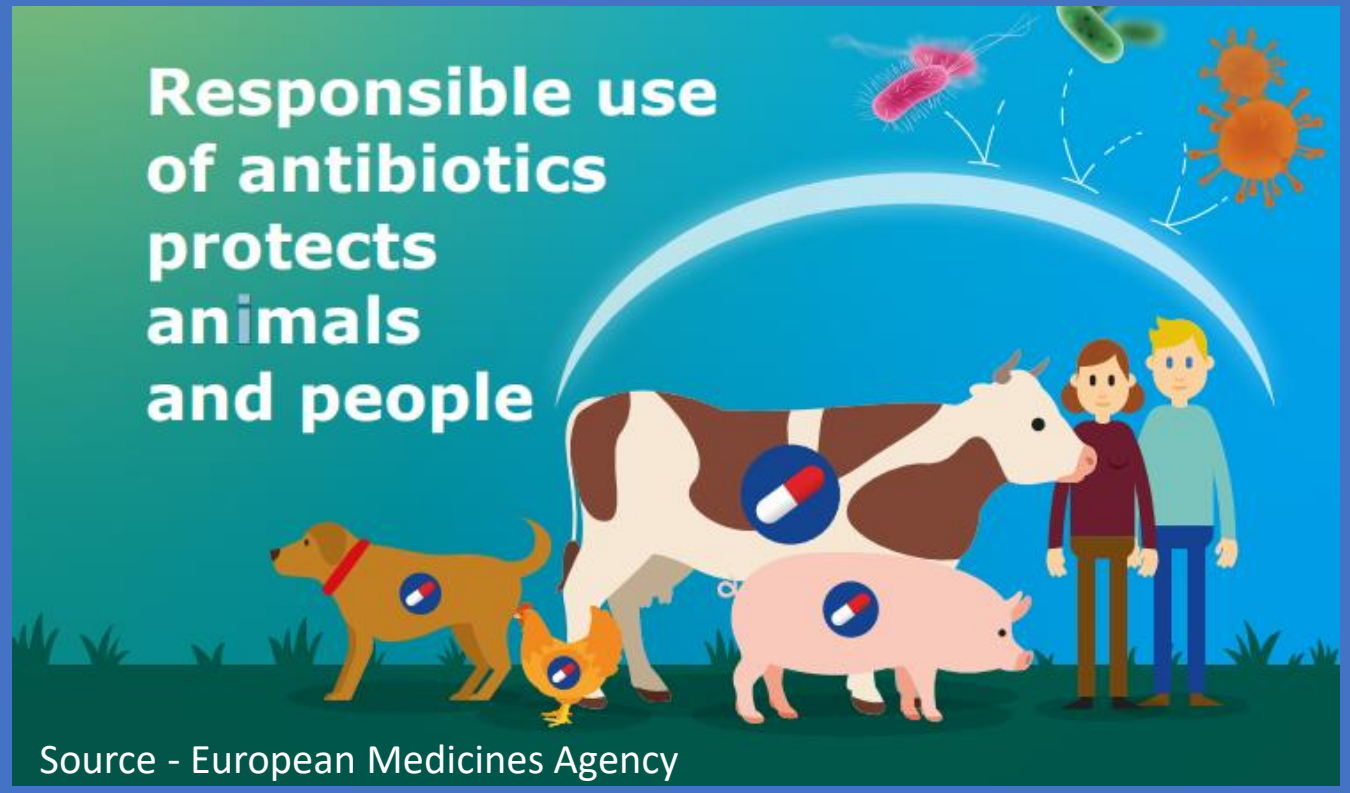
Antimicrobial Resistance (AMR)



Source - European Medicines Agency

Veterinary Medicines Section

Introduction

- The Veterinary Medicines Section within the Animal Health and Welfare Department (AHWD) is the National Competent Authority (NCA) in Malta for Veterinary Medicinal Products (VMPs).

- Main functions of the Veterinary Medicines Section:
  1. Regulates the placing on the market, retail, distribution and use of VMPs,
  2. Promotes the responsible use of good quality, safe and effective VMPs.

Structure & function of bacteria

Cell structure	Function of cell structure
Cytoplasm	- Contains high concentrations of enzymes, metabolites, and salts - Contains ribosomes which is important for protein synthesis of the cell - Contains granules which store carbohydrates and energy - Contains nuclear matter
Nuclear matter (Nucleoid and plasmids)	- The nucleoid is distributed throughout the cytoplasm (that is not membrane bound) which contains the cell's genetic materials (DNA) and is responsible for replication -Plasmids – contain other (extrachromosomal) DNA content to overcome stressful conditions
Flagellum	- extracellular appendage needed for motility
Pili	- Slender, hairlike appendages found on the surface of many bacteria. - To adhere to host surfaces.

Structure & function of bacteria

Cell structure	Function of cell structure
Cell/plasma membrane	- Composed of proteins and lipids - Regulates the flow of nutrients - Prevents loss of cell contents - Carries out necessary cellular functions, including energy generation, protein secretion, chromosome segregation, and active transport of nutrients
Cell wall	- A rigid wall outside the membrane consisting of peptidoglycans, -Determines the shape of the bacterial cell and provides the cell with mechanical protection - Gram-positive bacteria – have thick peptidoglycan layer that retains the blue dye of the Gram stain by trapping it in the cell - Gram-negative bacteria – have thin peptidoglycan layer and the blue dye is easily washed out of the cell
Capsule	- Thick outer layer made up of viscous polysaccharide gel with a definite boundary - Protects against ingestion and destruction by white blood cells

Antimicrobial VS Antibiotic

- Antimicrobial: *"Any substance with a direct action **on micro-organisms** used for treatment or prevention of infections, including antibiotics, antivirals, antifungals and anti-protozoals"*

- Antibiotic (antibacterial): *"Any substance with a direct action **on bacteria** that is used for treatment or prevention of infections"*

As defined in Regulation (EU) 2019/6

How do antibiotics work?

1. Targeting the cell wall causing loss of mechanical protection of bacterium:
   - Beta – lactams (e.g. amoxicillin, benzylpenicillin & ceftiofur),
   - Glycopeptides (e.g. vancomycin),
   - Bacitracin

2. Targeting the plasma membrane leading to loss of cell contents and inability to carry out vital cellular functions such as protein synthesis:
   - Polymycin B
   - Colistin

How do antibiotics work?

3. Targeting ribosomes (factories of proteinsynthesis) leading to the inability to produce enzymes:

- Aminoglycosides (e.g. streptomycin, paromomycin & neomycin),
- Tetrayclines (e.g. oxytetracyline),
- Macrolides (e.g. tylosine & spiramycin)

4. Targeting the replication process of bacteria by interfering with DNA synthesis:

- Fluoroquinolones – interfere with the process of DNA & RNA synthesis (e.g. enrofloxacin & ciprofloxacin)
- Sulphonamides - inhibit the action of enzymes responsible for the synthesis of folic acid (essential component of the DNA)

What is Antimicrobial Resistance (AMR)?

"The ability of micro-organisms to survive or to grow in the presence of a concentration of an antimicrobial agent which is usually sufficient to inhibit or kill micro-organisms of the same species"

As defined in Regulation (*EU) 2019/6*

The One Health Principle

Source EMA LEAFLET ON Categorization of antibiotics

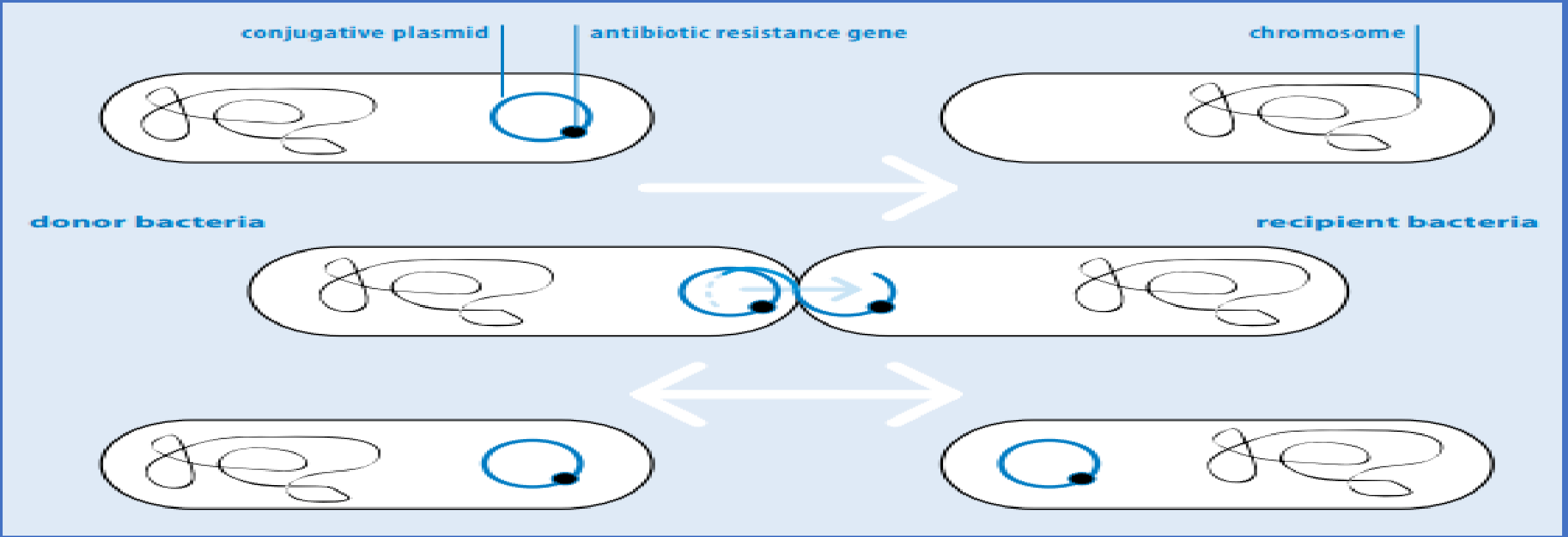
How does AMR develop?

1. <u>Horizontal Gene Transfer</u>

- The resistant gene is transferred from one bacterium to another
- Promotes the simultaneous spread of resistance to several different classes of antibiotics.
- Intensive farming promotes this

How does AMR develop?

1. Horizontal Gene Transfer



Source - *Tackling antibiotic resistance from a food safety perspective in Europe* (2011) published by WHO Regional office for Europe

How does AMR develop?

2. Chromosomal resistance

- A bacterium is resistant through a novel DNA mutation
- The spread of the strain is the principal method of spreading the resistance
- As bacteria reproduce very rapidly, bacteria with this new resistance can become rapidly dominant within a bacterial population with a person or animal.

How does AMR develop?

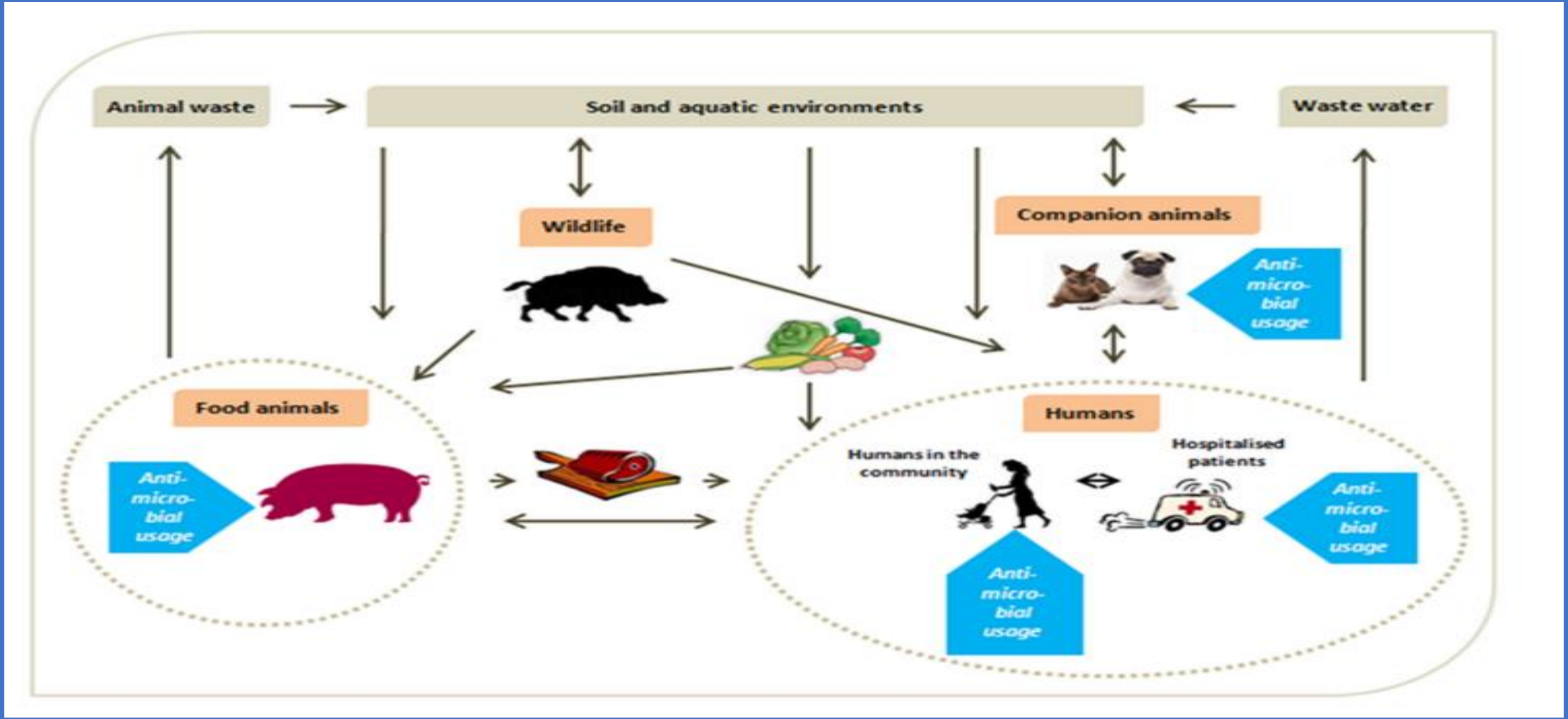
3. Cross-resistance

- The ability of one resistance gene to confer resistance to two or more antibiotics that usually belong to the same antibiotic class

4. Co-resistance

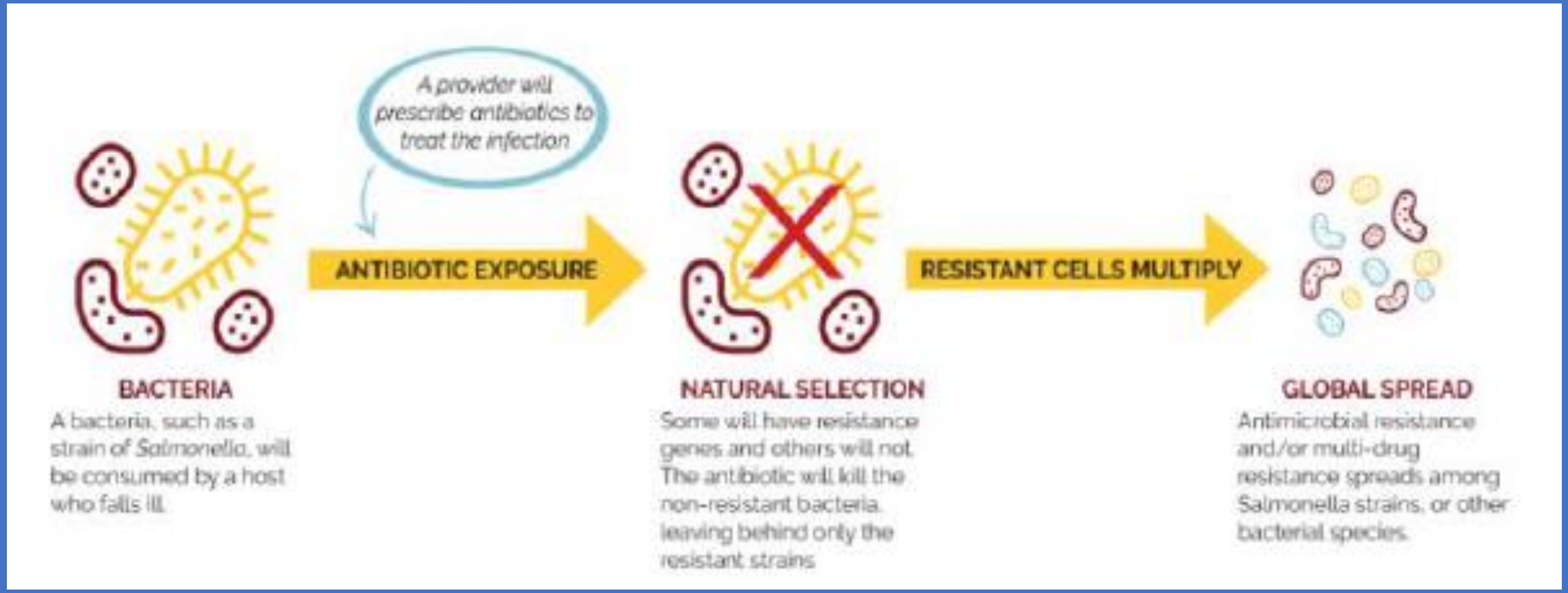
- Different resistant genes that confer resistance to different antibiotic classes are often located together in the DNA of the bacteria and can be transferred simultaneously

How resistance spreads amongst humans, animals and the environment – One Health Approach



Source – Information session on antimicrobial resistance published by European Medicines Agency held by EMA on 19th September 2017 (© European Medicines Agency)

Global Spread of resistant bacteria



Source: Centre for Animal Health and Food Safety - University of Minnesota

https://cahfs.umn.edu/antimicrobial-resistance-multidrug-resistant-salmonella

Highest Priority Critically Important Antimicrobials – WHO

Class of antimicrobials	Reasons for being critically important
Quinolones: *Marbofloxaxin, Enrofloxacin, Levofloxacin*	- **Quinolone-resistant *Salmonella* and *E.coli* in animals has developed**
3rd and higher generation cephalosporins: *Ceftiofur, ceftizoxime*	- **Cephalosporin-resistant Salmonella and *E.coli* in animals has developed**
Macrolides and ketolides: *Spiramycin, Tylosin*	- **Macrolide-resistant Campylobacter spp. in animals (*Campylobacter jejuni* in poultry) has developed** - **One of the few available treatment for serious Campylobacter infections in children, particularly in those whom quinolones are contraindicated**

Source – *Critically Important Antimicrobials for Human Medicine – 6th Revision 2018*

(https://apps.who.int/iris/bitstream/handle/10665/312266/9789241515528-eng.pdf)

Highest Priority Critically Important Antimicrobials – WHO

Class of antimicrobials	Reasons for being critically important
Glycopeptide: *Avoparcin,* *Teicoplanin,* *Vancymycin*	- **When avoparcin was used as a growth promoter, vancomycin-resistant enterococci (VRE) have developed in food animals and were transmitted to humans** - **One of the few available treatment for serious enterococcal infections** - **Given the high incident of transmission of VRE from animals to humans and the consequences of treatment failure in such cases, glycopeptides are of the highest priority**
Polymyxins: *Colistin* *Polymyxin B*	- **Plasmid-mediated polymyxin-resistant E.coli in food animals has developed** - **One of the few available treatment for serious Enterobactericeae and *Pseudomonas aeruginosa* multi-resistant infections in humans especially in seriously ill patients.** - **Given the high incident of Enterobactericeae in humans, the number of serious cases where colistin is needed is substantial.**

Source – *Critically Important Antimicrobials for Human Medicine – 6th Revision 2018*

(https://apps.who.int/iris/bitstream/handle/10665/312266/9789241515528-eng.pdf)

Concepts of tackling AMR in animal health in the EU

As little as possible, as much as necessary:

Prudent use of antimicrobials

Prevention is Better than cure:

Avoiding the need for antimicrobials

These concepts are based on the ‘Guidelines for the prudent use of antimicrobials in veterinary medicine’

(https://ec.europa.eu/health/sites/health/files/antimicrobial_resistance/docs/2015_prudent_use_guidelines_en.pdf)

‘As Little as possible, as much as necessary’

1. Limiting the use of critically important antimicrobials to situations where there is no alternative

2. Using diagnostic and susceptibility tests to inform decisions about the choice of antimicrobials

3. Avoiding the preventive use of antimicrobials to compensate for biosecurity, bad-feeding practices and animal husbandry

4. Be informed about the use of antimicrobials from the product information leaflet

‘As Little as possible, as much as necessary’

5. Antimicrobial medicinal products should be used for METAPHYLAXIS* only when the risk of spread of an infection or of an infectious disease in a group of animals is high and where no appropriate alternatives are available

* The administration of a medicinal product to a group of animals after a diagnosis of clinical disease in part of the group has been established, with the aim of treating the clinically sick animals and controlling the spread of the disease to animals in close contact and at risk and which may already be subclinically infected (As defined in Regulation (*EU) 2019/6)*

‘As Little as possible, as much as necessary’

6. Drawing up guidelines or recommendations setting out the preferred choices of antimicrobials in animals by considering the AMR situation in Malta

Record keeping is very important

Vets and farmers have a major role

‘Prevention is better than cure’

1. Enhancing the environment in animal houses: improved ventilation and building design

2. Improving good hygiene practice and biosecurity

3 . Using vaccinations to eliminate or reduce the need for antimicrobials

‘Prevention is better than cure’

1. Drawing up health plans between the farmer and the veterinarian to provide a means to assess objectively factors affecting animal health and welfare

2. Improving the feed quality (example reducing mycotoxins in poultry feed)

3. Using pre- and pro- biotics to improve the gut health

Practical considerations of antimicrobials on farms

✓ Expiry of VMPs (loss of efficacy)

✓Storage and issues of stability of VMPs (temperature & humidity control)

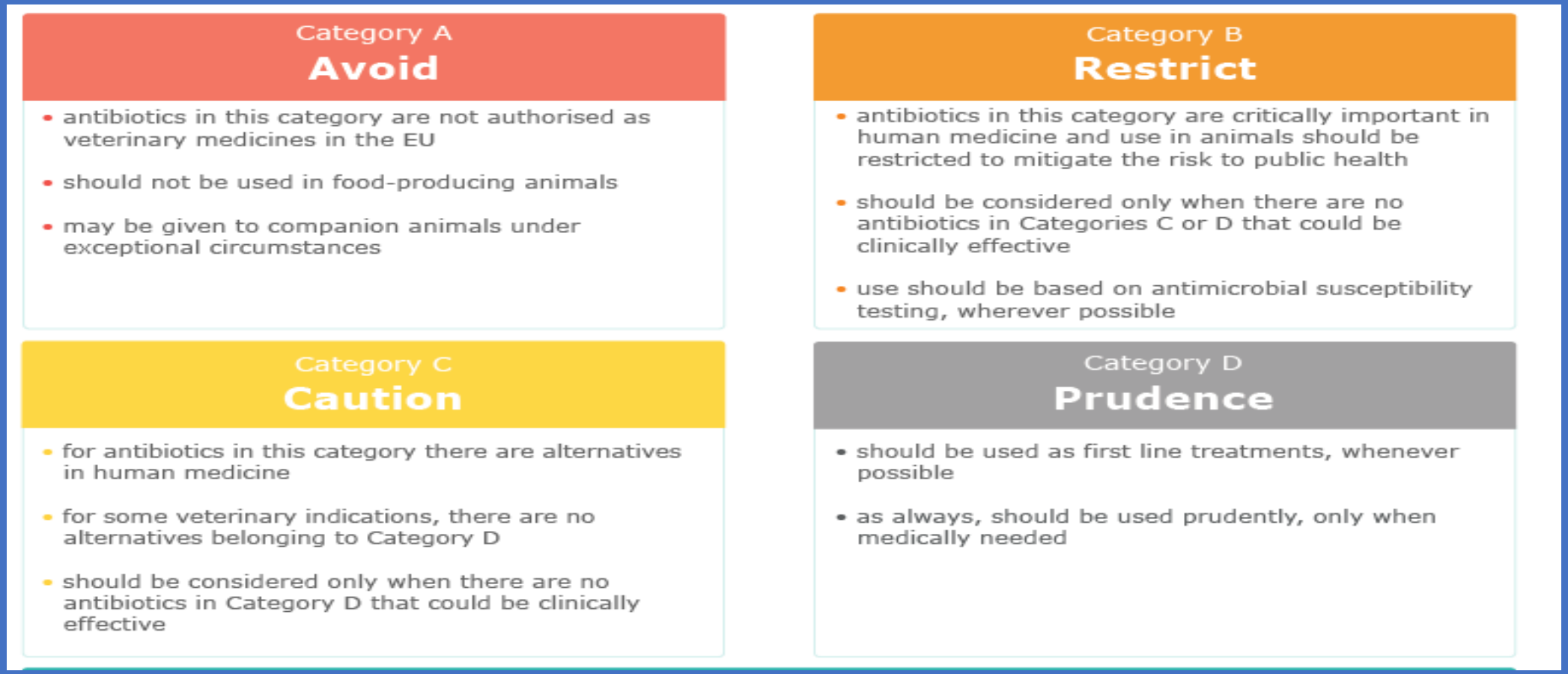
✓Administration of VMPs on farms:

1. administration records,
2. accuracy of weight-based doses,

✓Access to VMPs:

1. Registered medicines in Malta,
2. Registered veterinary pharmacies, wholesale dealers and medicated feed mills and traders in Malta

EMA ANTIBIOTIC CATEGORISATION



Source – *EMA* https://bit.ly/30ZEuRi

Class A to AVOID

Category A

Avoid

- antibiotics in this category are not authorised as veterinary medicines in the EU
- should not be used in food-producing animals
- may be given to companion animals under exceptional circumstances

Source – *EMA*

https://bit.ly/30ZEuRi

Class B to RESTRICT

Category B
Restrict

- antibiotics in this category are critically important in human medicine and use in animals should be restricted to mitigate the risk to public health
- should be considered only when there are no antibiotics in Categories C or D that could be clinically effective
- use should be based on antimicrobial susceptibility testing, wherever possible

Source – *EMA* https://bit.ly/30ZEuRi

Class C CAUTION

Category C
Caution

- for antibiotics in this category there are alternatives in human medicine
- for some veterinary indications, there are no alternatives belonging to Category D
- should be considered only when there are no antibiotics in Category D that could be clinically effective

Source – *EMA*

https://bit.ly/30ZEuRi

Class D PRUDENCE

Category D

Prudence

- should be used as first line treatments, whenever possible
- as always, should be used prudently, only when medically needed

Source – *EMA*

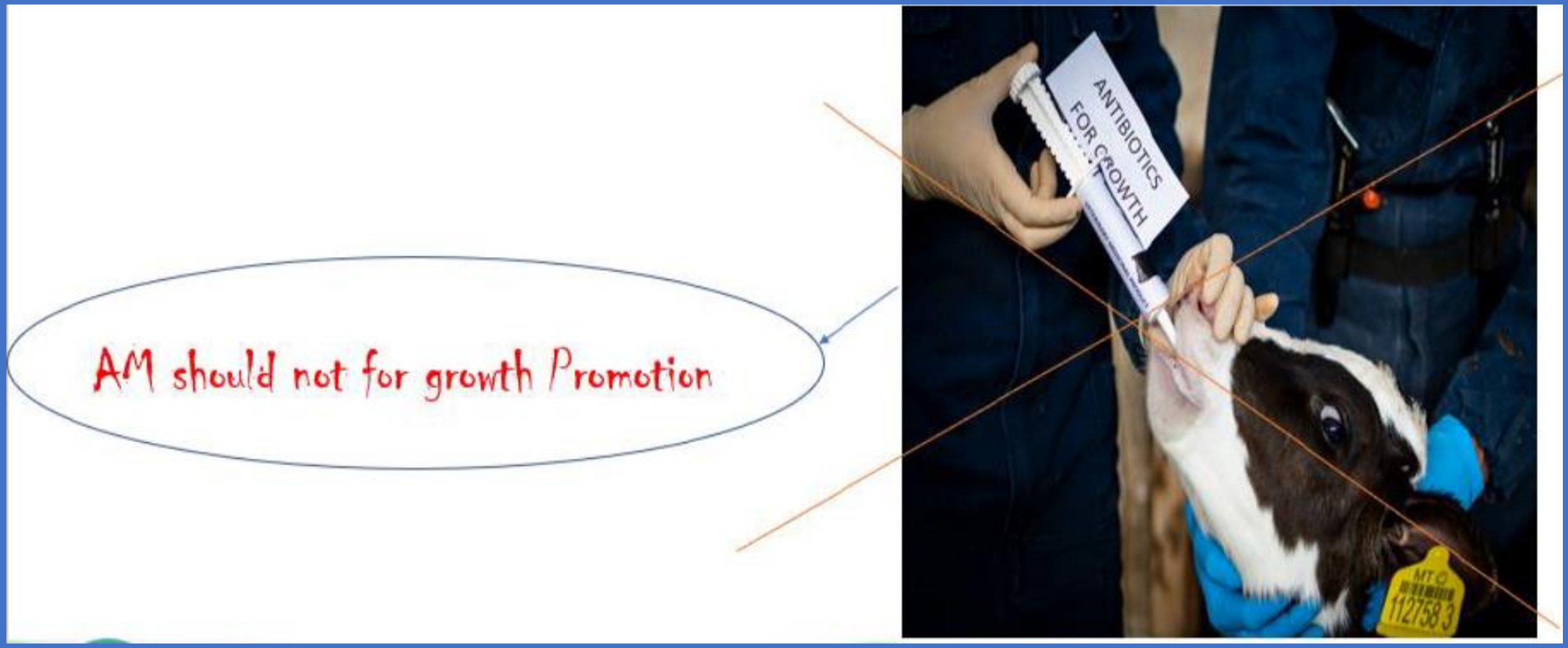
https://bit.ly/30ZEuRi

All COUNTRIES EFFECTED AND WORK TOGETHER

Antibiotics should not be used for prevention

AM should be not used routinely to compensate poor hygiene poor animal husbandry (prevention)

Antibiotics should not be used for growth promotion



Further Reading

1. REGULATION (EU) 2019/6 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R0006&from=EN

2. Guidelines for the prudent use of antimicrobials in veterinary medicine (2015/C 299/04): https://ec.europa.eu/health/sites/health/files/antimicrobial_resistance/docs/2015_prudent_use_guidelines_en.pdf

3. List of registered medicines in Malta: https://agriculture.gov.mt/en/nvl/Documents/authLicSchemes/listVetMeds.pdf

4. List of stakeholders: https://agriculture.gov.mt/en/nvl/Documents/stakeInfo/mainStakeholders.pdf

5. Veterinary Medicines Section website: https://agriculture.gov.mt/en/nvl/Pages/usefulInfo.aspx