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WOAH Regional workshop on interpretation of AMU /AMR data to improve evidence-based decision making in Asia and the Pacific.

How to use AMR/AMU integrated surveillance data to aid the decision making process.

Christopher Teale, APHA, UK

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Different Types of Analysis of AMU/AMR Data:

- Descriptive analysis of AMU/AMR data.
- Univariate analysis (logistic regression).
- Multivariate analysis (development of more complex models).

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Use of Clinical Breakpoints (CBPs) or Epidemiological Cut-Off Values (ECOFFs / ECVs) to Determine "AMR"

- CBP – related to therapeutic outcome
- ECOFF – phenotypically detectable acquired resistance

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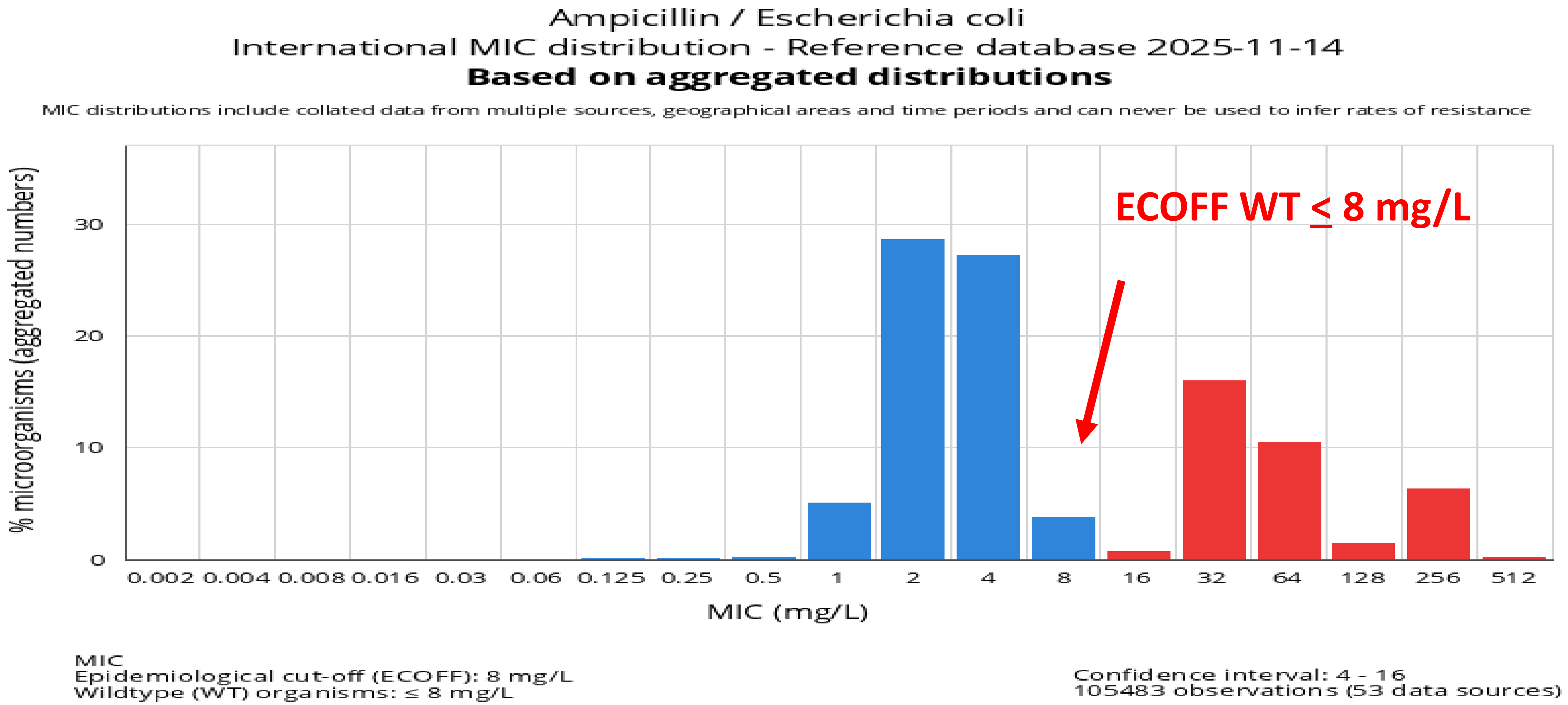
Example of an MIC Distribution from EUCAST:



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An available veterinary CBP for ampicillin:

Enterobacterales	S	I	R
CLSI bovine metritis ampicillin	≤ 0.03	0.06-1.2	≥ 0.25

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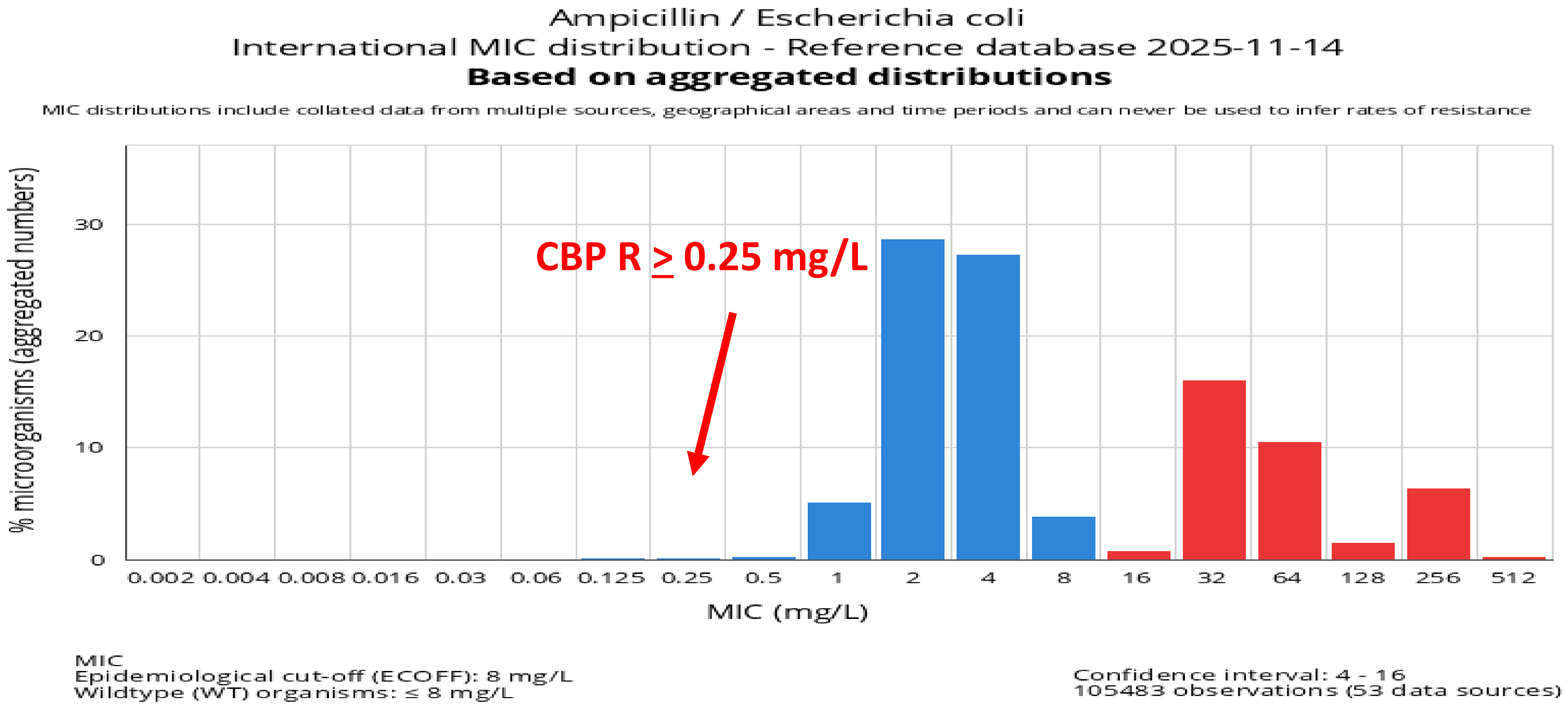
Example of an MIC Distribution from EUCAST:



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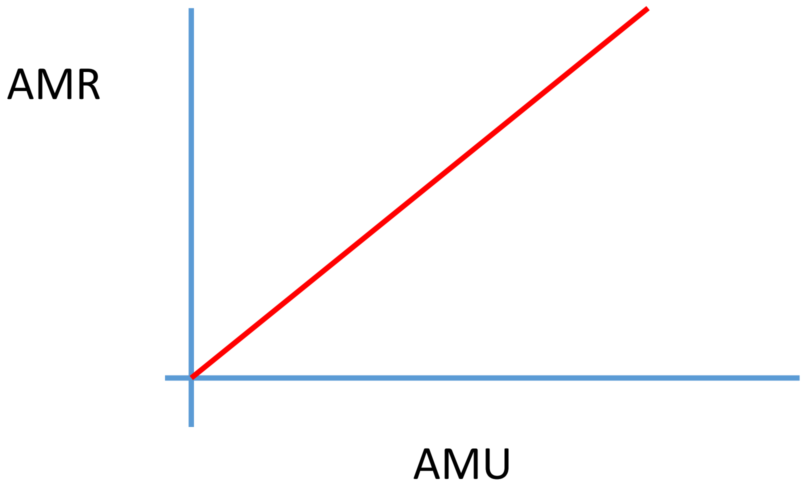
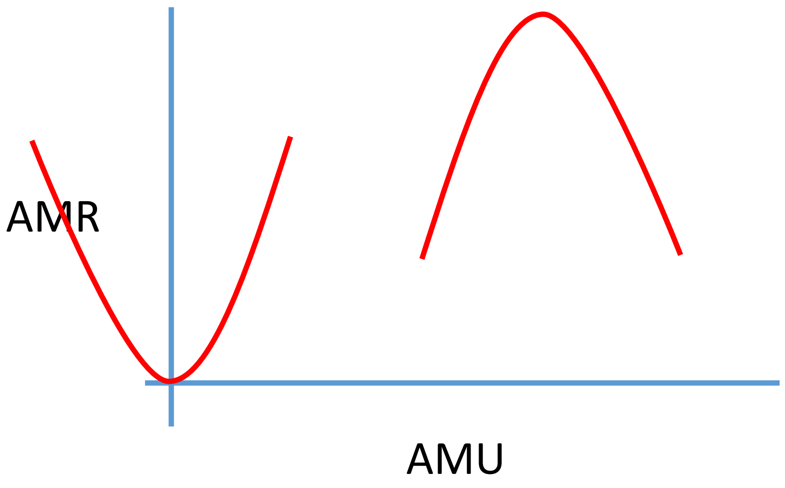
Method of Analysis:

- Logistic regression main method used in studies of association between AMU and AMR
  - AMR is a binary / categorical outcome (R/S)



- Quadratic regression.
  - Used where both variables are measured as continuous variables.
  - Used where the relationship between variables is expected to be a U-shaped curve (or an inverted U shaped curve)



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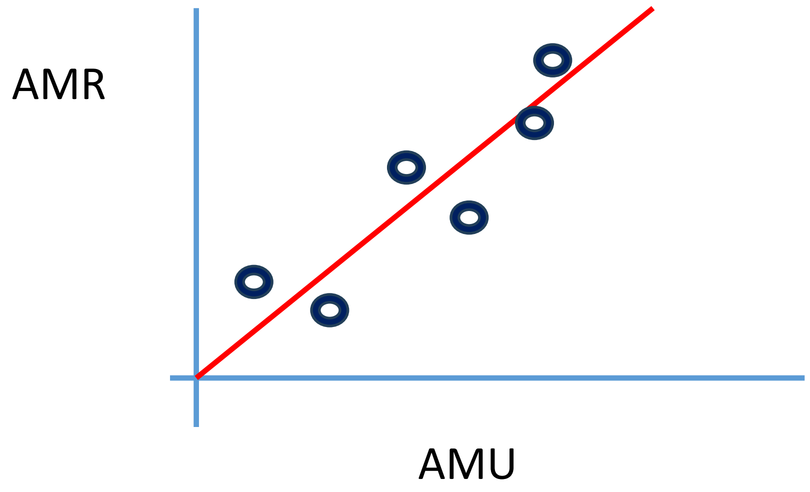
Individual Data Points:

- Multiple countries – JIACRA.
- Single country analysis – data points over time (UK).
- Could be done at with points representing regions or at individual farm level.



Associations between AMU and AMR

Strength of Associations.

[Associations don’t necessarily indicate causal relationships].

When do we see strong associations and when do we see weaker associations?

Can we explain any observed differences?

Occurrence of the Bacterial Organism.

- INDICATOR ORGANISMS
  - *E. coli*, enterococci
  - Ubiquitous – present in the intestine of almost all food animals.
- ZOONOTIC ORGANISMS
  - *Salmonella*, *Campylobacter*
  - *Salmonella* not ubiquitous
- VETERINARY PATHOGENS
  - e.g. *Pasteurella multocida*
  - Not necessarily ubiquitous

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Occurrence of the Bacterial Organism.

FARM 1

If only Farm 1 has the target bacteria, but we measured AMU in all 4 farms, then the use in Farms 2,3 and 4 might not be relevant to Farm 1.

FARM 4

FARM 3

FARM 2

Ubiquitous Bacterial Organisms – e.g. Indicator Organisms.

AMU on all farms is appropriate for ubiquitous organisms.

The sampling strategy also relevant.

FARM 1

FARM 4

FARM 3

FARM 2

Sampling strategy – randomized, representative.

Sampling strategy for ubiquitous organisms should be randomised and representative of target population, or will skew data.

FARM 1

FARM 4

FARM 3

FARM 2

Randomised, representative sampling.

- EU Monitoring
  - Collect caecal samples from healthy animals at slaughter.
  - One sample per slaughter batch in fattening pigs.
  - 60% of national production to be included in the sampling frame.
  - Need to avoid clustering
  - Need to ensure sampling is representative of the target population.

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Clonal Spread – e.g. Multi-Drug Resistant *Salmonella* Kentucky ST198

- MDR *Salmonella* Kentucky ST198
- Multiple *gyrA* mutations resulting in high level ciprofloxacin resistance (ciprofloxacin MIC $\geq$ 4mg/L).
- Often carries extensive additional resistance.
- Prevalent in parts of North Africa and middle East (where it was first detected).
- Poultry and humans.
- Detected in other regions now e.g. Europe.

- AMU could influence occurrence of MDR *S.* Kentucky ST198, but resistance has already emerged and appears to be stable.

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Clonal Spread – e.g. Multi-Drug Resistant *Salmonella* Kentucky ST198

Le Hello et al, JID

1960s – ST198 ciprofloxacin susceptible
1990s – integration of SGI1-K into chromosome
1990s – first *gyrA* mutation
2000s – second *gyrA* mutation, *parC* mutation.

SGI1 – Occurrence in some common *Salmonella* serovars (Beutlich et al. 2011)

- *Salmonella* Typhimurium SGI-1

aadA2	*sul1Δ*	*floR*	*tet*(G)	*blaPSE*	*sul1*

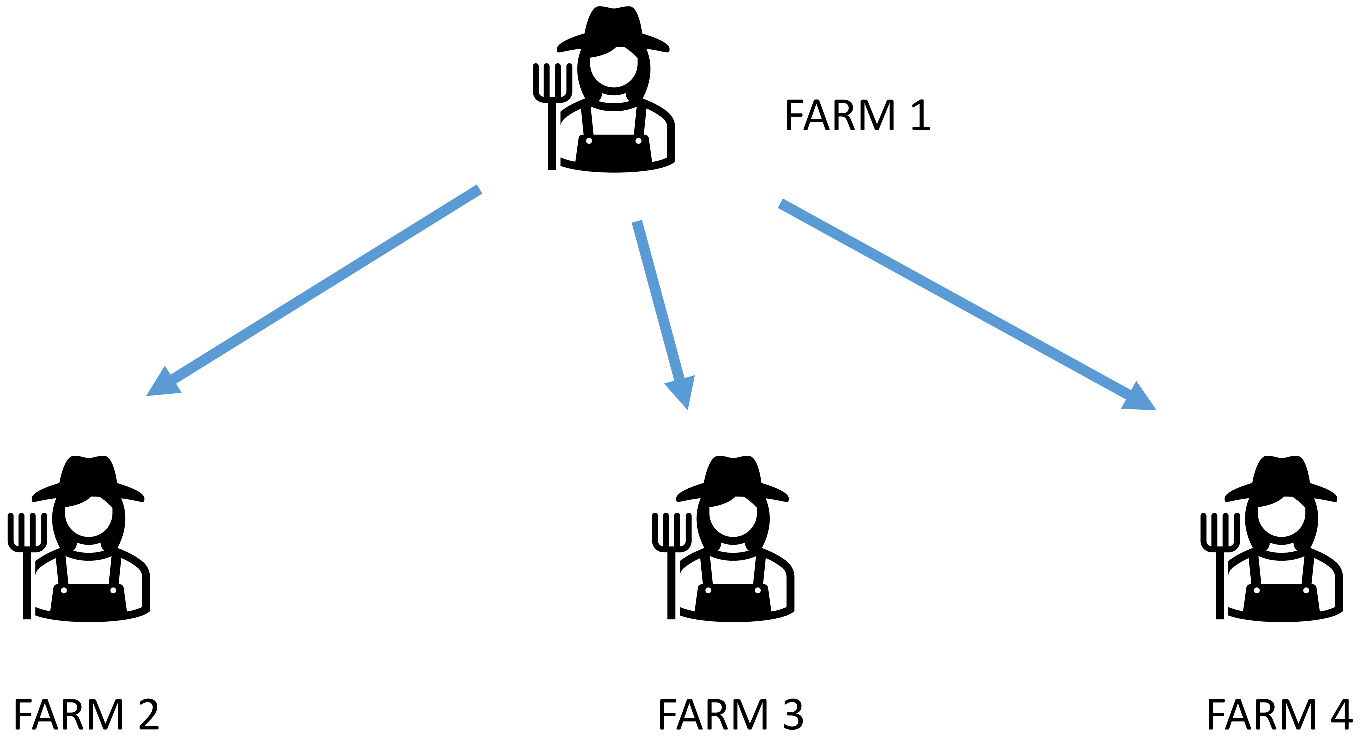
- *Salmonella* Derby SGI-1A and SGI-1C

aadA2	*sul1Δ*	*floR*	*tet*(G)	*blaPSE*	*sul1*	*aadA2*	*dfrA10*	*sul1*

Clonal Spread – e.g. Multi-Drug Resistant *Salmonella* Infantis

- MDR *Salmonella* Infantis
- *S.* Infantis with CTX-M-1 in Europe
- *S*. Infantis with CTX-M-65 in the Americas
- pESI plasmid (“plasmid for emerging *S*. Infantis)
    - Megaplasmid
    - Virulence, resistance and environmental survival genes…
    - Resistance – CTX-M-1, *tet*(A), *sul1, dfrA1, dfrA14*
    - Virulence/ colonisation – fimbriae, yersiniabactin
    - *qacE1, mer*

Clonal Spread – Epidemiological Factors.



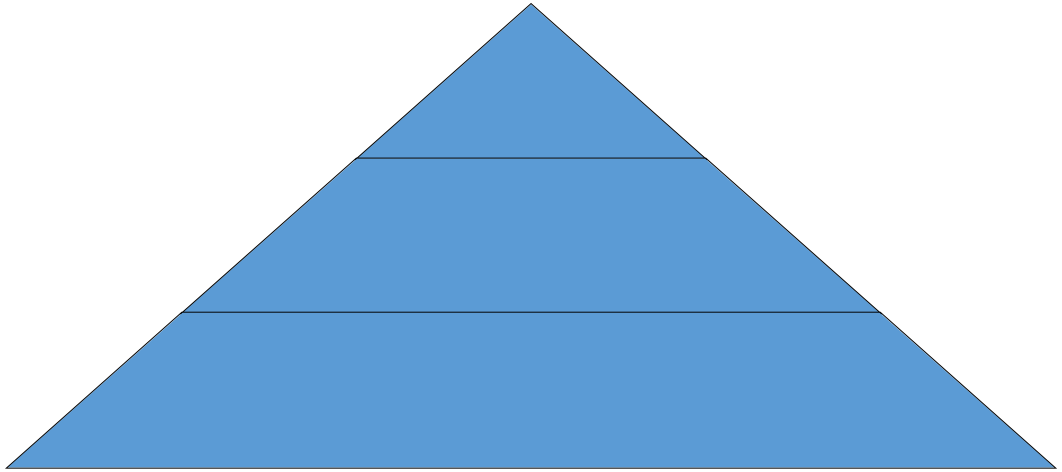
FARM 1 SUPPLIES FARMS 2, 3 AND 4 WITH ANIMALS.

IF FARM 1 HAS SALMONELLA IT IS LIKELY TO BE TRANSFERRED TO FARMS 2,3 AND 4.

THE OCCURRENCE OF AMR MAY NOT BE PRIMARILY AMU IN THIS CASE.

Clonal Spread – Influenced by Many Factors.

- Pyramidal production systems (pigs, poultry).
- If resistance occurs at the top of the pyramid, it also tends to occur in the multiplier stages.



- Spread through contaminated feed / food.
- Environment
- Animal Movements
- Human Travel
- Antimicrobial usage
- [Water supply].

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Relationship between AMU and AMR

- Consider 100 pig herds

- To assess the relationship between AMU and AMR optimal to use indicator organisms which are ubiquitous (present in all herds), so ALL herds provide results for analysis and can be included (*E. coli*, *E. faecalis, E. faecium*).
- If we considered AMC and AMR for *Salmonella*, then not all herds will be *Salmonella* positive (depending on *Salmonella* prevalence).
- Confounding variables. For example, *Salmonella* positive herds (red dots) may all have been supplied with pigs from one herd (orange dot) and in that case, the occurrence of the *Salmonella* and its associated resistance would be heavily influenced by the movement of pigs.

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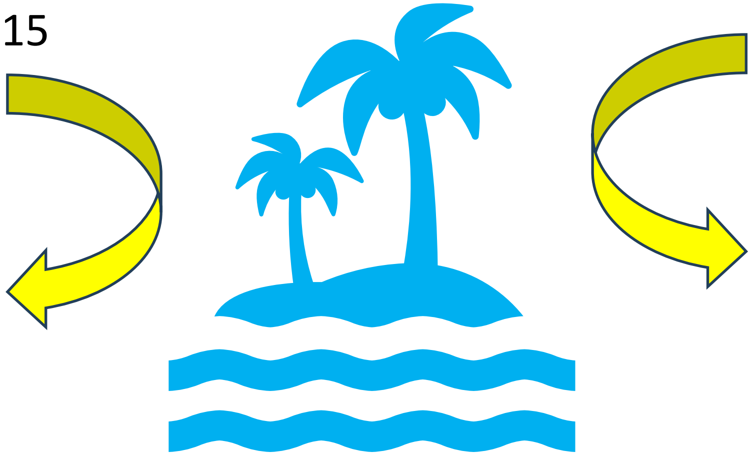
Occurrence of the Resistance Gene.

*bla*CTX-M-15

vanA



If there is no resistance,

- perfect biosecurity
- resistance mechanism not yet evolved

...AMU won't correlate with AMR.

The optimal combination for AMU/AMR analysis?

Ubiquitous organism

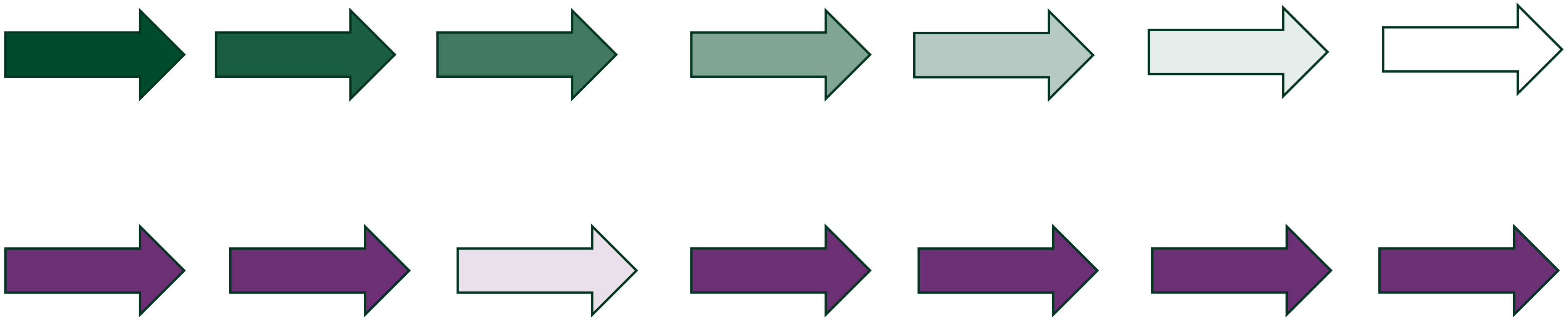
No external AMR gene required (mutational resistance)

Fluoroquinolone + *E. coli* – generally see strong associations AMU and AMR.

Occurrence or Prevalence of Resistance Genes.

DILUTION

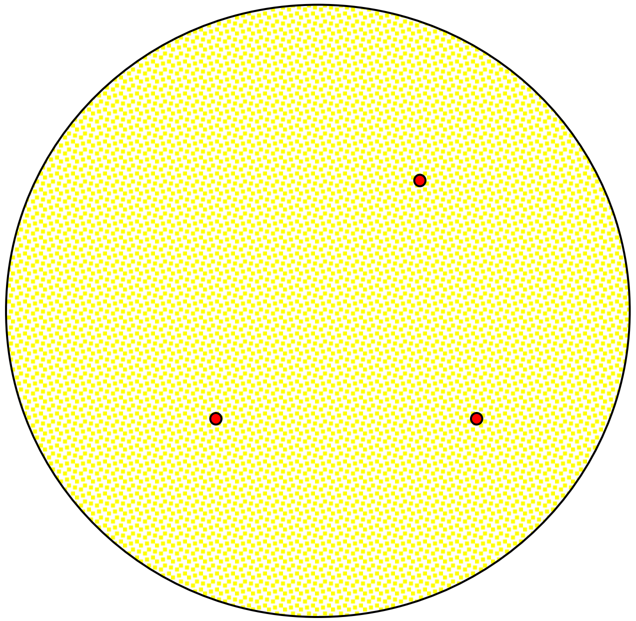
CHEMICAL CONTAMINANT



BACTERIAL CONTAMINANT

AMPLIFICATION POSSIBLE

Selective Culture Media.



Select the minority resistant population

Kill all the sensitive bacteria

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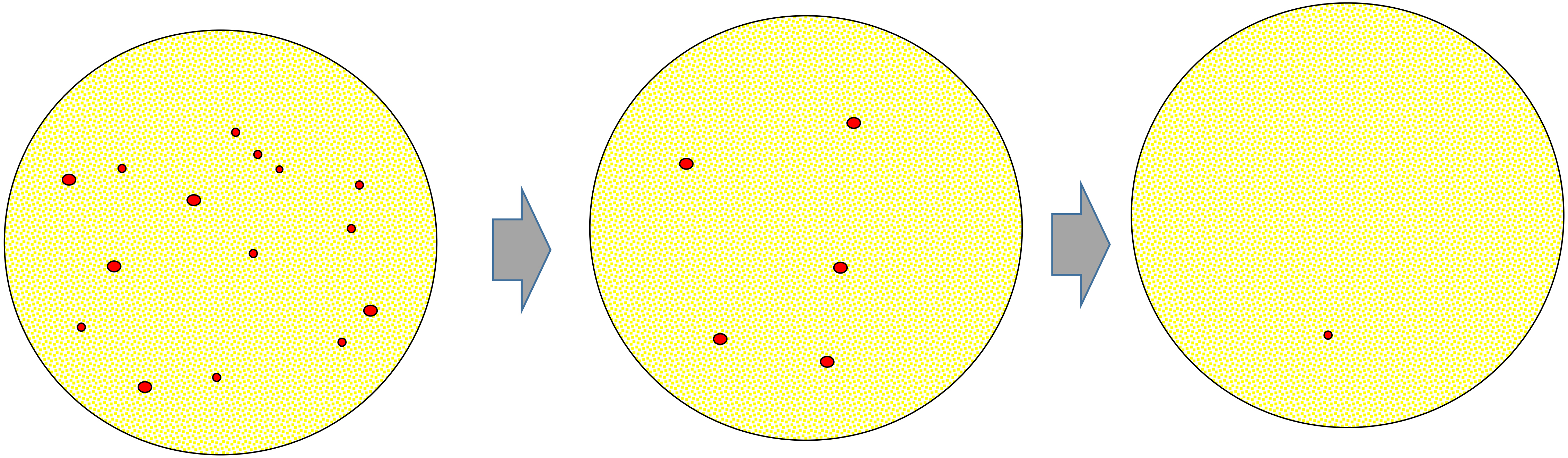
What happens if you stop using antimicrobials?

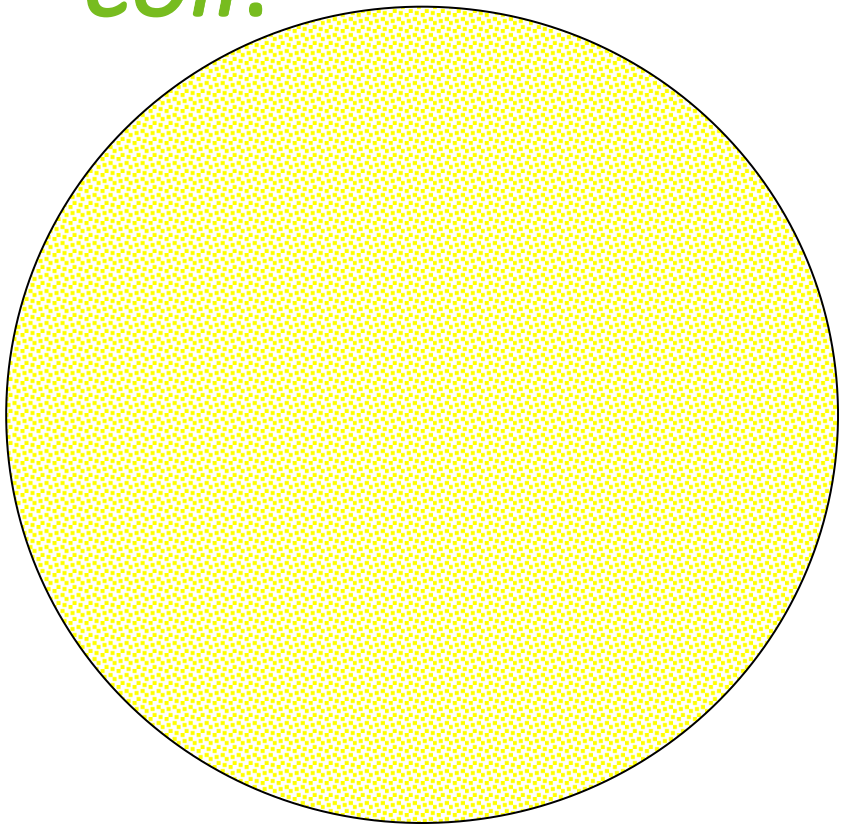
Slow decay in proportion of resistant bacteria over time.

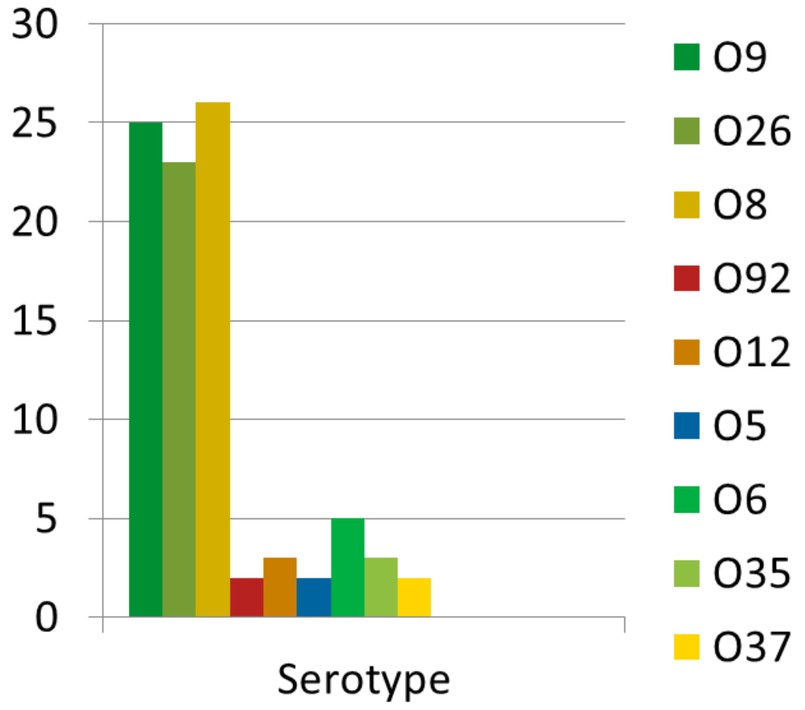
Selective culture – may not detect this decline.

JIACRA 3 – use of selective culture.



Culture of intestinal contents for *E. coli*.





10^8 *E. coli* / g intestinal contents.

E. coli – epidemiology.

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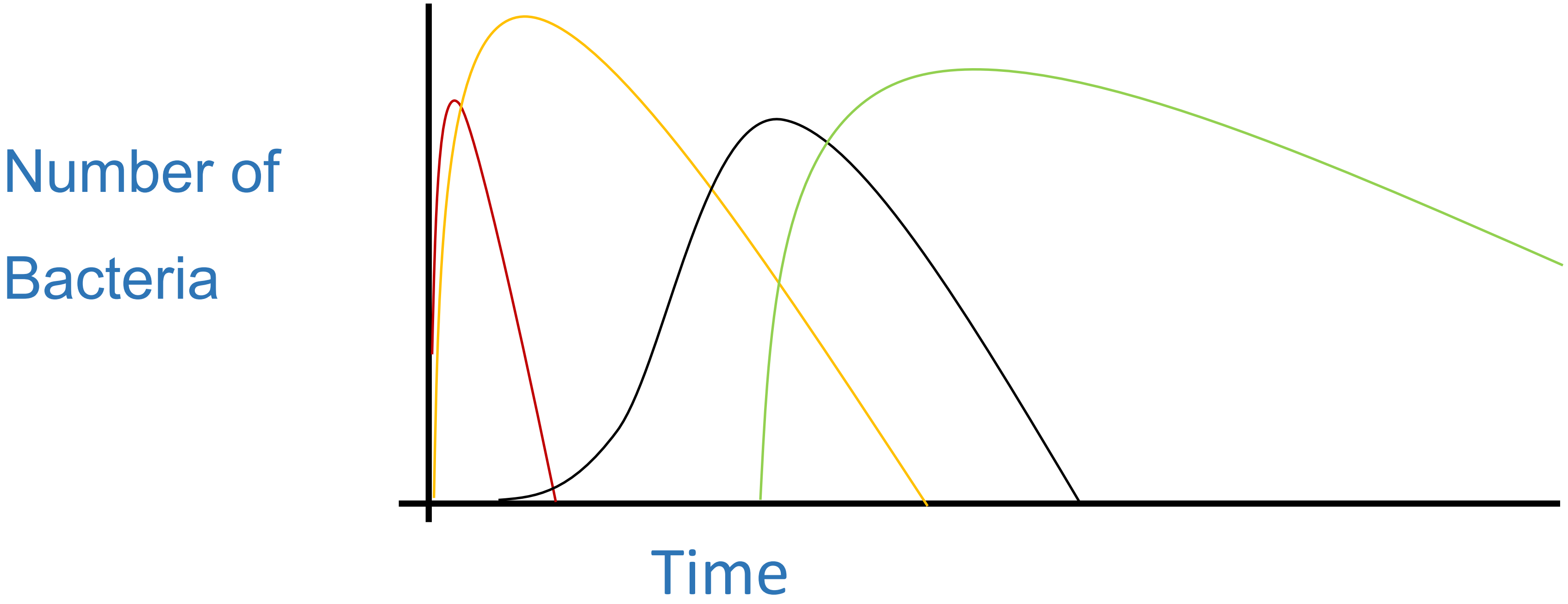
- Different strains of *E. coli* tend to be adapted to colonise animals of different ages.
- Young animals tend to be colonised with different strains from older animals.



E. coli – epidemiology.

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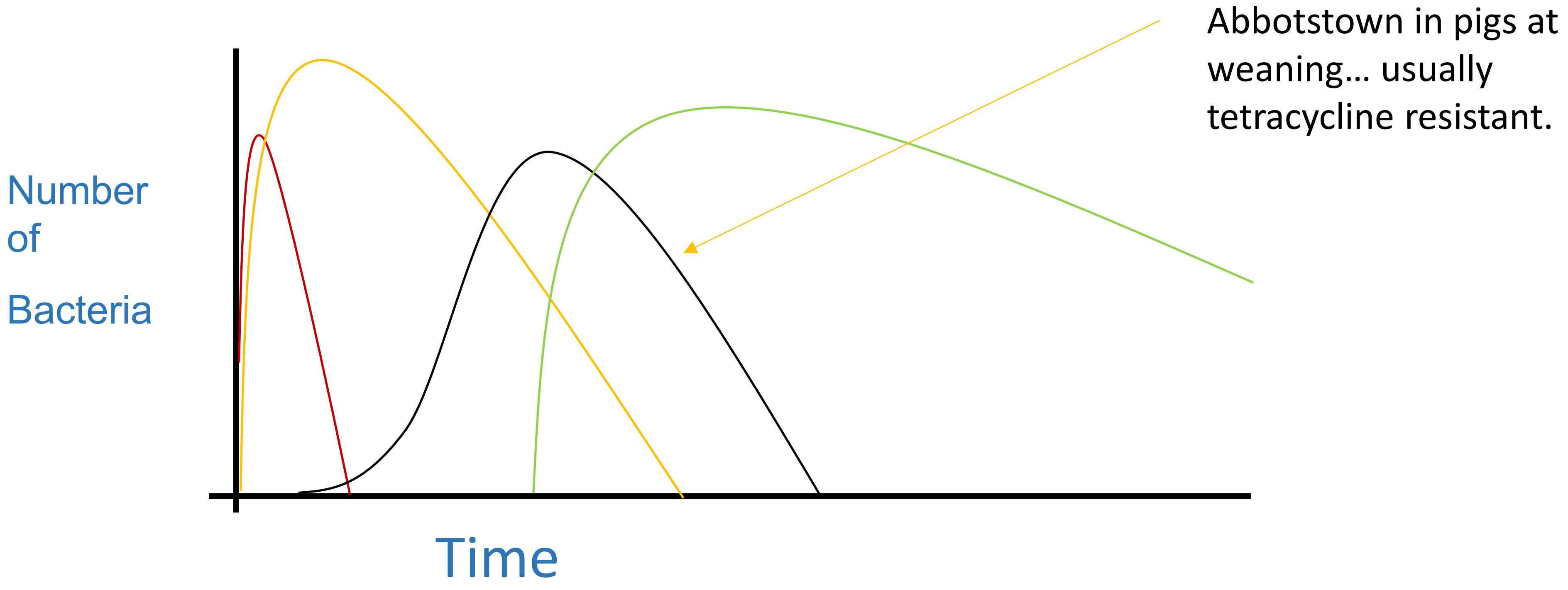

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Use of the Data:

- AMU / AMR association ✓
- Calculate predicted change in AMR for a given reduction/ increase in AMU ✓
- Antimicrobial Stewardship
- Investigation of Outliers
- Trend Analysis

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Antimicrobial Stewardship:

- Use of AMU/AMR data to investigate the impact of antimicrobial stewardship measures and long-term impact on AMU and AMR.
  - Identified stewardship measures in pig and cattle production.
  - Characterised long-term effects on colistin use and resistance.
- Demonstration of reduction of exposure (AMU).
- Concomitant marked decline in AMR.

Decrease in colistin resistance among young bovine and pig productions in France: relationship with colistin usage and stewardship measures

Claire Chauvin[1]*, Eric Jouy[2], Anne Chevance[3], Corinne Jaureguy[4], Xavier Sauzea[5], Nathalie Jarrige[6], Géraldine Cazeau[6], Agnès Perrin-Guyomard[7], Magdéléna Chanteperdrix[8], Anne Hemonic[9], Alexandre Poissonnet[9] and Delphine Urban[3]

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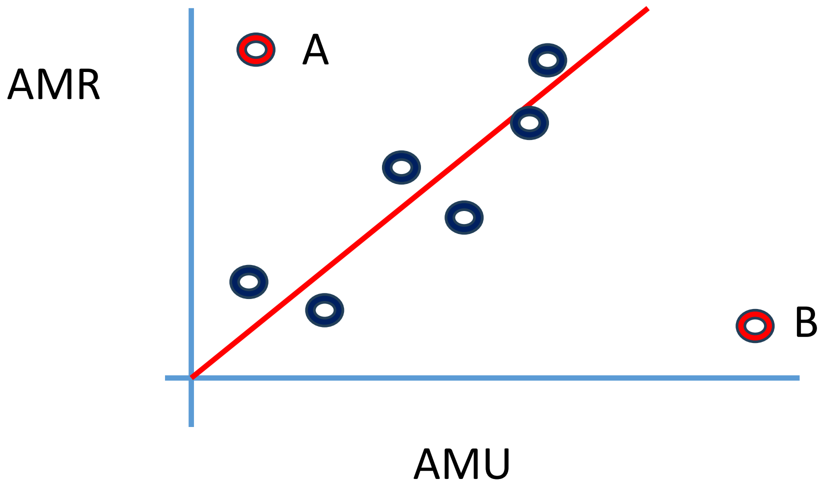
- Trend Analysis

Investigation of Outliers:

- Outlier A has low AMU but high AMR
  - ? Poor infection control
  - ? Historical use
  - ? Use in other epidemiologically linked sectors
- Outlier B has high AMU but low AMR
  - ? Good infection control
  - ? Resistance genes not yet emerged or not present



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Use of the Data:

- AMU / AMR association ✓
- Calculate predicted change in AMR for a given reduction/ increase in AMU ✓
- Antimicrobial Stewardship ✓
- Investigation of Outliers ✓
- Trend Analysis / Longitudinal Analysis ✓

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Longitudinal / Temporal Trend Analysis:

- Can combine AMR results for different species, weighted by population size at slaughter.
- Code for analysing data has been made available by EFSA (see JIACRA reports)

Decreasing antimicrobial resistance in representative UK livestock species was associated with reduced total sales of antimicrobials in the last decade

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