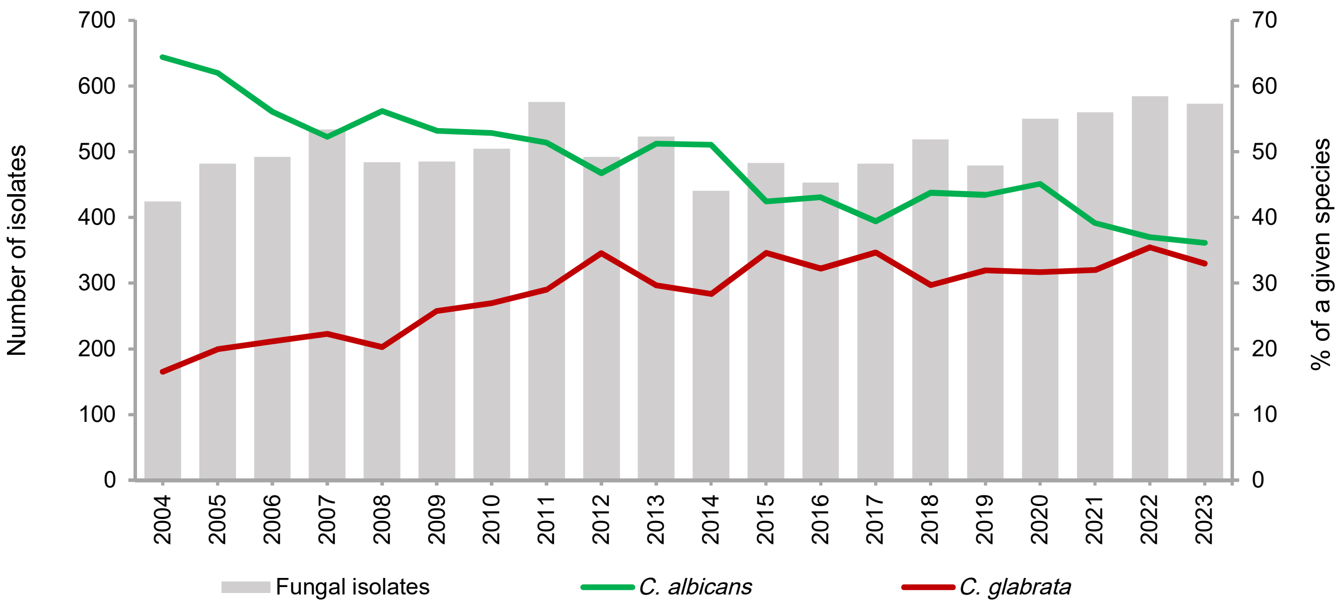
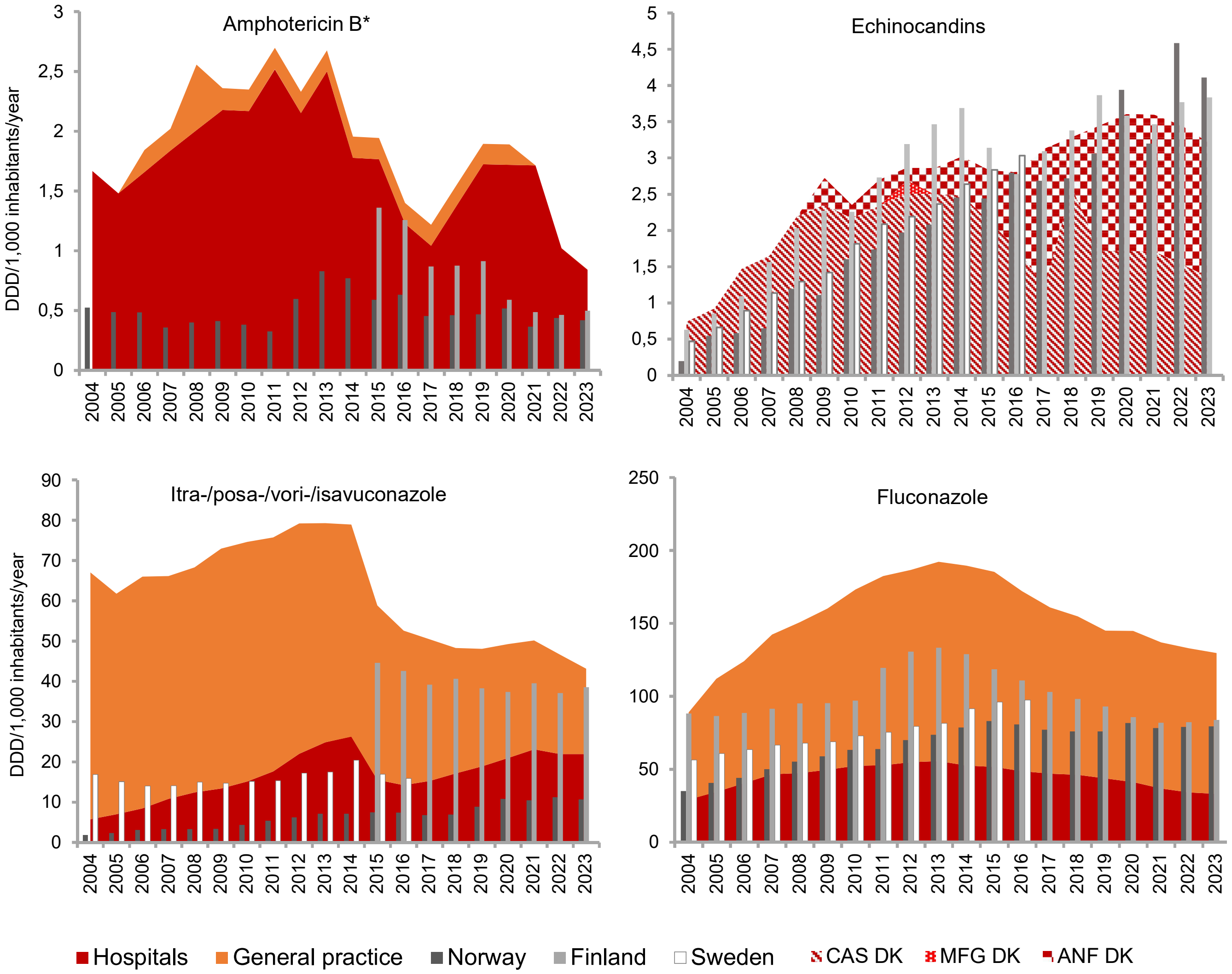


Figure 3 Systemic antifungal usage in the Nordic countries. Data for Denmark is shown for both primary sector (GP) and hospital use
DANMAP 2024



ANF: Anidulafungin. MFG: Micafungin. CAS: Caspofungin. *) Lipid formulations of amphotericin B have recently been assigned a separate, higher DDD from the conventional formulations due to a considerably higher dosage; updated DDDs used here. The figures above are based on own calculations based on data from Sundhedsdatastyrelsen (www.medstat.dk) and www.dst.dk, data from www.hfi.no (Norway) and www.fimea.fi (Finland) (provided via personal correspondence). Data from Sweden (www.socialstyrelse.se) not available after 2016. Updated amphotericin B DDDs not available from Sweden or Finland (prior to 2015). Part of the decline in hospital azole use after 2014 is caused by technical issues following a change in posaconazole DDDs and available formulations

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continued ... Textbox 8.1

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Textbox 8.2

Azole resistance in clinical isolates of *A. fumigatus* - the first 5 years of surveillance

Karen MT Astvad, Karin M Jørgensen, Nissrine Abou-Chakra, Jan B Gertsen, Lise Kristensen, Flemming S Rosenvinge, Lisbeth Lützen, Jette M Bangsborg, Michael Pedersen, Sofia Sulim, Marc TK Nielsen, Turid S Søndergaard, Maiken C Arendrup. Thanks to Bent L Røder for his participation during previous years.

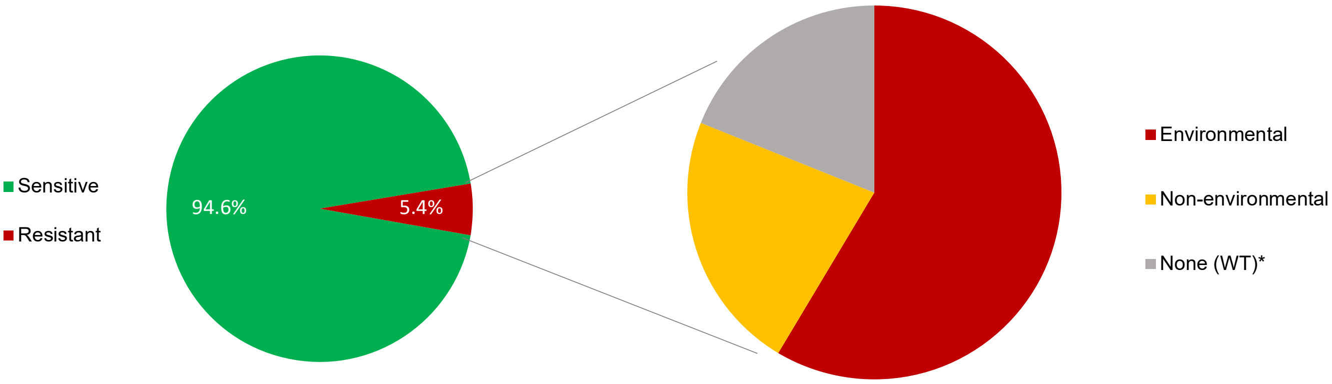
Aspergillus can cause disease in vulnerable patients with decreased immune response or severely impacted lung function. The azoles are the most efficacious and the only orally available treatment options. Consequently, azole-resistance constitutes a clinical problem in the management of these patients[1]. Resistance can develop during long term patient treatment but has also been shown to emerge in the environment due to agri- and horticultural azole fungicide use. Such isolates have unique *cyp51A* target gene mutations, of which the most common ones involve TR_{34}/L98H and TR_{46}/Y121F/T289A ± other alterations in the Cyp51A protein [2]. As these isolates can cause infection in patients not previously treated and therefore not suspected of azole resistant infection, the mortality can be high unless promptly diagnosed and the patient treated with alternative drug classes[3]. Internationally it is recommended that alternative treatment should be used empirically, when the azole resistance rates exceeds 10%[4]. Denmark instituted a voluntary azole resistance surveillance in October 2018 with all clinical isolates of *A. fumigatus* being susceptibility tested using the EUCAST MIC or azole agar screening methods. Azole resistant isolates were *Cyp51A* sequenced [5]. Here we report new data from the fifth year (October 2022- September 2023) in a 5-year context.

A total of 729 isolates from 588 patients were included during the 5th year, giving a total of 4184 isolates from 3131 patients over the 5 years. The majority of cultured isolates came from respiratory tract samples (85%; 3568/4184) or from ear samples (13%; 544/4184). The number of annual isolates decreased from 978 to 729 over the 5 years. The reason for this is unknown, but may involve changes in sampling during the COVID-19 period, local laboratory practises and advances in cystic fibrosis treatment resulting in decreased risk of airway infections. The amphotericin B coverage remained high (99.8%), whereas 5.9% (245/4184) of isolates displayed resistance to at least one azole, with resistance rates for the individual azoles ranging from 5.3%-5.5%. Based on sequencing of the *Cyp51A* target gene in isolates from patients with resistance (5.4%, 169/3131), more than half of the resistance (59%) was caused by environmental alternations, mainly TR_{34}/L98H, which is associated with pan-azole resistance (Figure 1). TR_{46}/Y121F/T289A was only detected in year 3 and 5. Almost half (43%) of patients with resistant isolates also had susceptible/*Cyp51A* wild-type isolates within the same year.

Conclusion
The overall resistance (5.9% of isolates) remained below the 10% mark. Environmental resistance, especially that caused by the TR_{34}/L98H mechanism associated with pan-azole resistance, is well established Denmark and is found in approximately 3.2% of culture-positive patients annually. A plethora of other alterations were detected in the remaining resistant isolates. No increase in resistance has been demonstrated over the last 5 years; however, much lower levels of resistance were found in a previous study from 2010-14[6]. TR_{46}/Y121F/T289A was detected only in the second half of the period, coinciding with the findings in the environment in 2021-2022 (but not 2020), together indicating that resistance may be slowly developing and continued resistance monitoring is important [7]. Finally, the diverse picture of patients harbouring both susceptible and resistant isolates underscores the need for susceptibility testing of all isolates as patients may be simultaneously or sequentially infected by multiple isolates, and a given treatment may not provide coverage for all.

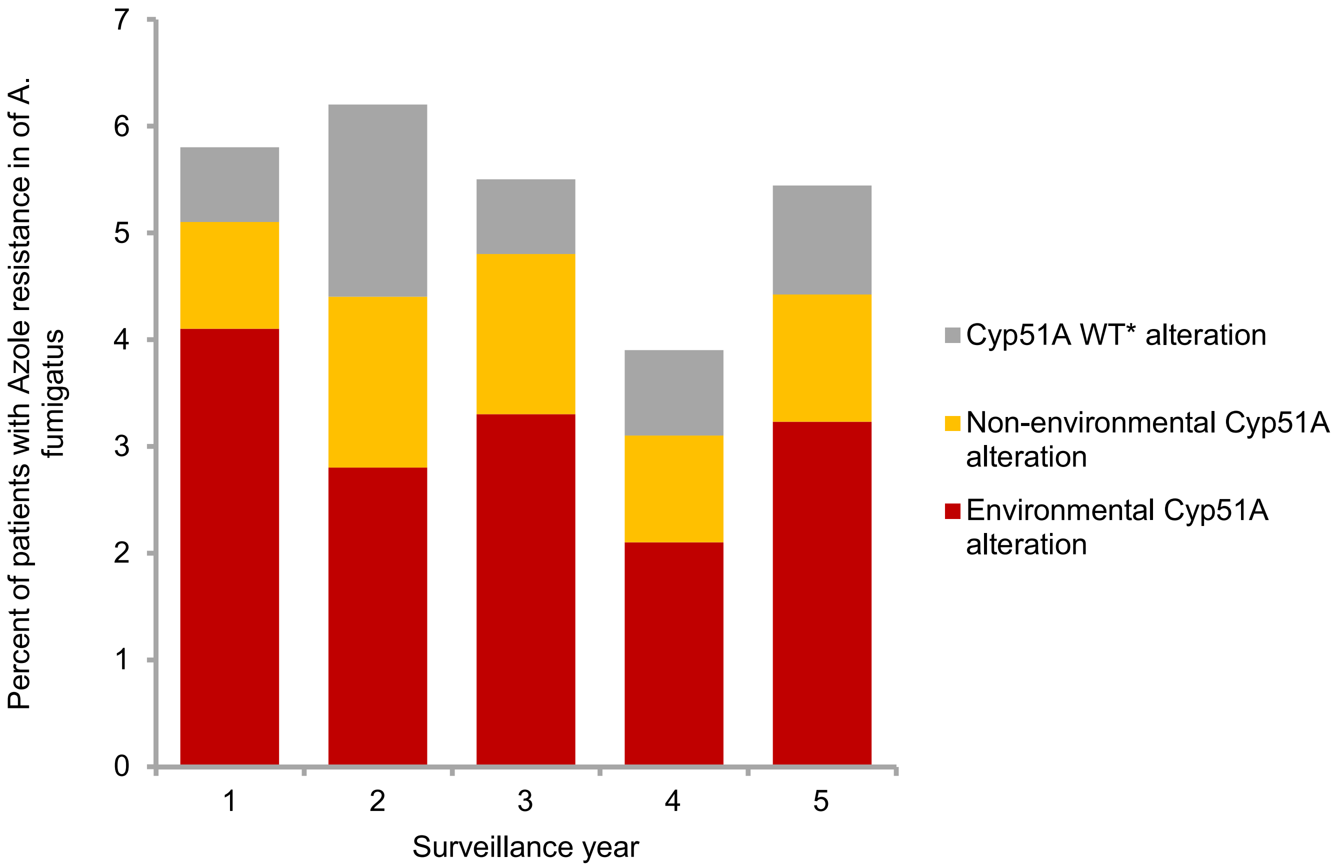
continued ... Textbox 8.2

Figure 1 The proportion of patients with susceptible or resistant isolates (left) and the associated Cyp51A alterations in the resistant isolates (right). Of note patients may harbour both resistant and susceptible isolates (not detailed here) DANMAP 2024



TR34/TR46 var.: Isolates with TR_{34}/L98H or TR_{46}/Y121F/T289A may also have additional alterations not detailed further here. R (WT)*: Resistant isolates that were Cyp51A wildtype or had Cyp51A alterations not uniformly associated with elevated azole MICs

Figure 2 The annual percentage of patients with resistant isolates and the proportion of environmental resistance mechanisms (TR_{34} or TR_{46}) compared to other resistance mechanisms DANMAP 2024



*) Cyp51A wildtype/with alterations not uniformly associated with elevated azole MICs

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Textbox 8.3

Mycoplasma genitalium

New *Mycoplasma genitalium* (MG) cases are defined similar to *Chlamydia trachomatis* (CT) cases by a timespan of at least 42 days since the last positive analysis result. The same case definition applies to negative results, with the exception that a positive case can start within the 42-day window of a negative case. The data presented here have been extracted from The Danish Microbiology Database (MiBa) in 2025.

In 2023, an increased number of positive cases were observed compared to 2022 (4,972 vs 4,343). This was a result of an increased number of tests performed, resulting in a lower positive rate (from 12.4% to 11.9%). In 2024 however, the number of positive cases was similar to 2022 (4,352 cases), and the positive rate continued to decrease compared to 2023 (11.6% vs 11.9%).

Treatment for MG in Denmark is based on the European guidelines described by the International Union against Sexually Transmitted Infections (IUSTI), backed by the WHO and ECDC. The guideline recommends that treatment for MG is guided by the detection of macrolide resistance mutations (MRM) due to high rates of macrolide resistance, globally and in Denmark. As seen in Figure 1, the macrolide resistance rate rose gradually from 50% in 2011 to 64.8% in 2024 in the Danish population.

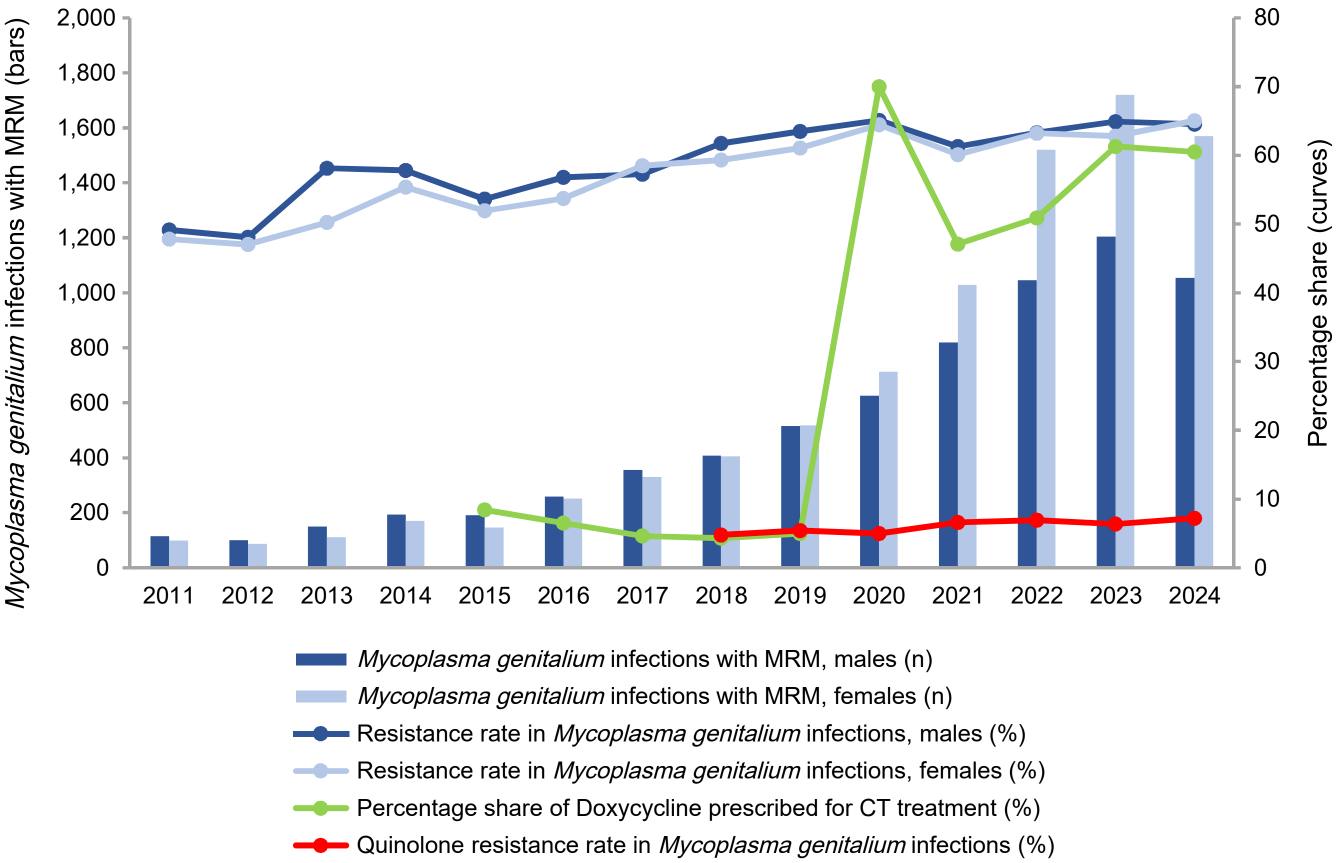
There is an increased awareness of the correlation between the treatment of CT with azithromycin and MRM in MG infections. Since 2019, SSI and international guidelines have recommended a change in first-line therapy for CT from azithromycin 1 g single dose to doxycycline 100 mg twice daily for 7 days. The purpose is to more effectively treat rectal CT infections, as well as decrease the selection of MRM in MG. This has led to a decline in azithromycin use and an increase in the use of doxycycline for the treatment of uncomplicated CT infections in Denmark (Figure 1). Data extracted from the Register of Pharmaceutical Sales indicate that the total number of azithromycin prescriptions issued for CT/MG infections dropped from 4.8 prescriptions per 1000 inhabitants in 2019 to 1.8 in 2024. Likewise, doxycycline for CT/ MG infections rose from 0.2 prescriptions per 1000 inhabitants in 2019 to 3 in 2024 (Figure 1). However, since the MRM rate continues to increase, a further reduction in the use of azithromycin for CT infections is desirable.

In a recent study by Drud, ST. *et al* (2025), resistance data from MG cases between 2014 and 2024 were extracted from MiBa and matched to a previous CT infection. Each MG case was categorized by the time since the latest CT infection: group 1: 15 - 365 days since latest CT infection, group 2: 366-1,095 days, control group: >1,095 days or no CT. Here, individuals in group 1 had the highest MRM rate of 76%, compared to 66% in group 2, and 56% in the control group. This pattern was observed across all years of the study period and confirms the association between MG MRM and CT treatment with azithromycin.

The recommended second-line treatment for MG is 400 mg moxifloxacin once daily (fluoroquinolone) for seven days. In cases where moxifloxacin treatment fails, detection of quinolone resistance-associated mutations (QRAM) is recommended to discriminate between reinfection and resistance. At Statens Serum Insitut, quinolone resistance rates are monitored by testing up to 500 randomly selected MG positive samples per year for QRAM. QRAM were detected in 4.8% (3 of 63) of samples in 2018 and in 7.2% (35 of 486) of samples in 2024, indicating a gradual increase in the resistance rate for quinolones in Denmark. Similarly, dual-class (macrolide and quinolone) resistance rates increased from 1.6% in 2019 to 7.7% in 2024.

In the absence of suitable and efficient third-line treatments for MG it is recommended to strengthen diagnostic stewardship aiming at limiting testing for MG in symptomatic individuals, and to reduce the use of azithromycin to treat CT.

Figure 1 Number of *Mycoplasma genitalium* infections (n) with macrolide resistance mutations (bars), percentage of macrolide resistance mutations, percentage of quinolone resistance-associated mutations and percentage share of Doxycycline prescriptions prescribed for *Chlamydia trachomatis* Infections, Denmark, 2011-2024 DANMAP 2024



MRM = Macrolide resistance mutations
CT = *Chlamydia trachomatis*

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Textbox 9.1

Antimicrobial resistance in clinical isolates from dogs and cats

In Denmark, reports on antimicrobial resistance in canine and feline pathogens have been published sporadically over the years, last time in DANMAP 2022. Susceptibility results have been reported for *Escherichia coli* and *Staphylococcus pseudintermedius*, which are the most frequently isolated bacterial pathogens of companion animals and the primary causes of urinary tract and skin infections, respectively. These species can have important resistant and multidrug-resistant phenotypes. Of particular concern are methicillin-resistant *S. pseudintermedius* (MRSP) and extended-spectrum cephalosporinase- (ESC) producing *E. coli*, which have emerged worldwide in the last two decades and constitute a threat to animal health, as they are well-known nosocomial pathogens that are resistant to all veterinary-licensed beta-lactams and commonly, other antibiotic classes too [1]. *E. coli* and to a lesser extent *S. pseudintermedius* are also pathogens of public health relevance due to the risk of zoonotic transmission.

Materials and Methods

MIC data were retrieved for 470 *S. pseudintermedius* and 401 *E. coli* isolates obtained in 2023-2024 from various infections in dogs and cats (Table 1). Diagnostic specimens had been shipped from primary care and referral veterinary hospitals from across Denmark to the diagnostic laboratory Sund Vet Diagnostik at the University of Copenhagen. For duplicates retrieved from a single patient at one point in time (e.g. two *S. pseudintermedius* from right and left ear, respectively), MIC data for only one randomly selected isolate was kept. Susceptibility testing was done using broth microdilution with the commercial Sensititre plates COMPGP1F for gram-positives and COMPGPN1F for gram-negatives (ThermoFisher Scientific). Interpretation of MIC data was according to clinical breakpoints published by the Clinical and Laboratory Standards Institute (CLSI) [2,3].

Table 1 Origin of *E. coli* and *S. pseudintermedius* isolates obtained from clinical specimens in Sund Vet Diagnostik, 2023-2024

DANMAP 2024

	Staphylococcus pseudintermedius		*Escherichia coli*	
	Dogs	Cats	Dogs	Cats
Urinary tract	45	0	216	48
Other	421	4	121	16
Total	466	4	337	64

Results and Discussion

Results are displayed in Table 2 along with comparable data from the periods 2018-2019 and 2020-2022. Overall, resistance levels are very similar over the three time periods with very limited fluctuations. In *E. coli*, cefpodoxime is the best indicator of ESC-production among the antibiotics tested. In 2023-2024, 5% of *E. coli* isolates were resistant to this antibiotic, indicating fairly stable, low levels of ESCs in Danish dogs and cats. It is worth noting that over the years there is a slight tendency of declining resistance to ampicillin and sulfamethoxazole/trimethoprim, which represent antimicrobials recommended in Denmark as first-choice for urinary tract infections in dogs and cats [4]. In *S. pseudintermedius*, oxacillin is used as indicator for detection of MRSP. In all three time periods, 6% of *S. pseudintermedius* were oxacillin-resistant, indicating a stable low level of MRSP. Another antibiotic worth mentioning for this species is clindamycin, as this is the recommended first systemic choice for skin infections in dogs. The level of 27% clindamycin resistance is not low but in line with previous years. Importantly, resistance to this drug was shown to be much lower (around 14%) in Danish isolates from first-time canine pyoderma [5]. This indicates bias, most likely due to submission of samples from patients having been treated with antibiotics before.

As stated in chapter 4 (Table 4.1), all veterinary fluoroquinolone usage in Denmark is for treatment of companion animals. Levels of resistance to this critically-important drug class have been stable in recent years, except for a minor increase in *S. pseudintermedius* (Table 2). Importantly, the clinical breakpoints for this class, chloramphenicol and doxycycline were recently updated by CLSI [3], and for the most recent data (2023-2024) we have indicated resistance proportions according to both the old and the new breakpoints (Table 2). All the new breakpoints are remarkably lower than the old ones, which means that a much higher proportion of isolates are now classified as clinically resistant. For fluoroquinolones, this means a 2-3 times higher proportion of isolates classified as resistant to enro- and marbofloxacin (Table 2). The recent tendency of lowering

continued ... Textbox 9.1

breakpoints for several antibiotics is due to new knowledge on drug pharmacokinetics and/or pharmacodynamics. It has the implication that small animal practitioners will encounter more resistance and thereby more limited treatment options despite the overall average MICs being stable over the years.

Table 2 Percentages of antimicrobial-resistant clinical *E. coli* and *S. pseudintermedius* isolates from dogs and cats in Denmark. MIC data from 2018-2022 were interpreted using [2], whereas data from 2023-2024 were interpreted using both [2] and [3]
DANMAP 2024

Antimicrobial agent	*Escherichia coli*			*Staphylococcus pseudintermedius*		
	2018-2019 (N=441)	2020-2022 (n=559)	2023-2024 (n=401)[2]	2018-2019 (N=602)	2020-2022 (n=726)	2023-2024 (n=470)[2]
	%	%	%	%	%	%
Amikacin	2	1	2	1	1	-
Ampicillin[1]	25	22	19	70	65	74
Amoxicillin/clavulanic acid[1]	5	6	4	7	6	6
Cefazolin	-	-	-	7	6	6
Cefpodoxime	5	3	5	-	-	-
Chloramphenicol	4	2	3 / 61	21	20	21 / -[3]
Clindamycin	-	-	-	27	26	27
Doxycycline	8	4	4 / 99	29	28	22
Enrofloxacin	4	4	3 / 7	2	4	5 / 12
Erythromycin	-	-	-	28	26	26
Gentamicin	4	3	2	2	5	8
Imipenem	0	0	0	-	-	-
Marbofloxacin	3	4	3 / 9	3	4	6 / -[3]
Oxacillin	-	-	-	6	6	6
Sulfamethoxazole/trimethoprim	9	8	6	6	8	9

[1] Susceptibility data for ampicillin and amoxicillin/clavulanic acid in *E. coli* have been determined only for isolates from urinary tract infections, as isolates from other infections are unequivocally classified as resistant to these drugs according to CLSI breakpoints.
[2] In these columns, the numbers to the left of the forward slashes were interpreted like the 2018-2019 and 2020-2022 data using CLSI breakpoints from 2020 [2], whereas the numbers to the right of the slashes were interpreted using CLSI breakpoints from 2024 [3]. When only one number is present in a cell, it means that the old and new breakpoints are identical.
[3] The dash here indicates that MIC data could not be interpreted using the new breakpoints due to insufficient concentration ranges in the plates used for MIC testing

Conclusion
Levels of antibiotic resistance in *S. pseudintermedius* and *E. coli* from dogs and cats have been stable over the last seven years. Most importantly, the proportions of ESC-producing *E. coli* and MRSP did not change from around 5% in the entire period. Comparison of AMR levels across countries is currently difficult, but this is about to change with the EARS-Vet initiative [https://eu-jamrai.eu/surveillance/ears-vet/], which aims to monitor AMR in animal clinical isolates from across Europe. With a recent opening of AMR data submission, it is expected that a report with comparison of AMR data from different animal species (including dogs and cats) in European countries will become available in 2026.

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