



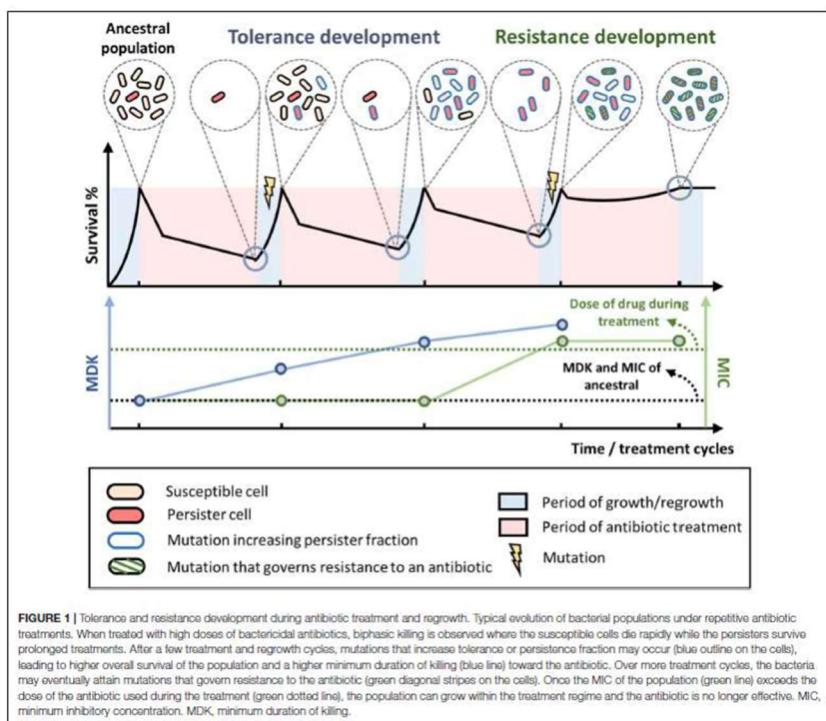
26/11/2025

# A strong regulation on antimicrobial use in the EU



# Antimicrobial resistance

## Development process

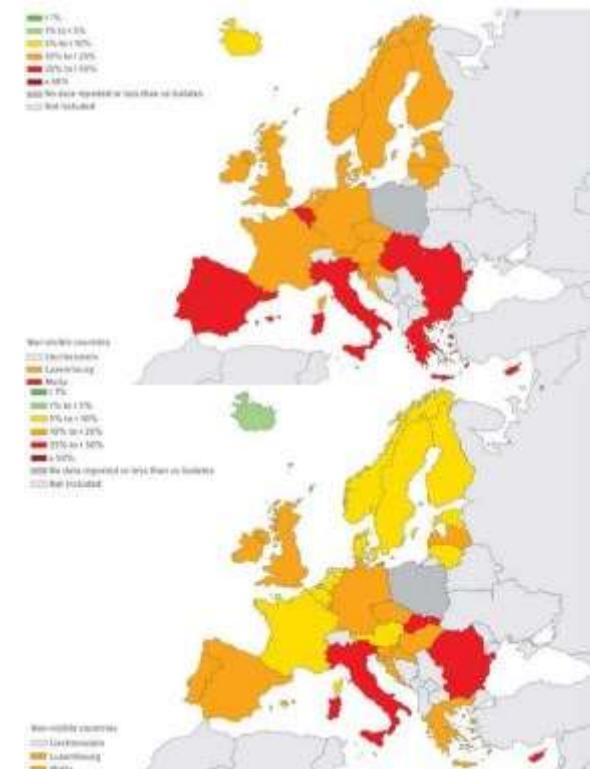


- Distinction between **tolerance** : protection against specific ATB, allowing them to grow at higher ATB level.
- and **resistance** : direct inactivation of the ATB, alteration of drug target to reduce binding affinity, decrease uptake or increasing efflux, redundant pathways to bypass the affected drug targets, and many more. Most common detection method : MIC (minimum inhibitory concentration).

# Antimicrobial resistance

## Antimicrobial resistance – a rising concern

- **1950** : Start to use ATB as growth promoters in animal feed
- **1969** : Swann Committee of the United Kingdom recommended that antibiotics used in human chemotherapy should not be used as in-feed antibiotics (e.g. tetracyclines).
- **1999** : EU restricts the use of ATB in feed as a precautionary measure to minimize the risk of the development of resistant bacteria and to preserve the efficacy of certain antibiotics used in human medicine
- **2006** EU bans all ATB use as growth promoters



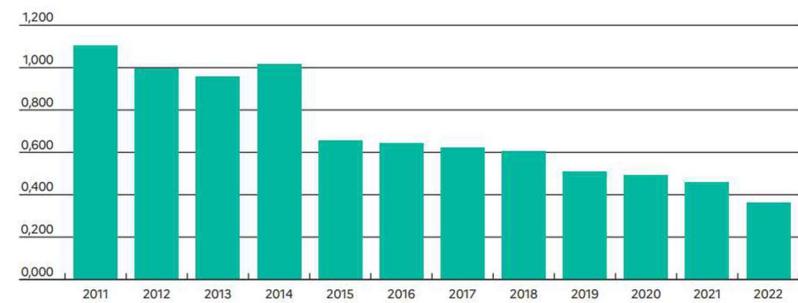
E.Coli % of invasive isolates with resistance to fluoroquinolones (top) & cephalosporin (bottom), 2014  
Da Costa et Machado 2017

# EU setting the path for antimicrobial free farming

## Antimicrobial resistances an ongoing concern for EU countries

- **2009** a work from the EU Commission estimates that infections linked to ATB resistance caused the death of over 25 000 patient in all member states, being linked to direct and indirect costs of more than 1,5 billions euros
- **2012-2017** France plan Eco Antibio 1 : reduction of ATB use by 25%
- **2017-2021** France plan Eco Antibio 2 : evaluate impact of first plan an maintain tendency to reduce ATB use, leading to a reduction of **52% of ATB use in France**

Figure 2. Exposition des porcs aux antibiotiques entre 2011 et 2022 (indicateur ALEA)

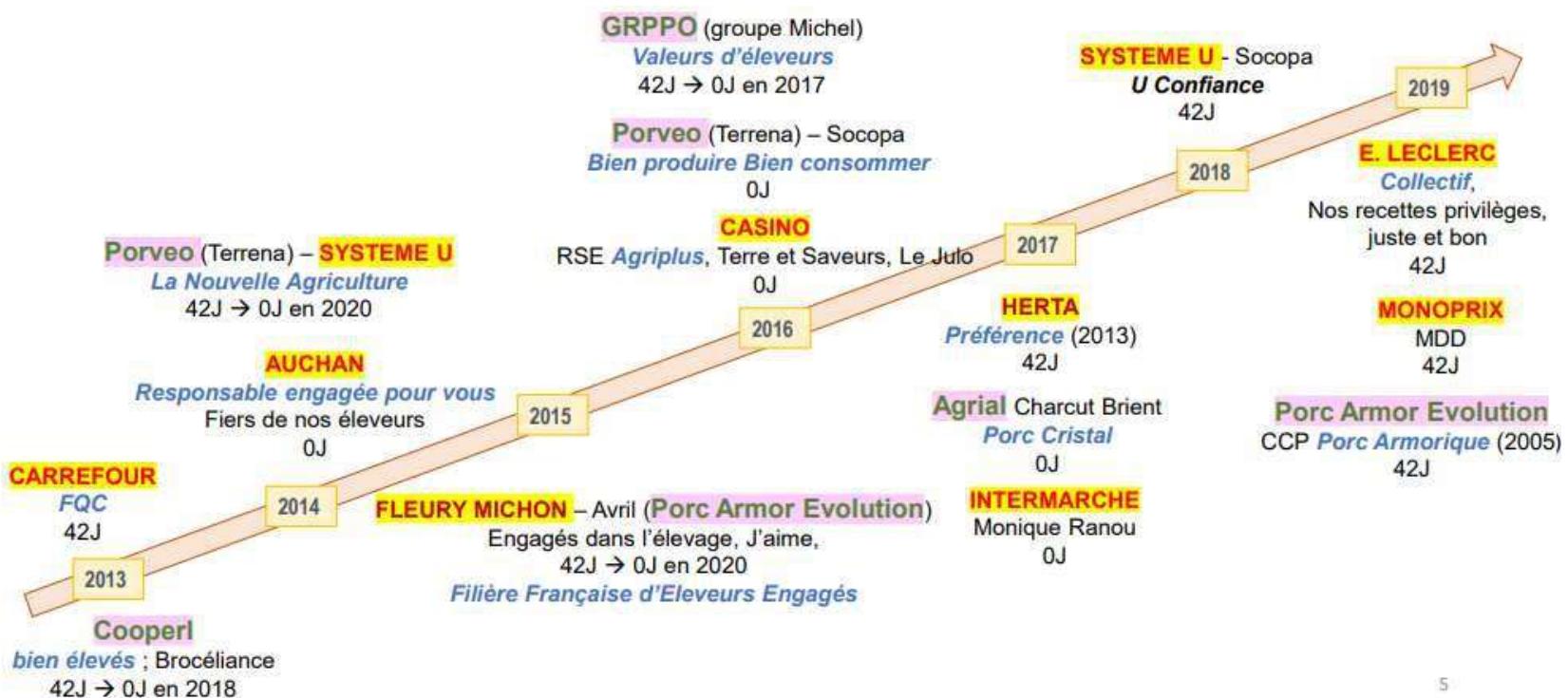


10. D'après le suivi des ventes de médicaments vétérinaires contenant des antibiotiques en France en 2022 réalisé par l'ANSES.

Plan Eco Antibio 2023

# EU setting the path for antimicrobial free farming

Numerous production chain programs without any antibiotic from birth or 42 days of age were set up in France



# EU setting the path for antimicrobial free farming

## Leading to a ban of ATB use in feed in 2019 in the EU

### Regulation 2019/4 on medicated Feed :

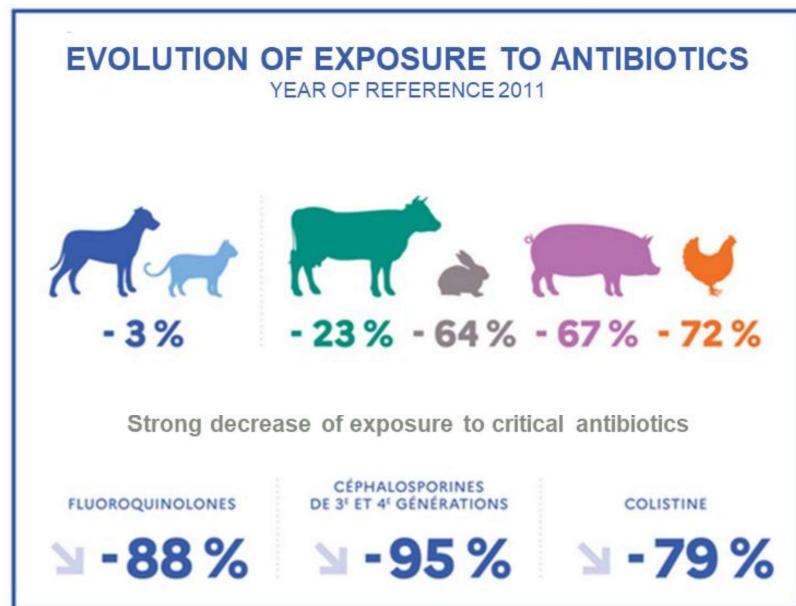
- No use of antimicrobial medicated feed for prophylaxis

### and 2019/6 on Veterinary Medicinal Products :

- No routine antimicrobial use and no use to compensate for poor hygiene and husbandry
  - Article 107.1 states: "*Antimicrobial medicinal products shall not be applied routinely nor used to compensate for poor hygiene, inadequate animal husbandry or lack of care or to compensate for poor farm management.*"
- No antimicrobial use for growth promotion
- Ban on prophylactic group treatments
- Restrictions on metaphylactic use of antimicrobials
- Article 107.4 states : "*Antimicrobial medicinal products shall be used for metaphylaxis only when the risk of spread of an infection or of an infectious disease in the group of animals is high and where no other appropriate alternatives are available.*"
- List of antibiotics to be reserved for human use
- Collection of antibiotic-usage data by animal species

# EU setting the path for antimicrobial free farming

## Strong goals to continue ATB use reduction



Evolution of animal exposure from 2011 to 2022 (ANSES).

Table 3 Antibiotic use per PCU by species in France in 2007 and 2020 (mg/kg) <sup>[7][69]</sup>

	Cattle	Pigs	Poultry	Sheep/Goats	Rabbits
2007	71	349	125	61	2538
2020	38	73	64	51	775
Reduction	-46%	-79%	-49%	-16%	-69%

2022 Nunan

New target in the EU Farm to Fork program : reduction of antibiotic use in farms by further 50% from 2018 to 2030.



# **Do ZnO and CuSO<sub>4</sub> contribute to antimicrobial resistance development ?**

## EU setting the path as well for reduced level of ZnO

### Avoiding strong environmental impact

- Zinc essential micro-nutrient for plant growth and development
- But accumulation in soils lead to
  - phytotoxicity – decreased yield and quality of crops
  - Altered soil microbial diversity causing ecological imbalances

Zinc pollution can further impair the survival growth and survival of aquatic organism and lead to oxygen depletion in water.

# **EU setting the path for low level ZnO**

## **Ban on the use of zinc oxide at full therapeutic doses**

In 2017 the European Medicine Agency's Committee for Medicinal Products for Veterinary Use recommended :

- To forbid the use of therapeutical zinc oxide because of harmful environmental effects
- also warned of evidence of a potential increased antibiotic-resistant bacteria when including ZnO, especially regarding methicillin-resistant *Staphylococcus aureus*

In 2022 Ban from the European Comission of the use of zinc oxide at full therapeutic doses

- France and Belgium already banned it in 2021.
- ZnO is still allowed in piglet feed up to 150 ppm

# EU setting the path for antimicrobial free farming and reduced level of ZnO

## What about copper levels?

Reminder : the development of resistance is promoted through (sub therapeutic) ATB or heavy metals used at inhibitory and not lethal level – allowing resistance to emerge.

High copper sulfate levels in feed

- absorption of a small proportion in the gut of the animal
- huge amount are spread as manure on fields
- accumulation in soil, water etc
- allows for resistance development both in the gut but also in the environment.

**Reduced copper susceptibility and allied decrease in multiple ATB susceptibilities was reported in organism from soils containing high levels of copper (near maximum concentrations allowed by the European Union)**

Copper regulation by the EU

2003

First reduction of copper levels in feed

2019

Second reduction of copper levels in feed

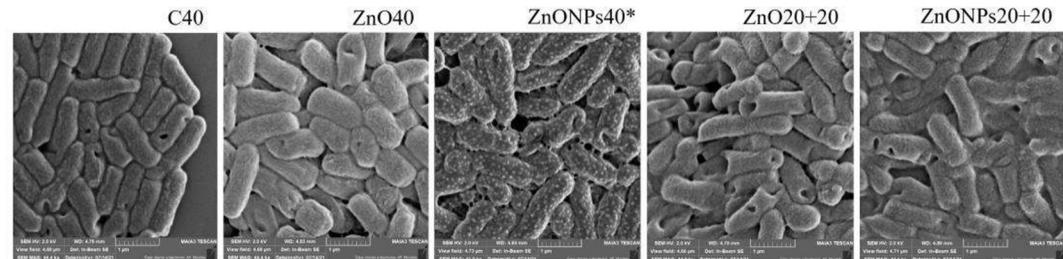
# Clear evidence of extended zink exposure leading to multi drug resistance development

A.

Groups of ATB	ATB	EUCAST MIC breakpoints [mg/l] > R		MIC [mg/l]			
		C40	ZnO40	ZnONPs 40	ZnO 20+20	ZnONPs 20+20	
Cephalosporines	CFZ	4	2	4	2	2	2
	CTZ	4	0.25	0.5	0.25	0.25	0.25
Aminoglycosides	GEN	2	1	2	0.5	1	0.5
	AMK	8	2	8	1	4	1
Sulfonamides	NTL	2	0.25	1	0.25	0.25	0.25
	TOB	2	0.5	1	0.5	0.5	0.5
Sulfonamides	SXT	4	0.03/0.6	0.06/1.19	0.03/0.6	0.03/0.6	0.03/0.6
Amphenicols	CHL	8	0.5	0.5	1	0.5	0.5

(A) Changes in minimum inhibitory concentration of antibiotics: CFZ, CTZ, GEN, AMK, NTL, TOB, SXT, and CHL. The dark red color indicates the breakpoint value has been reached, the light red color indicates the increasing of MIC value after treatment in comparison to C40 without reaching the breakpoint. The light green color depicts decreased values of MIC after treatment in comparison to that of C40;

B.



(B) cell morphology after various treatments

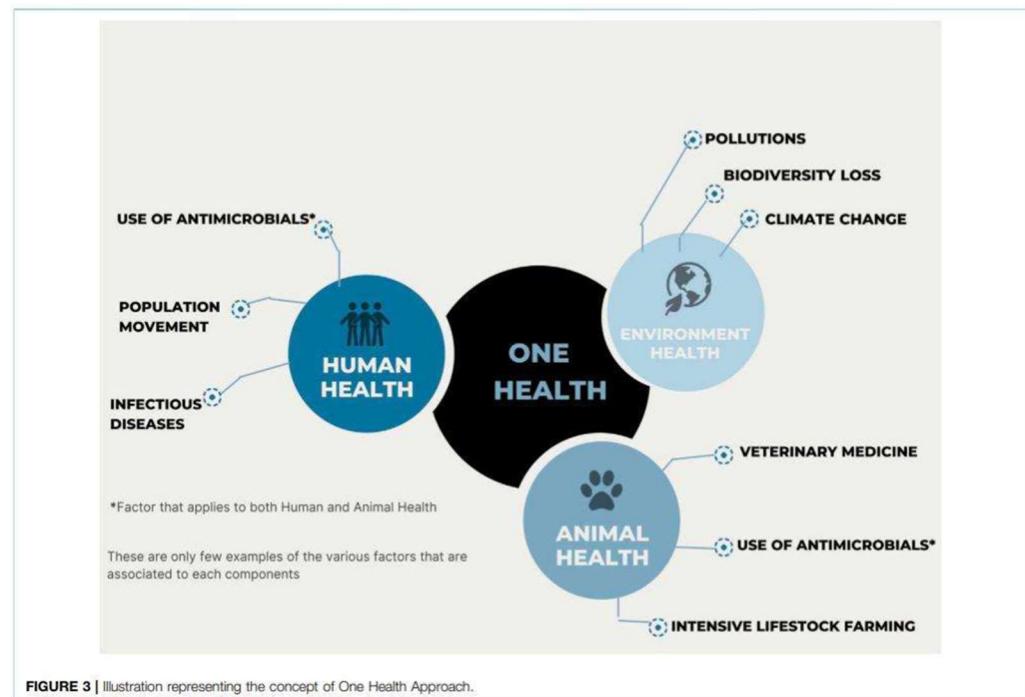
## Extended ZnO/ZnONPs exposure increased antibiotic resistance

Previous studies showed a link between zinc and the evolution of bacterial antibiotic resistance (36). In our study, an extended exposure to ZnO led to the increased MIC of aminoglycosides (GEN, AMK, NTL, TOB), cephalosporins (CFZ, CTZ), and sulfonamides (SXT), indicating potential development of resistance. According to the EUCAST, the critical breakpoint limit was reached for GEN, AMK, and CFZ (30). In the treatment with ZnO stopped at 20th sub-culture, the MIC values returned to the original levels, with the exception of AMK.

# One health approach

## Applied bans show result : decrease in prevalence of resistance of certain ATB

- Importance of removing systematic use of antibiotic as growth promoter and applying a responsible use of antibiotic when treatment is necessary
- Importance of one health approach to keep efficient antibiotics for human health, with strict rules being implemented and followed.
- Importance of governmental legislation implementation and continued monitoring and improving of our practices





# Thank you for your time !

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