National risikovurdering af antibiotikaklasser til kvæg

Christian Østergaard Andersen, SSI
Robert Skov, SSI
Ute Wolff Sönksen, SSI
Peter Damborg, KU
Luca Guardabassi, KU
Liza Rosenbaum Nielsen, KU
I samarbejde med Håkan Vigre (DTU), som har deltaget på lige vilkår, men ikke er en del af Dansk Veterinær Konsortium



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Håkan Vigre (DTU Fødevareinstituttet) har bidraget til udarbejdelsen af rapporten i samarbejde med Københavns Universitet og Statens Serum Institut; Dansk Veterinær Konsortium (DK-VET).

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Udarbejdet af Christian Østergaard Andersen, SSI, Robert Skov, SSI, Ute Wolff Sönksen, SSI, Peter Damborg, KU, Luca Guardabassi, KU, Liza Rosenbaum Nielsen, KU. I samarbejde med Håkan Vigre (DTU).

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Summary

This document presents an updated risk ranking of all antimicrobial classes used in Danish cattle production, based on their potential public health risk in Denmark, defined as the likelihood that use in cattle leads to increased resistance in humans and the consequences for the human healthcare system stemming from this resistance.

The ranking is based on the WHO framework for Medically Important Antimicrobials, adapted to Danish clinical practice. A primary ranking assigns antimicrobial classes to six categories (1 = lowest to 6 = highest risk) based on their clinical importance in Danish human medicine and on evidence for resistance transmission from cattle. A secondary ranking orders drugs within each category using human consumption levels, assuming that higher use in humans increases the likelihood that resistance originating in cattle will be selected and become established.

The highest-risk categories include fluoroquinolones and 3rd/4th generation cephalosporins, followed by aminopenicillins with β-lactamase inhibitors and apramycin (due to cross-resistance concerns with gentamicin used in hospitals). The report explains key deviations from the WHO list, notably the lower ranking of colistin in Denmark due to limited evidence of spillover and the availability of alternative human treatment options. In that regard, the authors recommend that potential changes in colistin use are followed by appropriate monitoring of associated resistance traits.

The document concludes that the ranking is relative, time-limited, and context-specific, and should be regularly re-evaluated and updated as resistance patterns, clinical guidelines, and antimicrobial use change over time. It stresses the importance of national surveillance and highlights colistin, apramycin, and tetracyclines as classes requiring particular attention in future evaluations.

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Purpose

The purpose of this risk assessment, or strictly speaking risk ranking, is to rank the antimicrobials used in the Danish cattle production according to their public health risks in Denmark. With public health risk we mean the *likelihood* that use of an antimicrobial in cattle will result in increased resistance in humans, and the *consequence* of this resistance. Special issues of particular relevance to antimicrobial use in cattle and resistance development are described in an appendix.

Principles and methodology

This risk ranking aims to combine internationally agreed standardized principles with insights from the Danish cattle production and human health in Denmark. It builds upon knowledge established from 30 years of surveillance of antimicrobial use (AMU) and antimicrobial resistance (AMR) in both food production and humans via the Danish surveillance programme DANMAP, including associated research on resistance genes, their dispersion and transmission and their possible impact on human health in Denmark.

The situation in the human sector in Denmark is favorable due to the proportionally higher use of penicillins than broader spectrum antibiotics in both primary care and hospital care. The primary use of such narrow-spectrum antibiotics reduces the overall antibiotic selection pressure in both society and vulnerable patient populations. To protect this situation, it is crucial to take both general (e.g. in society) and specific use (e.g. in critically ill patients) into account. Whenever relevant, knowledge specific to Danish conditions and circumstances can therefore overrule international recommendations in the methodology applied.

The present risk ranking is based on the risk assessment framework underpinning the World Health Organization (WHO) list of Medically Important Antimicrobials (MIA), which explicitly considers both clinical importance for human medicine and the potential for transmission of AMR to humans (WHO, 2024). The WHO MIA framework has subsequently informed the Antimicrobial Advice ad hoc Expert Group (AMEG) classification developed by the European Medicines Agency (EMA) (EMA, 2019). The WHO framework was selected because it captures the key factors relevant for public health decision-making. It was preferred over the EMA AMEG classification, because the latter includes an animal health-specific criterion on the availability of veterinary treatment alternatives, which falls outside the scope of the present assessment, focused exclusively on human health. The primary focus of this ranking is antimicrobial classes and subclasses currently authorized for use in cattle in Denmark. In addition, colistin and gentamicin were ranked, since these drugs were previously authorized for use in cattle in Denmark and because they are considered among last resort antibiotics in international risk rankings (colistin), or play a central role in Danish empiric treatment of hospitalized patients (gentamicin)

The WHO MIA list is based on two main criteria and classifies antimicrobial agents according to:

C1) their importance for treating serious diseases in humans.

C2) the potential for AMR to be transmitted to humans as a consequence of antimicrobial use in veterinary medicine and agriculture.

In our risk ranking, the methodology was adapted to better reflect and fit the Danish situation. As criterion C1 mirrors national choices in clinical treatment practices, it was agreed to broaden the definitions of C1 to include reflections on general usage (e.g. important antimicrobials in primary care) and the Danish AWaRe classification (Anhøj et al., 2022) in addition to antimicrobials needed for intensive care and treatment of rare infections or for critically ill patients suffering from bacteremia. Consensus on this adaptation was reached through discussions in a series of meetings among experts from SSI (Christian Østergaard Andersen,

Robert Skov and Ute Wolff Sönksen), UCPH (Peter Damborg, Luca Guardabassi, and Liza Rosenbaum Nielsen), and DTU (Håkan Vigre), supported by national data on human antimicrobial consumption and knowledge in regards to levels of AMR in human clinical infections.

Primary ranking

Antimicrobial classes and subclasses authorized for use in Danish cattle production were ranked according to their clinical importance in the Danish healthcare system, defined as their essential role in the treatment of bacterial infections in humans, including life-threatening conditions where effective therapeutic alternatives are limited or absent (WHO criterion C1). The ranking also incorporated the second WHO criterion (C2), which reflects scientific evidence on the potential for AMR to be transmitted to humans as a consequence of AMU in Danish cattle production. Based on these two criteria, antimicrobial classes were assigned to six hierarchical categories, ranging from 1 (lowest importance) to 6 (highest importance). This represented an adaptation of the WHO classification, which groups antimicrobials into four categories (Important Antimicrobials, Highly Important Antimicrobials, Critically Important Antimicrobials, and Highest Priority Critically Important Antimicrobials). We expanded the number of categories to six to allow a more nuanced differentiation of clinical importance and public health relevance in Denmark, thereby improving the usefulness of the framework for policy-making and risk management.

Secondary ranking

A secondary ranking criterion was applied to order the antimicrobials within each category defined by the primary ranking. This secondary criterion was based on the assumption that the primary determinant of the emergence and spread of resistant bacteria and resistance genes in the human population – upon transmission from animals - is the selective pressure exerted by AMU in Danish healthcare. Accordingly, antimicrobial classes within each category were ranked according to their level of consumption in the Danish human population, encompassing both hospital and primary care settings. In practical terms, when two antimicrobial classes were considered equally important for treating human infections, the class with higher use in humans was considered to pose a greater potential public health risk, as higher consumption increases the likelihood that resistance originating in the animal population will be selected and become established in humans. This secondary ranking criterion is a pragmatic simplification, as the actual risk of resistance transmission also depends on additional factors that are difficult to assess consistently across antimicrobial classes (e.g., genetic location of resistance determinants, potential for co-selection, associated fitness costs, and host adaptation of resistant bacteria of animal origin) as well as usage within specific, often vulnerable, patient populations, where consumption may be high, prolonged, and combined with other antimicrobials, which will not be mirrored in the total amount used nationally.

Results and discussion

The final outcomes of the risk ranking are presented in Table 1, and the following two paragraphs elaborate how the two ranking criteria contributed to the final ranking.

Table 1. Ranking of antimicrobial classes and subclasses authorized for use in the Danish cattle production, as well as colistin and gentamicin. Categories 1-6 reflect the primary ranking criteria, while ordering within categories follows the secondary ranking criterion (consumption in the Danish human population); darker shading indicates higher consumption within categories.

Antimicrobial class (ranked from highest risk at the top to lowest risk at the bottom)	Primary Ranking[a]	Secondary Ranking[b]
Fluoroquinolones	6	0.40
3rd and 4th gen. Cephalosporins	6	0.16
Aminopenicillins + β-lactamase inhibitors	5	0.88
Aminoglycoside I (apramycin/gentamicin)	5	0.04 (gentamicin)
Tetracyclines	4	1.89
Macrolides	4	1.68
Aminopenicillins	4	1.67[c]
Polymyxins (colistin)	4	0.02
1st gen. cephalosporins	4	0.0008
Lincosamides	3	0.13
Amphenicols	3	0
Pleuromutilines	3	0
Beta-lactamase-susceptible penicillins (e.g. benzylpenicillin)	2	3.70
Beta-lactamase-resistant penicillins (e.g. cloxacillin)	2	2.10
Sulfonamides/TMP	2	0.43/0.58
Aminoglycoside II (Neomycin/paromomycin/dihydrostreptomycin/ framycetin)	1	0

[a] *Clinical importance of the antimicrobial class for the treatment of serious bacterial infections in humans in Denmark, based on the WHO classification adapted to the Danish healthcare context, and scientific evidence on the potential for AMR to be transmitted to humans as a consequence of AMU in Danish cattle production.*

[b] *Level of antimicrobial consumption in the Danish human population, based on national use data expressed as DID (defined daily doses per 1,000 inhabitants per day).*

[c] *Consumption of aminopenicillins includes aminopenicillins combined with β-lactamase inhibitors.*

Adaptation of the WHO MIA list to the Danish context (Primary Ranking Criterion)

Table 2 provides an overview of similarities and differences between our primary ranking (categories 1-6) and the WHO MIA list. The ranks of the WHO MIA list are not directly comparable with those of our current ranking system (Table 1). Nevertheless, we summarize in the following our rationale for the most pronounced differences seen between scores of the WHO MIA list and our current ranking of antibiotics.

Colistin differs from the highest WHO category HPCIA ('highest-priority critically important antimicrobials') in the present ranking where it is classified as the third-highest risk category. Available Danish surveillance provides little evidence that the cattle population constitutes an important source of plasmid-mediated colistin resistance in humans. No phenotypic colistin resistance was detected among 1,418 indicator *Escherichia coli* isolates collected from Danish cattle through DANMAP surveillance during 2015–2024, or among 101 clinical Enterobacterales isolates from mastitis cases in 2024 (Danmap, 2024). DANMAP likewise reported no colistin resistance in indicator *E. coli* from Danish pigs and broilers during this period. This is consistent with the low occurrence of plasmid-associated *mcr* genes among Danish human clinical isolates in 2021–2025, in which only 37 of 14,558 isolates were positive (0.25%; Frederik Boëtius Hertz, Rigshospitalet, personal communication). This should be interpreted as limited evidence of livestock-to-human spillover rather than proof of its absence, because not all livestock indicator isolates have undergone comprehensive genomic screening for mcr variants. In addition, the availability in human medicine of alternative antimicrobials with less side effects for selected cases of infections caused by carbapenemase-producing bacteria, makes colistin less prone to being the only treatment choice than used to be the case earlier.

Aminoglycosides used in cattle production, which are all grouped into the WHO category CIA ('critically important antimicrobials'), were split into two categories with different risks to human health: **apramycin** and **gentamicin** were ranked in the second-highest risk category in our classification system because of their potential to select for resistance to gentamicin, a critical antimicrobial used for treatment of bacteraemia in Danish hospitals. Conversely, **neomycin**, its analogues **paromomycin and framycetin**, and **dihydrostreptomycin** were assigned to the lowest risk category given their limited relevance for human medicine (only topical neomycin products) and the apparent lack of cross-resistance to other aminoglycosides used in human medicine.

Aminopenicillins and **tetracyclines** represent the WHO category HIA ('highly important antimicrobials') and in our classification belong to what can be considered a higher risk category, reflecting public health concerns. In particular, aminopenicillins are used for multiple infection types in human medicine, and as the first choice in several hospitals for treatment of septicaemia. Furthermore, a significant association has been shown at the EU level between aminopenicillin use and resistance in food animals and resistance in human *E. coli* invasive infections (ECDC/EFSA/EMA, 2024). Tetracyclines are widely used in primary care, including for infections caused by *Borrelia* and *Mycoplasma*. LA-MRSA CC398 has been detected at low prevalence in Danish veal and dairy herds, and Danish bovine LA-MRSA CC398 isolates have been shown to carry tetracycline-resistance genes. Hansen et al. (2019) found that 20 isolates examined in one study carried *tet(M)*, and nine additionally carried *tet(K)*. Tetracycline use could therefore contribute to the co-selection or persistence of LA-MRSA where it occurs, although Danish cattle are currently considered a minor reservoir compared with pigs. This remains relevant to the Danish healthcare system, where maintaining a low prevalence of MRSA is a priority.

Aminopenicillins with β-lactamase inhibitors were ranked higher than **aminopenicillins without β-lactamase inhibitors** because of their broader spectrum, higher selection pressure, and consequently higher AMR risk for human health, in line with the AMEG classification.

First-generation cephalosporins, which belong in the WHO HIA category, were ranked in category 4, since their antimicrobial spectrum is similar to that of aminopenicillins. Currently, this class is only used sparsely in Danish healthcare. Accordingly, it is ranked lowest amongst the antimicrobials of category 4.

Macrolides, which belong to the second highest WHO category (CIA), were in our ranking graded lower than gentamicin and aminopenicillins combined with β-lactamase inhibitors due to their lower importance in Danish healthcare for the treatment of serious infections compared to gentamicin and aminopenicillins combined with β-lactamase inhibitors. Macrolides are still important for treatment of commonly occurring infections in the primary sector (e.g. *Mycoplasma* infections in children and adolescents) as well as for usage in patients with allergy to beta-lactams.

Table 2. Ranking of antimicrobials used in cattle production based on clinical importance in Danish healthcare (Criterion 1) and comparison to the WHO MIA list.

Antimicrobial class	DK 2026	WHO 2024*
Fluoroquinolones	6	HPCIA
3rd and 4th gen. cephalosporins	6	HPCIA
Aminopenicillins + β-lactamase Inhibitors	5	HIA
Aminoglycosides I (apramycin)	5	CIA
Aminopenicillins	4	HIA
Tetracyclines	4	HIA
Macrolides	4	CIA
Polymyxins (colistin)	4	HPCIA
1st gen. cephalosporins	4	HIA
Lincosamides	3	HIA
Amphenicols	3	HIA
Pleuromutilins	3	IA
Beta-lactamase-susceptible penicillins	2	HIA
Beta-lactamase-resistant penicillins	2	HIA
Sulfonamides and TMP	2	HIA
Aminoglycosides II (neomycin/paromomycin/dihydrostreptomycin/framycetin)	1	CIA

* HPCIA. High-priority critically important antimicrobials; CIA, critically important antimicrobials; HIA, highly important antimicrobials; IA, important antimicrobials

Consumption in the Danish human population (Secondary Ranking Criterion)

Human consumption data from DANMAP 2024 show that β-lactamase-sensitive penicillins are by far the most widely used antimicrobials in Danish healthcare, followed by tetracyclines, macrolides, and aminopenicillins with and without β-lactamase inhibitors. Consumption of all other antimicrobial classes is substantially lower, irrespective of the metric used (Table 1).

Concluding remarks

Antimicrobials authorized currently or previously for use in cattle were ranked relative to each other according to the human risk associated with their use in Danish cattle production. No attempt was made to estimate the absolute risk related to the use of the antimicrobial classes in cattle production, as this is not possible given the current level of knowledge. Although quantitative estimation is not feasible, there is scientific evidence that the use of any antimicrobial class in livestock can contribute to human health risks related to AMR.

This risk ranking highlights the importance of integrated national surveillance systems in supporting evidence-based risk assessment and policy-making. Compared with previous assessments, the present approach is semi-quantitative, enabling direct comparison across all antimicrobial classes by assigning a relative risk level to each class. It provides a flexible basis for future updates and can be readily adapted as new evidence emerges or as patterns of AMU and AMR change over time. Consequently, the results are inherently time-limited and should be regularly re-evaluated in light of updates to national clinical guidelines for the treatment of serious infections, as well as ongoing monitoring of antimicrobial consumption in humans and the epidemiology of AMR in both human and zoonotic pathogens.

In line with the time-limited nature of the present risk ranking, particular attention should be given to antimicrobial classes for which changes in use may have important public health implications. For colistin and apramycin/gentamicin, the authors recommend that potential changes in veterinary use of these antimicrobials are followed by appropriate monitoring of associated resistance traits. This is particularly relevant because colistin is ranked as posing a lower risk to human health in Denmark than apramycin and gentamicin and may therefore represent a valuable potential alternative for treatment of infections like diarrhoea in calves.

Notably, this risk ranking is specific to the current Danish context and may not apply to other countries, as the associated human health risk depends on national patterns of AMR and AMU.

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