

# Prudent use of antimicrobials according to the new legislation on veterinary drugs

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# Outline

- Introduction
- New European legislation about antimicrobials
- Prudent use of antimicrobials
- The use of these drugs under field conditions
- The epidemiological approach
- Conclusions

# Introduction

# Introduction

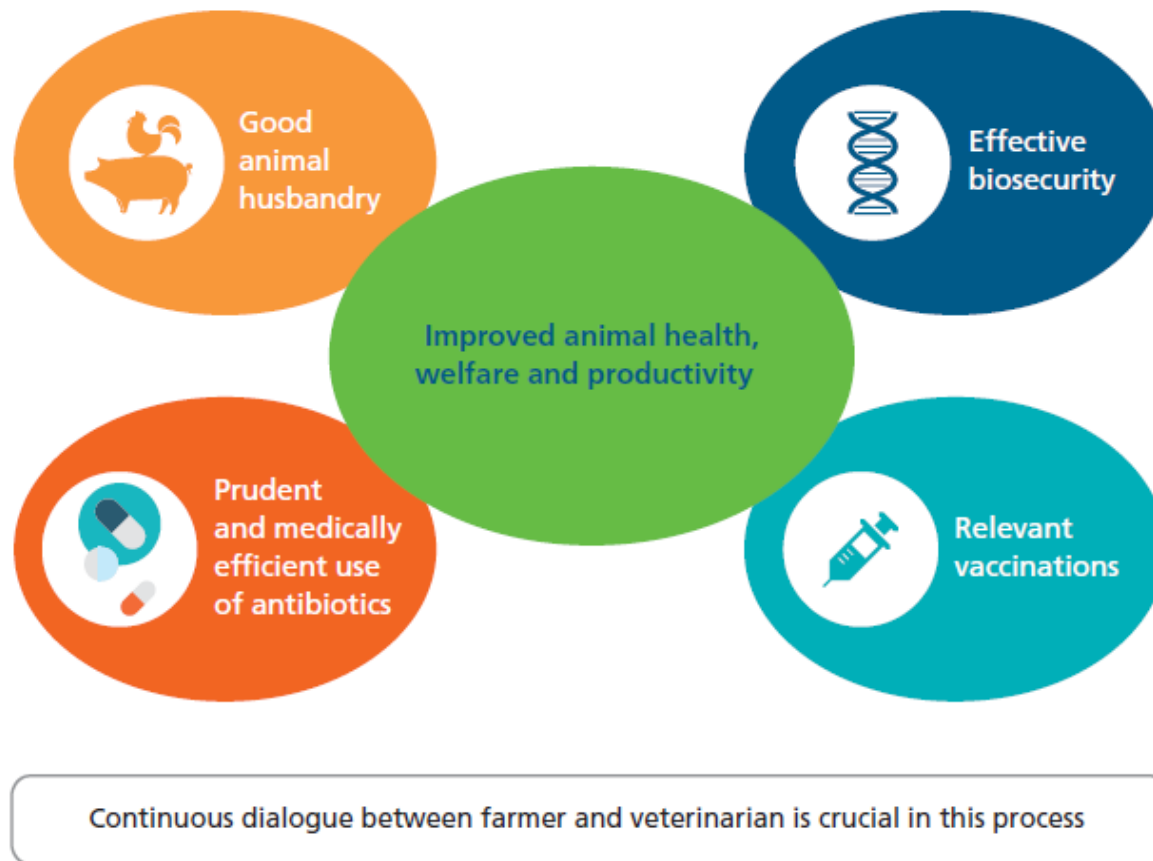
- Drugs used to treat/control diseases in livestock:
  - Antimicrobials
    - Antibiotics
    - Anti-protazoals
    - Antifungals
    - Antivirals
  - Antiparasitics
  - Anti-inflammatory
- Drugs used to manage reproduction
- Other drugs.
  - Anesthetics – Marginal use

# Introduction

- **Veterinary Medicinal Product (VMP):** Chemical mixture that contains one or several drugs. It contains:
  - One or several drugs
  - Excipients
  - Stabilizers
- These registration procedures have been developed to assure that the VMP is **secure for the user (veterinary or farmer), the target species, the environment and for the consumer (food safety).**
- **The VMP must be efficacious.**
- After registering the VMP, the use of any veterinary medicinal product is clearly specified in the summary of product characteristics (SPC).
- To meet all these requirements, registration procedure is time-consuming and expensive for pharmaceutical companies.

# Introduction

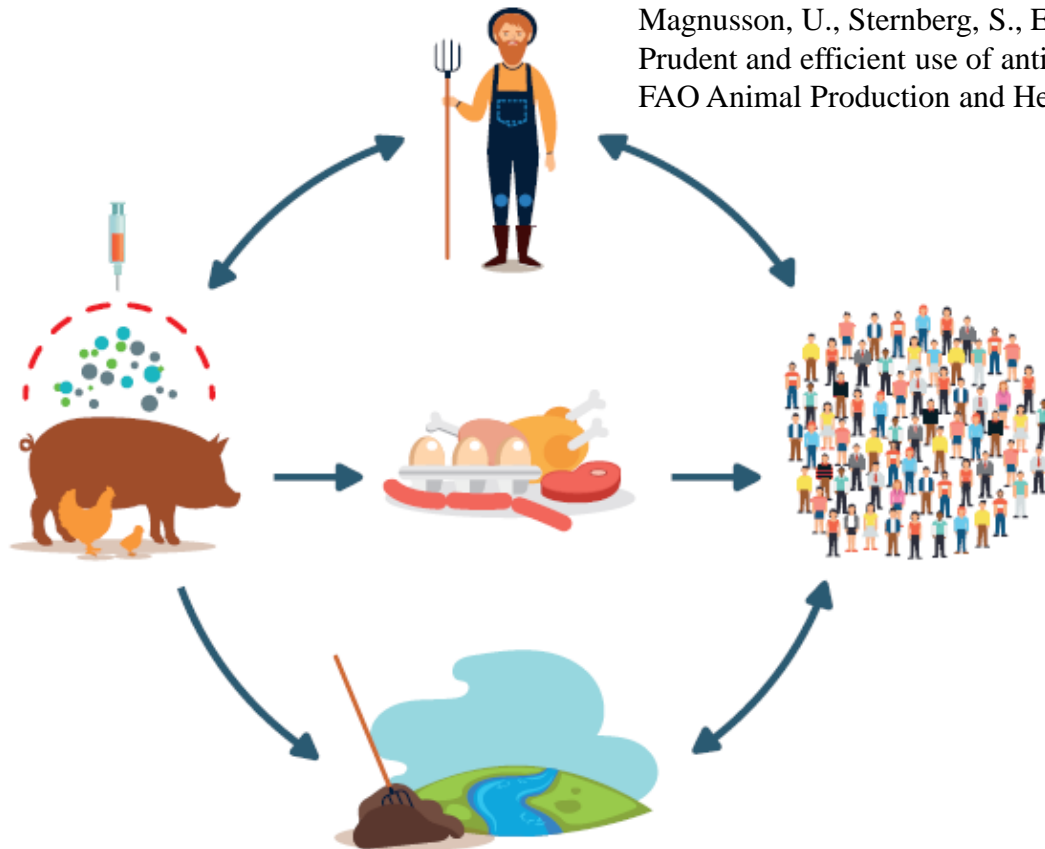
FIGURE 4  
Key elements of holistic animal health management



Magnusson, U., Sternberg, S., Eklund, G., Rozstalnyy, A. 2019. Prudent and efficient use of antimicrobials in pigs and poultry. FAO Animal Production and Health Manual 23. Rome. FAO

# Introduction

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Prudent and efficient use of antimicrobials in pigs and poultry.  
FAO Animal Production and Health Manual 23. Rome. FAO



Possible routes of transmission of resistant bacteria and resistance genes  
from livestock to the general human population

# Introduction

- **Therapeutics:** Treat sick animals affected of bacterial diseases. It is a mandatory clinical act for a veterinarian in order to ensure the welfare of the animals and comply with their code of ethics.



- **Metaphylaxis:** Treat sick and risk population affected of bacterial diseases only when the risk of spreading an infection or an infectious disease in a group of animals is high and adequate alternatives are not available.



- **Prophylaxis:** Treat animals apparently healthy but with high risk to suffer a bacterial disease.



# New European legislation

# European legislation

- There are specific European legislation about the prudent use of antimicrobials.

11.9.2015

EN

Official Journal of the European Union

C 299/7

## COMMISSION NOTICE

### Guidelines for the prudent use of antimicrobials in veterinary medicine

(2015/C 299/04)



- There are recommendations from many organizations like the one published by the Federation of veterinarians of Europe (FVE)
- A new legislation has been recently approved for veterinary medicinal products in Europe (EU/2019/6) where a special attention has been addressed to antimicrobials and particularly antibiotics.

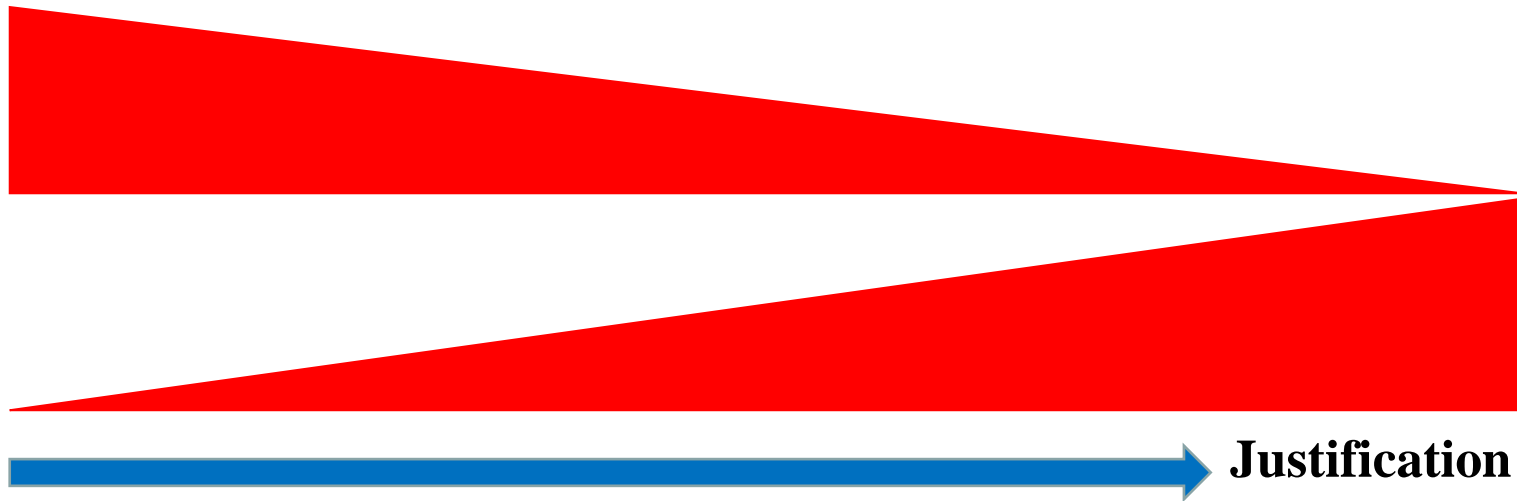
# European legislation

- Avoid the routinely metaphylactic and prophylactic use of antibiotics.
- The metaphylactic and prophylactic use is not forbidden but it is strictly regulated.

**Therapeutics**

**Metaphylaxis**

**Prophylaxis**



# European legislation

- There is a recent recommendation of EMA (EMA, AMEG 2019) that now comprises four categories of antimicrobials, from A to D. This recommendation is linked with the new legislation:
- **Category A (“Avoid”)** includes antimicrobial classes not currently authorized in veterinary medicine in the EU (not possible in livestock/NO MRL).
- **Category B (“Restrict”)** refers to quinolones, 3rd- and 4th-generation cephalosporins and polymyxins. Use of these antimicrobials in animals should be restricted to mitigate the risk to public health.
- **Category C (“Caution”)**. These antimicrobials should only be used when there are no antimicrobial substances in Category D that would be effective.
- **Category D (“Prudence”)** is the lowest risk category. Antimicrobials belonging to this category can be used in animals in a prudent manner. This means that unnecessary use and long treatment periods should be avoided and group treatment should be restricted to situations where individual treatment is not feasible.

# European legislation

**Cuadro 2. Categorización de los antimicrobianos según la Agencia Europea del Medicamento del año 2019.**

Categoría de antimicrobianos	Familias de antimicrobianos
Categoría A	Familias para uso solo en medicina humana. No hay límites máximos de residuos en porcino
Categoría B	Cefalosporinas de tercera y cuarta generación Polimixinas (sulfato de colistina) Quinolonas
Categoría C	Aminoglucósidos y <u>aminociclotoles</u> <b>D</b> Fenicoles Macrólidos Pleuromutilinas Lincosamidas Aminopenicilinas en combinación con inhibidores de las $\beta$ -lactamasas (amoxicilina-ácido clavulánico)
Categoría D	Aminopenicilinas sin inhibidores de las $\beta$ -lactamasas (amoxicilina) Penicilinas naturales (de espectro reducido) Tetraciclinas Sulfamidas

*Está en fase de consulta y solo se han indicado las familias con registro en medicina porcina para las categorías B, C y D.  
Fuente: EMA/AMEG, 2019.*

# European legislation

- **In summary, a good use of antimicrobials imply that veterinarians must justify not only the use of antimicrobials but also the selection of the antimicrobial to treat bacterial diseases following prudent use of antimicrobials.**
- There are European countries with a very strict regulation of antimicrobial families (even voluntary banned).



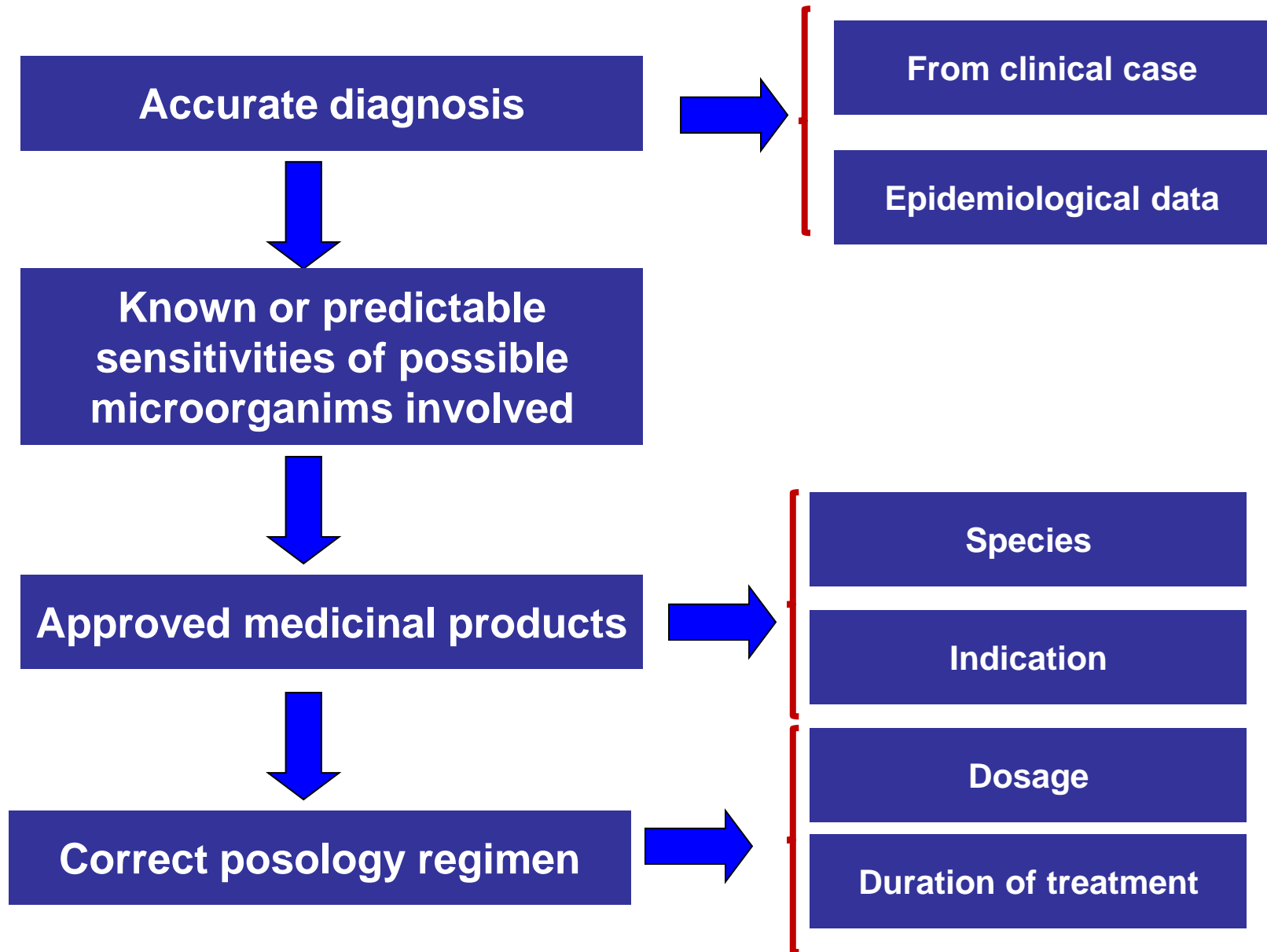
# **Prudent use of antimicrobials**

# Prudent use of antimicrobials

- Prudent use of antimicrobials is an integral part of the good veterinary practices.
- It is a way of working to maximize clinical efficacy and minimize the selection of resistant microorganisms.
- The principle of prudent use is a guide to optimize the use of antimicrobials.



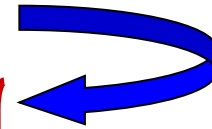
# Prudent and practical use of antimicrobials (theory)



**The use under practical conditions**

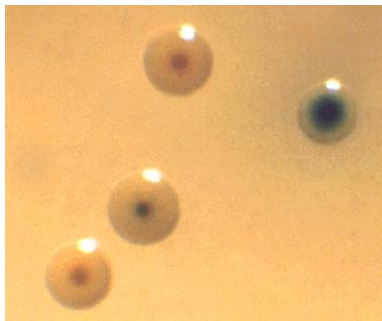
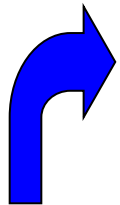
# Avoid the use of antibiotics

Environment



Facility  
Biosecurity  
Temperature, ventilation....

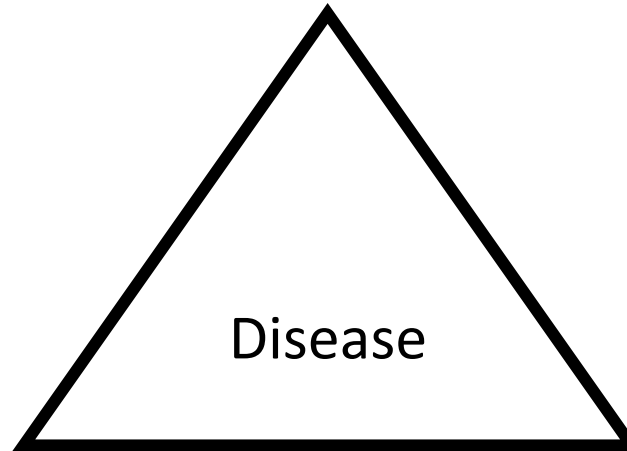
Prophylaxis  
Microorganisms



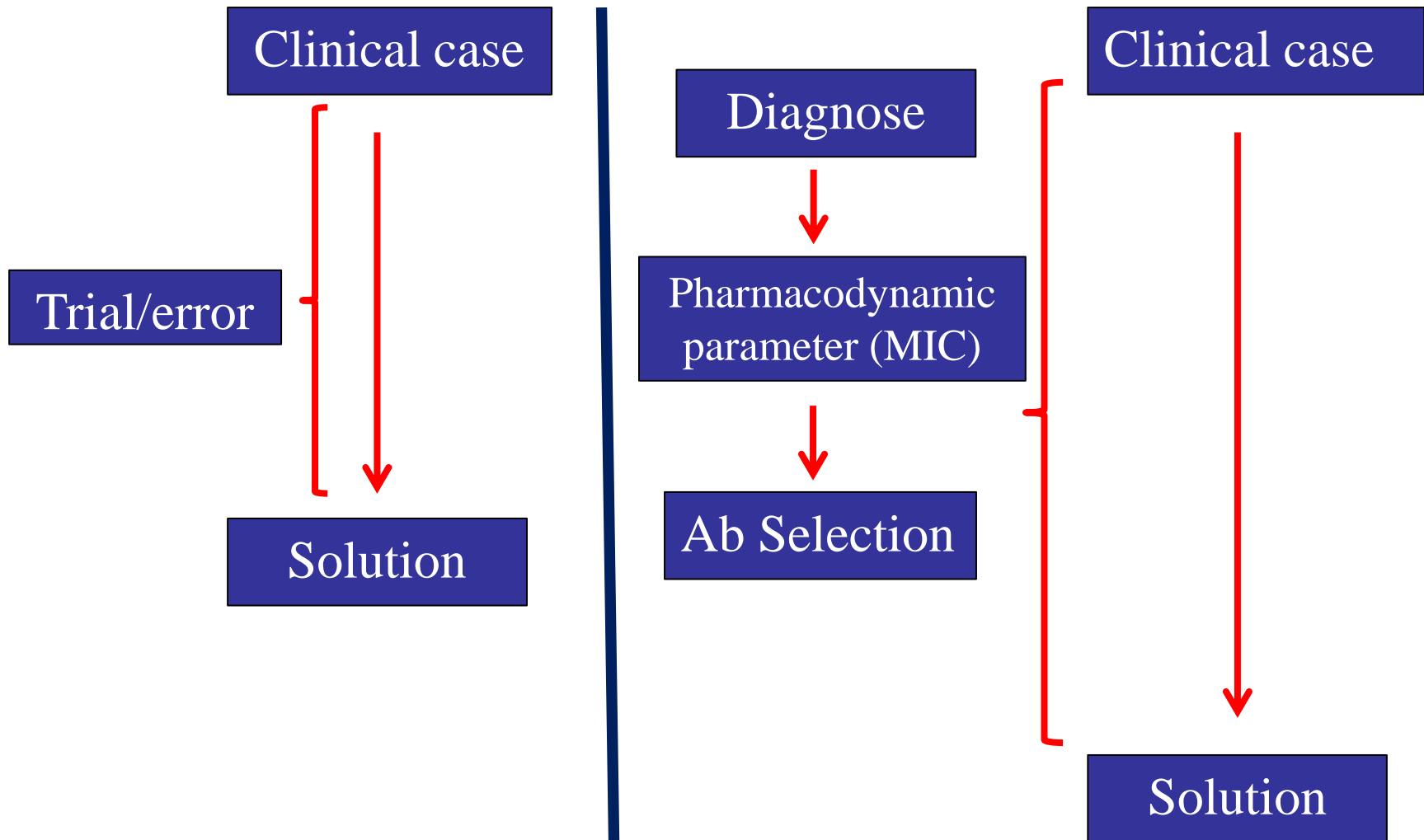
Nutrition  
welfare



Disease



# Prudent and practical use of antimicrobials (practice)

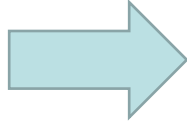
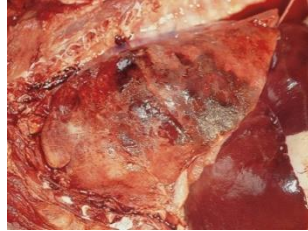


# Prudent use of antimicrobials



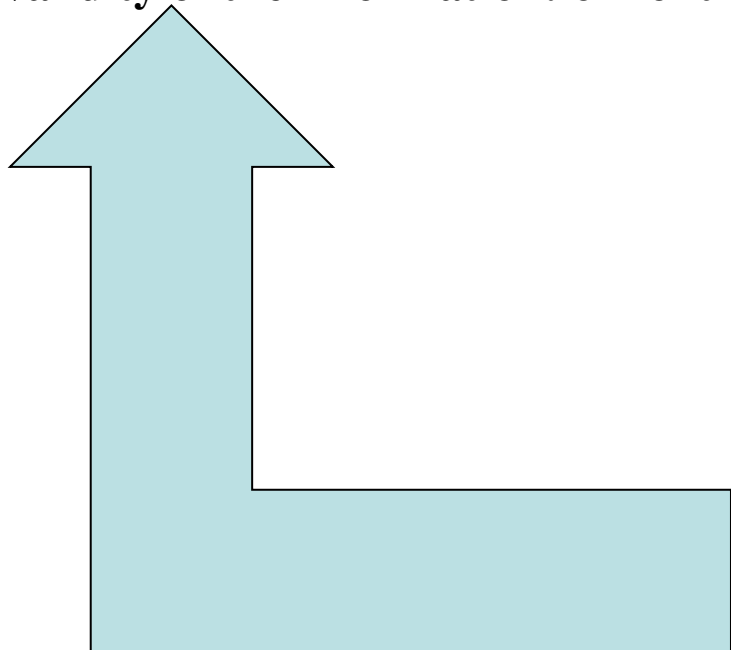
**Sow unit**

**Fattening farm**

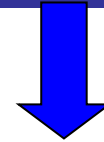


**Epidemiological link**

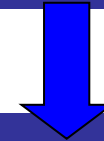
**Validity of the information: 6 months**



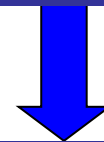
**Clinical samples**



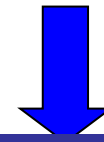
**Microbiological isolation**



**Bacteria identification**



**MIC determination**



**Pharmacological  
interpretation for  
practitioners**

# Prudent use of antimicrobials

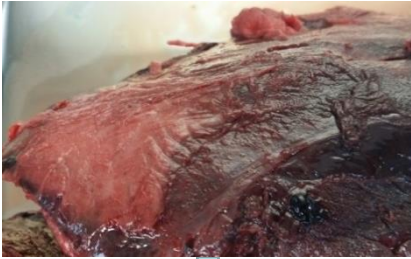
- Bovine: Country of origin: Ireland, French, Poland, etc...



- Avian species: Vertical system of production— Hatchery facility/reproductive farms.

# Prudent use of antimicrobials

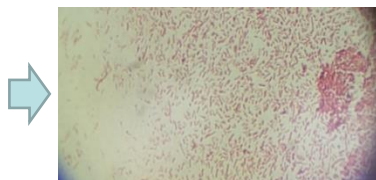
## 1. Sample



## 2. Pure culture



GRAM

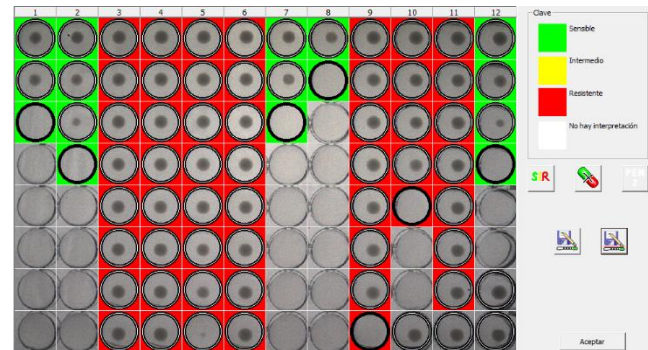


## 3. IDENTIFICACIÓN

*MALDI-TOF*



*MIC determination*



# Prudent use of antimicrobials

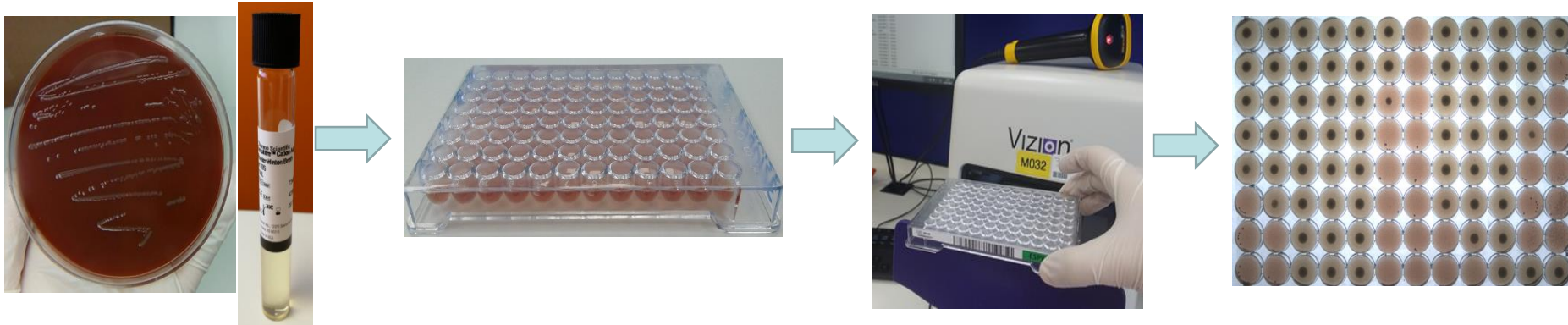
Inóculo

Inoculación

Incubación

Lectura

Interpretación y emisión de resultados



PAQUETE MIC RESPIRATORIOS

	1	2	3	4	5	6	7	8	9	10	11	12
A	Enrofloxacina	Marbofloxacina	Tildipirosina	Tulatromicina	Tilmicosina	Tiamulina	Amoxiciclina	Florfenicol	Doxiciclina	Oxitetraciclina	Sulfamethoxazol/trimetoprim	Ceftiofur
B	Dil 2	Dil 2	Dil 2	Dil 2	Dil 2	Dil 2	Dil 2	Dil 2	Dil 2	Dil 2	Dil 2	Dil 2
C	Dil 3	Dil 3	Dil 3	Dil 3	Dil 3	Dil 3	Dil 3	Dil 3	Dil 3	Dil 3	Dil 3	Dil 3
D	Dil 4	Dil 4	Dil 4	Dil 4	Dil 4	Dil 4	Dil 4	Dil 4	Dil 4	Dil 4	Dil 4	Dil 4
E	Dil 5	Dil 5	Dil 5	Dil 5	Dil 5	Dil 5	Dil 5	Dil 5	Dil 5	Dil 5	Dil 5	Dil 5
F	Dil 6	Dil 6	Dil 6	Dil 6	Dil 6	Dil 6	Dil 6	Dil 6	Dil 6	Dil 6	Dil 6	Dil 6
G	Dil 7	Dil 7	Dil 7	Dil 7	Dil 7	Dil 7	Dil 7	Dil 7	Dil 7	Dil 7	Dil 7	Dil 7
H	Dil 8	Dil 8	Dil 8	Dil 8	Dil 8	Dil 8	Dil 8	Dil 8	Dil 8	CONTROL	CONTROL	CONTROL

Categoría B	Categoría C	Categoría D
Enrofloxacina	Florfenicol	Sulfametoxazol/tri metoprim
Marbofloxacina	Tiamulina	Amoxicilina
Ceftiofur	Tildipirosina	Oxitetraciclina
	Tulatromicina	Doxiciclina
	Tilmicosina	



# Prudent use of antimicrobials



antibiotics



Article

## Antimicrobial Stewardship for Respiratory Pathogens in Swine

Anna Vilaró <sup>1</sup>, Elena Novell <sup>1</sup>, Vicens Enrique-Tarancón <sup>1</sup>, Jordi Balielles <sup>1</sup>, Eduard Allué <sup>1</sup> and Lorenzo Fraile <sup>2,\*</sup>

► *Actinobacillus pleuropneumoniae*(Sample: 1,Strain: XXXXXXXX)

Cat	Antibiotics	Technique	Current analysis		XXXXXXXX 16/01/2018 Sow farm		XXXXXXXX-02/01/2018 Sow farm		XXXXXXXX-04/12/2018 Isowaan farm		XXXXXXXX-18/10/2018 Sow farm	
			CMI (µg/ml)	Result	CMI (µg/ml)	□	CMI (µg/ml)	□	CMI (µg/ml)	□	CMI (µg/ml)	□
D	Amoxicillin --- Beta-lactams	CMI	0.25	Sensible	0.25	□	0.25	□	0.25	□	0.25	□
D	Doxycycline --- Tetracyclines	CMI	2	Resistant	2	□	2	□	4	□	2	□
D	Sulfamethoxazol/Trimethoprim --- Sulfamides	CMI	4	Resistant	4	□	8	□	8	□	8	□
C	Florfenicol --- Fenicols	CMI	0.25	Sensible	0.25	□	0.25	□	0.25	□	0.25	□
C	Tiamulin --- Pleuromutlins	CMI	8	Sensible	16	□	16	□	8	□	16	□
C	Tildipirosin --- Macrolides	CMI	4	Sensible	4	□	4	□	4	□	4	□
C	Tilmicosin --- Macrolides	CMI	8	Sensible	8	□	16	□	8	□	16	□
C	Tulathromycin --- Macrolides	CMI	32	Sensible	32	□	64	□	16	□	32	□
B	Ceftiofur --- Cephalosporins	CMI	≤ 0.06	Sensible	≤ 0.06	□	≤ 0.06	□	≤ 0.06	□	≤ 0.06	□
B	Enrofloxacin --- Quinolones	CMI	≤ 0.03	Sensible	≤ 0.03	□	≤ 0.03	□	≤ 0.03	□	≤ 0.03	□

# Prudent use of antimicrobials



antibiotics



Article

## Antimicrobial Stewardship for Respiratory Pathogens in Swine

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and Lorenzo Fraile <sup>2,\*</sup>

**Table 4.** Antimicrobial stewardship for an *Actinobacillus pleuropneumoniae* strain isolated in a clinical case with reference report 2.

Antimicrobial Stewardship				
Clinical Case	Antimicrobial	EMA Category	Order of Use Proposed	Suggestion Inside Each Option
<i>Actinobacillus pleuropneumoniae</i> UG1970383	Amoxicillin	D	First option	1
	Florfenicol	C	Second option	1
	Tildipirosin	C	Second option	2
	Tiamulin/tilmicosin/tulathromycin	C	Second option	3
	Ceftiofur/enrofloxacin	B	Last option	1

# The epidemiological approach

# The epidemiological approach

## Robust for respiratory and systemic pathogens

### ► Streptococcus suis (Mostra: 1 - 2 - 3, Soca: UP1970840.01A)

Antibiòtics	Categoria	Mètode	Analítica actual		UP1970773 - 25/02/2019 Reg. anterior mateixa granja		CMI (µg/ml)	Resultat
			CMI (µg/ml)	Resultat	CMI (µg/ml)	Resultat		
Sulfametoxazol/Trimetoprim --- Sulfamida	C1	CMI	0,25	Sensible	0,25	Sensible	-	-
Tiamulina --- Pleuromutilines	C1	CMI	2	Sensible	2	Sensible	-	-
Florfenicol --- Fenicol	C1	CMI	2	Sensible	2	Sensible	-	-
Oxitetraciclina --- Tetraciclina	C1	CMI	> 8	Resistent	> 8	Resistent	-	-
Doxiciclina --- Tetraciclina	C1	CMI	16	Resistent	16	Resistent	-	-
Tildipirosina --- Macròlids	C1	CMI	> 64	Resistent	> 64	Resistent	-	-
Tilmicosina --- Macròlids	C1	CMI	> 64	Resistent	> 64	Resistent	-	-
Tulatromicina --- Macròlids	C1	CMI	> 64	Resistent	> 64	Resistent	-	-
Amoxicilina --- Beta-lactàmics	C2	CMI	<= 0,12	Sensible	<= 0,12	Sensible	-	-
Ceftiofur --- Cefalosporina	C2	CMI	0,12	Sensible	0,12	Sensible	-	-
Enrofloxacina --- Quinolones	C2	CMI	0,5	Resistent	1	Resistent	-	-
Marbofloxacina --- Quinolones	C2	CMI	1	Resistent	1	Resistent	-	-

Segons les recomanacions sobre l'ús prudent d'antimicrobians, aquests es classifiquen en tres categories: una (C1), dos (C2) y tres (C3). Els de categoria tres estan prohibits en veterinària. Els de categoria dos es poden utilitzar si no hi ha un antimicrobià de categoria u que es pugui utilitzar pel tractament del cas clínic. De moment, això és una recomanació que, en un breu període de temps, serà d'obligat compliment a l'hora de prescriure.

### ► Actinobacillus pleuropneumoniae (Muestra: 1, Cepa: UG1970316.01.0A)

Antibiòtics	Categoria	Mètode	Analítica actual		UG1970170.1 - 24/01/2019		UG1871964.1 - 19/12/2018	
			CMI (µg/ml)	Resultado	CMI (µg/ml)	Resultado	CMI (µg/ml)	Resultado
Sulfametoxazol/Trimetoprima --- Sulfamida	C1	CMI	<= 0,12	Sensible	<= 0,12	Sensible	<= 0,12	Sensible
Florfenicol --- Fenicol	C1	CMI	0,25	Sensible	0,25	Sensible	0,25	Sensible
Doxiciclina --- Tetraciclina	C1	CMI	0,5	Sensible	0,5	Sensible	0,5	Sensible
Oxitetraciclina --- Tetraciclina	C1	CMI	0,5	Sensible	0,5	Sensible	0,5	Sensible
Tildipirosina --- Macròlids	C1	CMI	8	Sensible	4	Sensible	4	Sensible
Tilmicosina --- Macròlids	C1	CMI	8	Sensible	8	Sensible	8	Sensible

### ► Actinobacillus pleuropneumoniae (Muestra: 1, Cepa: UG1970316.01.0A)

Antibiòtics	Categoria	Mètode	Analítica actual		UG1970170.1 - 24/01/2019		UG1871964.1 - 19/12/2018	
			CMI (µg/ml)	Resultado	CMI (µg/ml)	Resultado	CMI (µg/ml)	Resultado
Tiamulina --- pleuromutilinas	C1	CMI	16	Sensible	16	Sensible	16	Sensible
Tulatromicina --- Macròlids	C1	CMI	32	Sensible	32	Sensible	32	Sensible
Enrofloxacina --- Quinolones	C2	CMI	<= 0,03	Sensible	0,06	Sensible	<= 0,03	Sensible
Marbofloxacina --- Quinolones	C2	CMI	<= 0,03	Sensible	<= 0,03	Sensible	<= 0,03	Sensible
Ceftiofur --- Cefalosporina	C2	CMI	<= 0,06	Sensible	<= 0,06	Sensible	<= 0,06	Sensible
Amoxicilina --- Beta-lactàmics	C2	CMI	0,25	Sensible	0,25	Sensible	<= 0,12	Sensible

# The epidemiological approach

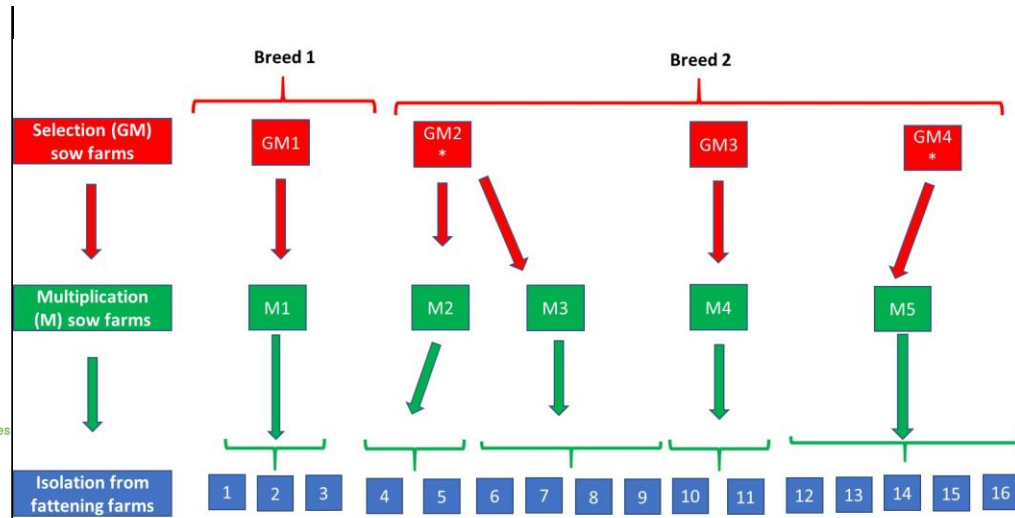
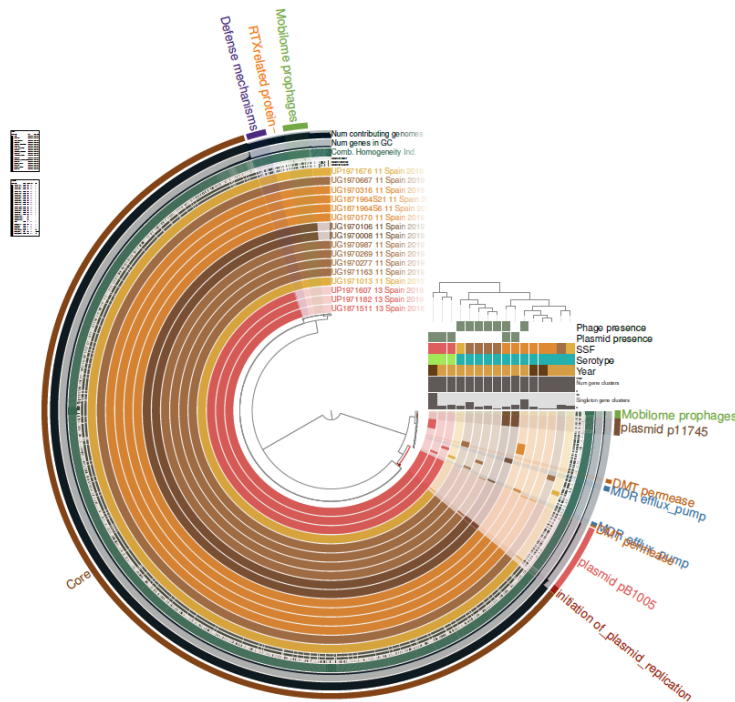
**Table 1.** Antimicrobial susceptibility pattern for the 13 clusters obtained from 162 *Actinobacillus pleuropneumoniae* isolates after a hierarchical clustering analysis. It is detailed in brackets the number of strains belonging to each cluster. Suitable antimicrobials are detailed in green color. The antimicrobials tested included amoxicillin (AMO), ceftiofur (CEF), doxycycline (DOX), enrofloxacin (ENR), florfenicol (FLO), sulfamethoxazole/trimethoprim (SFM), tiamulin (TIA), tilmicosin (TILM), tildipirosin (TILD), and tulathromycin (TUL).

Cluster	EMA Category									
	D				C			B		
	AMO	DOX	SFM	FLO	TIA	TILM	TILD	TUL	CEF	ENR
1 (33)	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
2 (2)	Green	Green	Green	Green	NP	Green	Green	Green	Green	Green
3 (20) **	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
4 (20)	Green	NP	Green	Green	Green	Green	Green	Green	Green	Green
5 (14)	Green	NP	NP	Green	Green	Green	Green	Green	Green	Green
6 (9)	Green	NP	Green	Green	Green	Green	Green	Green	Green	NP *
7 (28)	Green	NP	Green	Green	Green	Green	Green	Green	Green	NP
8 (10)	NP	NP	Green	Green	Green	Green	Green	Green	Green	Green
9 (14)	NP	NP	Green	Green	Green	Green	Green	Green	Green	NP
10 (4)	NP	NP *	Green	Green	Green	Green	Green	Green	Green	Green
11 (5)	Green	Green	Green	NP	Green	Green	Green	Green	Green	Green
12 (2)	Green	NP	NP	Green	Green	Green	Green	Green	Green	NP
13 (1)	NP	NP	Green	Green	Green	NP	NP	NP	Green	Green

\* Extremely high MIC values. \*\* MIC values for amoxicillin are lower than for cluster 1. NP (not possible and highlighted in red) means that the MIC value excludes this antimicrobial for the treatment of the bacterial infection at the registered dose. A recent recommendation from the European Medicine Agency (EMA) [6] comprises the antimicrobials in four categories, from A (avoid), B (restrict), C (caution) to D (prudence).

# The epidemiological approach

- We are collaborating with Lourdes Migura and Judith Guitart to demonstrate the epidemiological approach for *Actinobacillus pleuropneumoniae* and *Streptococcus suis* using whole genome sequencing.
- We have sound data for APP to be published in the short run:



# Conclusions

# Conclusions

- The new European legislation about the use of drugs is focused on the prudent use of antimicrobials (AB) in all veterinary species following one-health approach.
- It is necessary to establish a practical way to accomplish with a prudent use of AB under field conditions.
- A proposal to optimize the use of AB could be based on the vertical transmission of pathogens in livestock: Epidemiological approach.



**Thank you very much for your  
attention**

