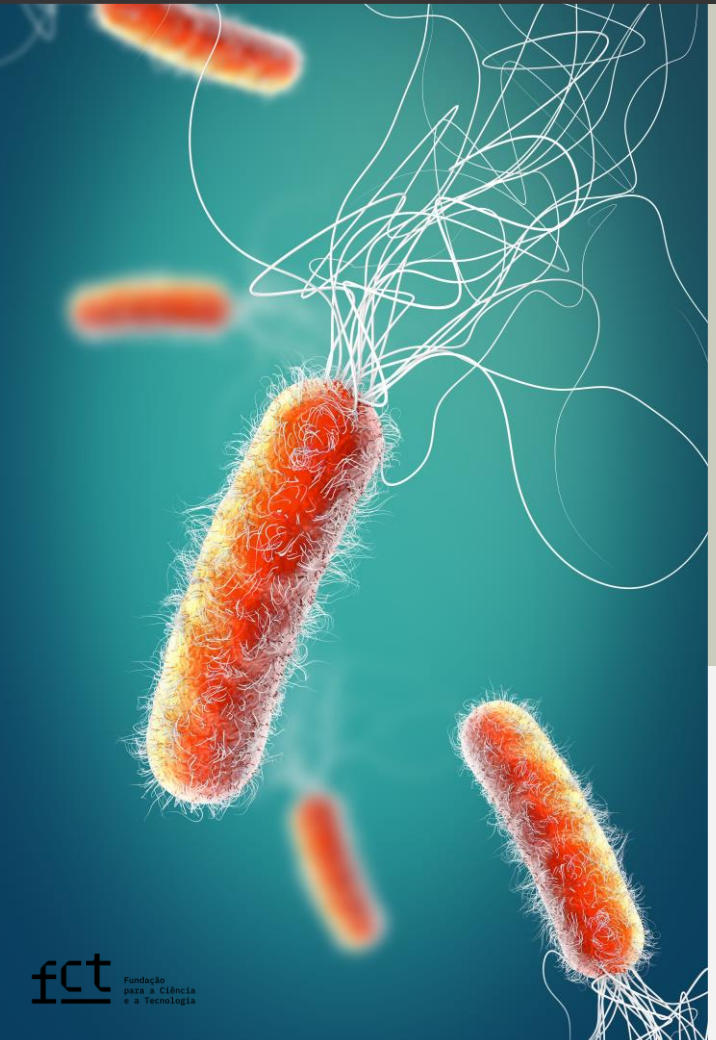

A Systematic Review and Meta-analysis on the Effectiveness of Antimicrobial Interventions to Tackle Antimicrobial Resistance in Animal Production

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Background – Antimicrobial Resistance

1 of the 3 main threats to populations, together with tabacco and obesity

Ranked by global BoD as the 3rd major cause of death

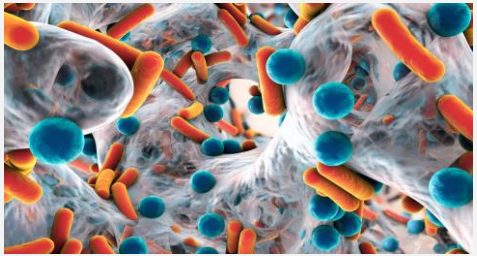
Dissemination from animals to workers or from food products to consumers

ARC, 2022; O'Neill, 2016

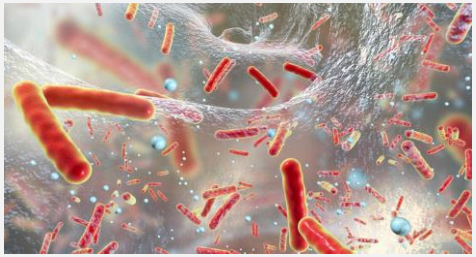
Background – Antimicrobial Selective Pressure

Inappropriate administration and over-use AM

Quick microbial adaptation in animal production



Emergence and spread of resistant bacteria



Why this study?

Interventions are needed to improve antimicrobials prudent use, reduce their selective pressure and prevent the emergence of new resistant strains

There is limited evidence concerning the effectiveness of such interventions

Types of Antimicrobial use in Animal Production

Conventional production	Organic production	Antibiotic-free farms
▪Antimicrobials used to prevent, control and treat diseases ▪Animals confined to smaller spaces	▪Therapeutic use of antimicrobials ▪Safeguard in the frequency of therapy ▪Longer withdrawal periods	▪Avoid antimicrobials usage ▪Animals that become sick are treated, relocated, lose their label

Group treatments	Antimicrobials for growth promotion
▪To treat, control or prevent infectious disease in a group of animals at risk of aquiring a specific infection and control its spread	▪Non-therapeutic reasons ▪Increase performance converting feed into meat

(EU) 2019/6; (EU) 2018/848 WOAH, 2021; Pesciaroli et al, 2020; Van Wagenberg et al, 2017

Material and Methods

Main topic	Objective	Time/ Languages
Interventions on AMU to tackle AMR emergence	Evaluate the effectiveness of global interventions to reduce veterinary antimicrobial usage in **chicken** and **pig** production	August 2022 EN, PT, ES, FR, IT

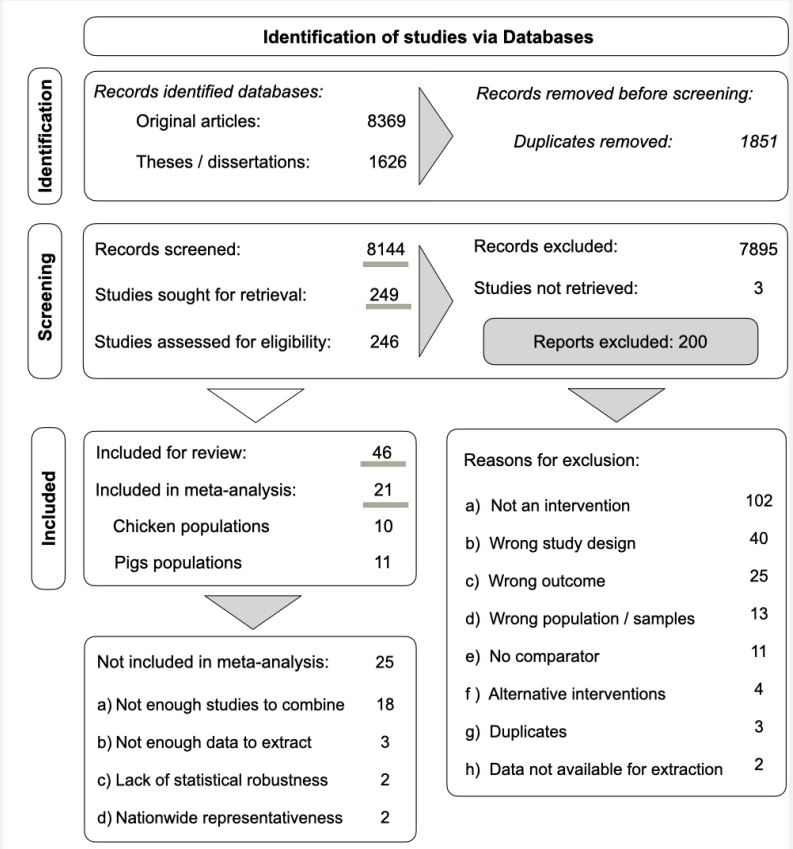
Exclusion criteria	Study Design & Statistical Analysis	Data source
(1) Prebiotics, probiotics, oils or extracts of plants (2) Studies addressing only organic production (3) experimental or ecological studies	Systematic review Meta-analysis *Preventive Veterinary Medicine* *doi: 10.1016/j.prevetmed.2023.106002*	Original articles: PubMed, Scopus, Cochrane Library, Web of Sciences Grey literature: RCAAP, WorldCat, Dans EASY

Material and Methods

-Study led according to PRISMA

-Protocol registered PROSPERO ID CRD42022335386

-Rayyan software to assist screening stages



Interventions on Reducing & Restricting Antimicrobial use

1. Use of antimicrobials only for therapeutic (organic production)
2. Prohibition of antimicrobials as growth promoters
3. Group treatment restrictions (for prophylactic and metaphylactic purposes)
4. Complete restriction of **specific** antimicrobials
5. Complete restriction of **all** antimicrobials (antibiotic-free environment)

Results

Table 2
Descriptive statistics of studies included in the systematic review for chickens' production.

	Restrictions on antimicrobials % (n)				
	Growth promoters $n = 6$	Non-therapeutic restriction $n = 12$	Complete restriction $n = 7$	Overall reduction $n = 1$	Total $n = 26$
Comparator					
Historical comparator	0	0	14.3 (1)	0	3.8 (1)
Before and after intervention	66.7 (4)	33.3 (4)	0	0	30.8 (8)
Same type of production	33.3 (2)	8.3 (1)	0	100.0 (1)	15.4 (4)
Different types of production	0	58.3 (7)	57.1 (4)	0	42.3 (11)
Associations AMU/AMR	0	0	28.6 (2)	0	7.7 (2)
Study design					
Cross-sectional	83.3 (5)	100.0 (12)	71.4 (5)	100.0 (1)	88.5 (23)
Cohort	0	0	14.3 (1)	0	3.8 (1)
Quasi-experimental	16.7 (1)	0	0	0	3.8 (1)
Not observable	0	0	14.3 (1)	0	3.8 (1)
Intervention year					
1995–2000	83.3 (5)	0	0	0	19.2 (5)
2011–2018	16.7 (1)	33.3 (4)	28.6 (2)	100.0 (1)	30.8 (8)
Not applicable/Not reported	0	66.3 (8)	71.4 (5)	0	50.0 (13)
Region					
America	0	8.3 (1)	71.4 (5)	0	23.1 (6)
Asia	33.3 (2)	25.0 (3)	14.3 (1)	0	23.1 (6)
Europe	66.7 (4)	66.7 (8)	14.3 (1)	100.0 (1)	53.8 (14)
Production type					
Conventional	33.3 (2)	8.3 (1)	14.3 (1)	100.0 (1)	19.2 (5)
Organic	16.7 (1)	58.3 (7)	28.6 (2)	0	38.5 (10)
Antibiotic-free	0	0	42.8 (3)	0	11.5 (3)
Not reported	50.0 (3)	33.4 (4)	14.3 (1)	0	30.8 (8)
Production system					
Indoor	33.3 (2)	8.3 (1)	0	100.0 (1)	15.4 (4)
Outdoor	16.7 (1)	33.4 (4)	42.9 (3)	0	30.8 (8)
Not reported	50.0 (3)	58.3 (7)	57.1 (4)	0	53.8 (14)
Sample type					
Animal	100.0 (6)	83.4 (10)	57.1 (4)	0	76.9 (20)
Environmental	0	8.3 (1)	14.3 (1)	100.0 (1)	11.5 (3)
Animal/environmental	0	8.3 (1)	28.6 (2)	0	11.5 (3)
Bacteria $n = 30$[b]					
Escherichia coli	0	50.0 (8)	57.1 (4)	100.0 (1)	43.3 (13)
Enterococcus spp.	66.6 (4)	6.2 (1)	14.3 (1)	0	20.0 (6)
Salmonella spp.	0	12.5 (2)	28.6 (2)	0	13.3 (4)
Campylobacter spp.	16.7 (1)	31.3 (5)	0	0	20.0 (6)
Clostridium perfringens	16.7 (1)	0	0	0	3.3 (1)

Table 3
Descriptive statistics of studies included in the systematic review for pig's production.

	Restrictions on antimicrobials % (n)				
	Growth promoters $n = 1$	Group treatment $n = 6$	Non-therapeutic restriction $n = 10$	Complete restriction $n = 10$	Total $n = 27$
Comparator					
Historical comparator	0	0	0	10.0 (1)	3.7 (1)
Before and after intervention	100.0 (1)	16.7 (1)	10.0 (1)	0	11.1 (3)
Same type of production	0	66.6 (4)	10.0 (1)	40.0 (4)	33.3 (9)
Different types of production	0	0	70.0 (7)	40.0 (4)	40.7 (11)
Associations AMU/AMR	0	16.7 (1)	10.0 (1)	10.0 (1)	11.1 (3)
Study design					
Cross-sectional	100.0 (1)	66.6 (4)	100.0 (10)	80.0 (8)	85.2 (23)
Cohort	0	0	0	10.0 (1)	3.7 (1)
Quasi-experimental	0	33.4 (2)	0	0	7.4 (2)
Not observable	0	0	0	10.0 (1)	3.7 (1)
Intervention year					
1995–2000	100.0 (1)	0	0	0	3.7 (1)
2011–2018	0	16.7 (1)	10.0 (1)	10.0 (1)	11.1 (3)
Not applicable/Not reported	0	83.3 (5)	90.0 (9)	90.0 (9)	85.2 (23)
Region					
Africa	0	0	10.0 (1)	0	3.7 (1)
America	0	33.3 (2)	10.0 (1)	50.0 (5)	29.6 (8)
Asia	0	33.3 (2)	20.0 (2)	20.0 (2)	22.2 (6)
Europe	100.0 (1)	33.3 (2)	60.0 (6)	30.0 (3)	44.4 (12)
Production type					
Conventional	100.0 (1)	50.0 (3)	10.0 (1)	40.0 (4)	33.3 (9)
Organic	0	16.7 (1)	70.0 (7)	0	29.7 (8)
Antibiotic-free	0	0	0	40.0 (4)	14.8 (4)
Not reported	0	33.3 (2)	20.0 (2)	20.0 (2)	22.2 (6)
Production system					
Indoor	0	50.0 (3)	0	30.0 (3)	22.2 (6)
Outdoor	0	16.7 (1)	30.0 (3)	20.0 (2)	22.2 (6)
Not reported	100.0 (1)	33.3 (2)	70.0 (7)	50.0 (5)	55.6 (15)
Sample type					
Animal	100.0 (1)	66.7 (4)	80.0 (8)	80.0 (8)	77.8 (21)
Environmental	0	0	0	10.0 (1)	3.7 (1)
Animal/environmental	0	33.3 (2)	20.0 (2)	10.0 (1)	18.5 (5)
Bacteria n = 31[a]					
Escherichia coli	0	100.0 (6)	42.8 (6)	60.0 (6)	58.1 (18)
Enterococcus spp.	100.0 (1)	0	14.3 (2)	10.0 (1)	12.9 (4)
Salmonella spp.	0	0	14.3 (2)	10.0 (1)	9.7 (3)
Campylobacter spp.	0	0	14.3 (2)	20.0 (2)	12.9 (4)
Staphylococcus aureus	0	0	14.3 (2)	0	6.4 (2)

Results

Protective Effect of the Interventions

For most antimicrobials in *E. coli* and *Campylobacter* isolates from **pig samples**

For most antimicrobials in *E. coli*, *Campylobacter* and *Enterococcus* isolates from **chicken samples**

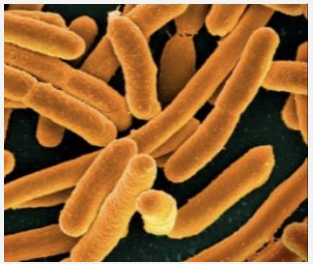
For all assessed antimicrobials in *E. coli* and conventionally raised pigs with group treatment restrictions

(Fluoro)quinolones: NAL - Nalidixic acid, CIP - Ciprofloxacin, ENR - Enrofloxacin, MBX - Marblofoxacin; 3rd generation cephalosporins: CTX - Cefotaxime, CFD - Ceftazidime, CEF - ceftiofur, CPD - Cefpodoxime; Sulphonamides/combinations: SXT - Sulfamethoxazole, TMP - Trimethoprim, SXT-TMP - Trimethoprim/Sulphamethoxazole; Tetracyclines: TET - Tetracycline; Penicillins: AMP - Ampicillin, MET - Methicillin, PIP - Piperacillin; Aminoglycosides: GEN - Gentamicin; KAN - Kanamycin; STR - Streptomycin; TBM - Tobramycin; Macrolides: AZM - Azithromycin, ERY - erythromycin; Polymyxins: COL - Colistin; MDR: Multi-drug resistance; ESBL: Extended spectrum beta-lactamases.

↑ odds of resistance for cephalosporins in *E. coli* (broilers) and to fluoroquinolones in *Campylobacter* (pigs) raised without antimicrobials

Comparator

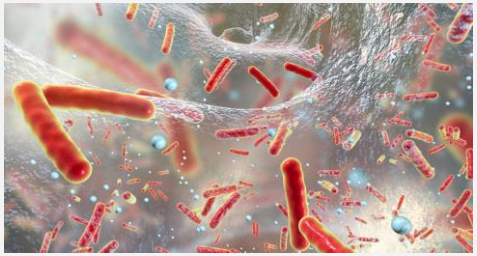
Conventionally raised animals (without intervention)



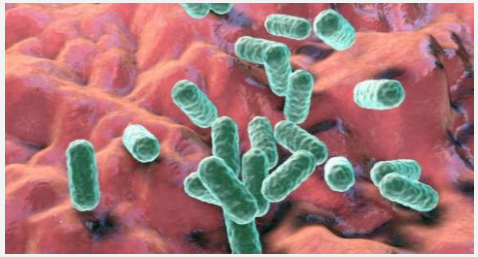
Discussion

Protective effect of reducing/restricting interventions to almost all antimicrobials for several species

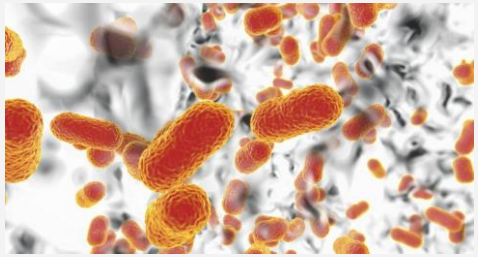
In order to ↓ antimicrobial selective pressure and resistance:



Transition of conventional to organic and antibiotic-free environments.



Group treatment restrictions should be extended to countries outside the EU.



AMR pre-movement testing to ↓ risk of contamination to other farms.

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