Dansk Veterinær Konsortium

KØBENHAVNS UNIVERSITET | STATENS SERUM INSTITUT

National risikovurdering af antibiotikaklasser til grise

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National risikovurdering af antibiotikaklasser til grise

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Summary

This document presents an updated risk ranking of all antimicrobial classes used in Danish pig production, based on their potential public health risk in Denmark, defined as the likelihood that use in pigs leads to increased resistance in humans and the consequences for the human healthcare system stemming from this resistance. It updates the previous Danish assessment from 2017 and is grounded in 30 years of integrated surveillance data from DANMAP.

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 pigs. 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 pigs 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 alternative human treatment options—while emphasizing that any change in colistin use must be conditional on strengthened monitoring of associated resistance traits.

The document concludes that the ranking is relative, time-limited, and context-specific, and should be regularly 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 pig production according to their public health risks in Denmark. With public health risk we mean the *likelihood* that use of an antimicrobial in pigs will result in increased resistance in humans, and the *consequence* of this resistance.

This work should be regarded as a continuation and update of a previous Danish risk assessment, completed in 2017.

The working group emphasizes that any changes in antimicrobial use in animals should only be implemented alongside close monitoring and surveillance. This is particularly important for colistin, for which any recommended change in use should be conditional on the establishment of an appropriate monitoring system.

Principles and methodology

This risk ranking attempts to combine internationally agreed standardized principles with insights from the Danish pig production and human health in Denmark. It builds upon knowledge established from 30 years of surveillance of antimicrobial use and antimicrobial resistance 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 high use of penicillins 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 therefore overrules international recommendations in the methodology applied.

The present risk ranking covers all antimicrobial classes and subclasses used in pig production in Denmark. It is based on the risk assessment framework underpinning the World Health Organization (WHO) list of Medically Important Antimicrobials (MIA)[1], which explicitly considers both clinical importance for human medicine and the potential for transmission of antimicrobial resistance to humans. The WHO MIA framework has subsequently informed the Antimicrobial Advice ad hoc Expert Group (AMEG) classification developed by the European Medicines Agency (EMA)[2]. The WHO framework was selected because it captures the key factors relevant for public health decision-making that were also addressed in the previous Danish risk assessment. 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. Furthermore, only antimicrobial classes and subclasses authorized for use in pigs in Denmark were included in the risk ranking.

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.

[1] World Health Organization. WHO's List of Medically Important Antimicrobials: a risk management tool for mitigating antimicrobial resistance due to non-human use. Geneva: World Health Organization; 2024. License: CC BY-NC-SA 3.0 IGO. Available online at https://www.who.int.

[2] European Medicines Agency (EMA). Categorisation of antibiotics in the European Union. Answer to the request from the European Commission for updating the scientific advice on the impact on public health and animal health of the use of antibiotics in animals Antimicrobial Advice ad hoc Expert Group (AMEG) (updated advice published Sep 2025). Available online at https://www.ema.europa.eu.

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C2) the potential for antimicrobial resistance (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 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 Jens Peter Nielsen), and DTU (Frank Møller Aarestrup and 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 used in Danish pig 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 antimicrobial use in Danish pig 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 antimicrobial use 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 are 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 pigs 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, which will not be mirrored in the total amount used nationally.

Results

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 used in pig production. 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)	5	0,04 (gentamicin)
Tetracyclines	4	1,89
Macrolides	4	1,68
Aminopenicillins	4	1,67[c]
Polymyxins (colistin)	4	0,02
Lincosamides	3	0,13
Amphenicols	3	0
Pleuromutilines	3	0
Penicillin	2	3,70
Sulfonamides/TMP	2	0,43/0,58
Aminoglycoside II (Neomycin/paromomycin/dihydrostreptomycin)	1	0
Aminocyclitols (Spectinomycin)	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.

[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.

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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), the WHO MIA list and the outcome of the previous risk assessment in 2017. 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. This is due to is limited

evidence of spillover of colistin resistance from pigs to humans in Denmark, since only 37 of 14,558 human clinical isolates (0.2%) from 2021-2025 contained the plasmid-associated colistin resistance gene mcr (personal communication, Frederik Boëtius Hertz, Rigshospitalet) and since there historically has been no indication of this gene in neither indicator nor clinical isolates from pigs in Denmark. In addition, the availability 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 pig 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** was ranked in the second-highest risk category in our classification system because of its potential to select for resistance to gentamicin, a critical antimicrobial used for treatment of bacteraemia in Danish hospitals. Conversely, **neomycin** ~~and the~~ , its analogue **paromomycin**, 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.

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Aminopenicillins and **tetracyclines** represent the WHO category HIA ('highly important antimicrobials') and in our classification belongs 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[3]. Tetracyclines are widely used in primary care, including for infections caused by *Borrelia* and *Mycoplasma*. Furthermore, there is evidence that tetracycline use in pigs contribute to the co-selection of livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA), which is a significant concern in the Danish healthcare system, where maintaining a low MRSA prevalence 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.

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. Albeit 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. They are therefore still to be used with caution in the veterinary food production.

[3] EFSA J. 2024 Feb 23;22(2):ep220201. doi: 10.2903/j.efsa.2024.p220201

Table 2. Ranking of antimicrobials used in pig production based on clinical importance in Danish healthcare (Criterion 1) and changes compared to the WHO MIA list and the previous Danish risk assessment (DK 2017).

Antimicrobial class	DK 2025	WHO 2024*	DK 2017
Fluoroquinolones	6	HPCIA	Very high risk
3rd and 4th gen. cephalosporins	6	HPCIA	Very high risk
Aminopenicillins + β-lactamase Inhibitors	5	HIA	High risk
Aminoglycosides I (apramycin)	5	CIA	High risk
Aminopenicillins	4	HIA	High risk
Tetracyclines	4	HIA	Medium risk
Macrolides	4	CIA	Medium risk
Polymyxins (colistin)	4	HPCIA	Very high risk
Lincosamides	3	HIA	Medium risk
Amphenicols	3	HIA	Medium risk
Pleuromutilins	3	IA	Medium risk
Penicillins	2	HIA	High risk
Sulfonamides and TMP	2	HIA	Medium risk
Aminoglycosides II (neomycin/paromomycin/dihydrostreptomycin)	1	CIA	Medium risk**
Aminocyclitols (spectinomycin)	1	IA	ND

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

** Paromomycin and dihydrostreptomycin were not assessed in the risk assessment from 2017.

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 ~~3~~1).

Table 3. Consumption of antimicrobial agents for systemic use in Danish health care, including both hospitals and primary care, expressed as DDD per 1000 inhabitants per day (DANMAP 2024).

Antimicrobial class	DDD/1000 inhabitants/day
β-lactamase sensitive penicillins	3,70
Tetracyclines	1,89
Macrolides	1,68
Aminopenicillins + β-lactamase inhibitors	0,88
Aminopenicillins	1,67[a]
Trimethoprim	0,36[b]
Lincosamides	0,13
Gentamicin	0,04
Sulfonamides	0,07[b]

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

[b] The human consumption of 337099 DDD (0,1549 DID) combination products with sulfonamides+trimethoprim is not included, as the consumption could not be split into the two individual compounds.

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Concluding remarks

In this work, we ranked antimicrobials relative to each other according to the human risk associated with their use in Danish pig production. No attempt was made to estimate the absolute risk related to the use of the antimicrobial in pig production, as this is not possible given the current level of knowledge. Although quantitative estimation is not feasible, there is strong 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 antimicrobial use 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, any modification of use in pig production should remain strictly conditional on continued, targeted surveillance of antimicrobial consumption and resistance trends. In addition, tetracyclines, whose ranking was unchanged in the present assessment, should be explicitly considered for re-evaluation in the next national risk assessment, or within the next 2–3 years, considering updated consumption data and emerging evidence on resistance dynamics. 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 antimicrobial use.

References

1. World Health Organization. (2024). WHO list of medically important antimicrobials: A risk management tool for mitigating antimicrobial resistance due to non-human use. https://cdn.who.int/media/docs/default-source/gcp/who-mia-list-2024-lv.pdf

2. European Medicines Agency. (2019). Categorisation of antibiotics in the European Union: Answer to the request from the European Commission for updating the scientific advice on the impact on public health and animal health of the use of antibiotics in animals (EMA/CVMP/CHMP/682198/2017). European Medicines Agency. https://www.ema.europa.eu/

3. European Centre for Disease Prevention and Control, European Food Safety Authority, & European Medicines Agency. (2024). Antimicrobial consumption and resistance in bacteria from humans and food-producing animals: Fourth joint inter-agency report on integrated analysis of antimicrobial agent consumption and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the EU/EEA (JIACRA IV 2019–2021). ECDC, EFSA, EMA. https://doi.org/10.2903/j.efsa.2024.8589