Harmonization in AMR Monitoring is the Way Forward

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Resistance & Food Safety

There are public concerns that people may acquire foodborne illnesses that cannot be appropriately treated with antibiotics as a result of antibiotic-resistant bacteria that are derived from food animals that have been treated with antibiotics.
Key Factors to Balance

• Science-based risk-benefit assessment vs. political decision
• Human health and food safety vs. animal health needs
  – Future animal protein availability and affordability
• Therapeutic use vs. performance use
• Veterinarian oversight vs. lay person use
• Unintended consequences vs. desired outcome
  – Risk-risk analysis
  – Risk-benefit analysis
Possible Actions

• Legislative
e.g. Prescription system i.e. access via control (feed mills, marketing channels)

• Veterinary oversight
  Responsible use, veterinarian network via communication and education

• Regulatory review process
  Resistance monitoring
  Use / sales data
  Risk assessments
Global "authority“ Reports/Recommendations since 1997

- WHO (Berlin, FQ, Global Principles of Use, Use Monitoring, Aquaculture)
- Europe (CVMP, EFSA, Health Ministers, etc.)
- Australia (JETACAR)
- U.S. (CDC, FDA, GAO, IOM, Public Health Action Plan, etc.)
- Canada (Adv. Com. Report, CCAR)
- OIE
- Codex
- Other reports from APUA, IFT, etc.
Summary of Actions and Recommendations
International and National Level

• Responsible Use
  – Appropriate veterinary antibiotic use practices described; education, disease prevention

• Resistance Monitoring

• Antibiotic sales Monitoring

• Regulatory Controls
  – Risk assessment-based regulatory decisions on microbial food safety guide decisions on product use:
    • Approval with appropriate label indications and use, prescription

• Research
  – New products
Risk Analysis Components

- Risk Analysis
  - Risk Assessment
    - Release
    - Exposure
  - Risk Management
  - Risk Communication
    - Consequence
What Should Risk-Based Evaluations Do?

• Provide detailed description of risk-generating system (causal pathway)
  – Requires multiple experts to be involved
  – Each step of the pathway is identified
  – Data gaps and research needs are noted

• Estimate of the probability and magnitude of consequence
  – This estimate can be used to support decisions

• Provide Risk Managers with intervention options to choose from based on their likelihood of efficiently reducing risk
  – Risk Assessors should ask Risk Managers what do they want? Value? What resources are available? [Risk Communication]
  – Need to provide a means to evaluate the effectiveness of the intervention option!
Risk assessment starts by connecting the causal chain

If there is NO connection there is NO RISK
The 3-step RA Process

✓ An antibiotic must select for foodborne bacteria that acquire antibiotic-resistance in food animals during treatment
  ✓ Release

✓ A person must ingest meat from a treated animal that is contaminated with those same antibiotic-resistant foodborne bacteria
  ✓ Exposure

✓ The person that ingests these bacteria must become sick with a bacterial infection that cannot be appropriately treated with antibiotics as a result of those animal-derived antibiotic-resistant bacteria
  ✓ Consequence
EPIDEMIOLOGY OF ANTIMICROBIAL RESISTANCE

Release

Exposure

Consequence

after Linton AH (1977), modified by Irwin RJ
Sample Origins

If the bacterial isolates will undergo susceptibility testing with the goal of using the data for risk assessment then the samples must originate from appropriate sources to provide data for the relevant steps of the risk assessment

• **Release**
  Samples should come from the farm

• **Exposure**
  Samples should come from slaughter houses or retail meat

• **Consequence**
  Samples should come from humans, ideally pre-treatment samples
CHAPTER 6.7.
HARMONISATION OF NATIONAL ANTIMICROBIAL RESISTANCE SURVEILLANCE AND MONITORING PROGRAMMES

ARTICLE 6.7.1.

Objective
This chapter provides a basis for:
1. development of national antimicrobial resistance surveillance and monitoring programmes;
2. harmonisation of existing national surveillance and monitoring programmes,
in animal and in products of animal origin intended for human consumption.

ARTICLE 6.7.2.

Purpose of surveillance and monitoring
1. Surveillance and monitoring of antimicrobial resistance is necessary to:
   a) follow trends in antimicrobial resistance in bacteria;
   b) detect the emergence of new antimicrobial resistance mechanisms;
   c) provide the data necessary for developing risk analyses with relevance for human and animal health;
   d) provide a basis for policy recommendations for animal and public health;
   e) provide information for risk analysis and promote risk management.

2. National antimicrobial resistance surveillance and monitoring programmes may include the following components:
   a) statistically based surveys (including statistically based programmes);
   b) seroepidemiology and testing of animals on the farm, at market or at slaughter;
   c) an organised national programme, sampling animals, birds, flocks, and vectors;
   d) analysis of veterinary practice and diagnostic laboratory records.

3. Countries should consider active surveillance and monitoring. Passive surveillance and monitoring may offer additional information.

4. Targeted surveillance is conducted through an active sampling scheme designed to meet programme objectives. Passive surveillance is conducted when samples are submitted to a laboratory for testing from sources outside the programme.
What Are You Measuring?

Minimal Inhibitory Concentration (MIC)

The lowest concentration of an antimicrobial agent that prevents visible growth (to the naked eye) of a microorganism in an agar or broth dilution susceptibility test.
AST Methods

British Society of Antimicrobial Chemotherapy (BSAC)

European Committee on Antimicrobial Susceptibility Testing (EuCAST)

Clinical and Laboratory Standards Institute (CLSI)
Question 1

What is 0.5 McFarland and why should we care?
The basic for each method

- Isolate bacterium in pure culture
- Inoculate broth
- Standardize turbidity 0.5 McFarland
Question 2

How many CLSI approved methods are there to do antimicrobial susceptibility testing?

What are they?
Agar Dilution Susceptibility Test

An *in vitro* antimicrobial susceptibility test method conducted using serial concentration of an antimicrobial agent incorporated into an agar growth medium in separate Petri dishes that are inoculated with a bacterial suspension to determine the minimal inhibitory concentration.
Agar Dilution
Agar Dilution
Agar Dilution

Incubate and record MIC
Agar Dilution

2 µg/ml  4 µg/ml  8 µg/ml
An *in vitro* antimicrobial susceptibility test conducted using serial concentrations of an antimicrobial agent incorporated in liquid nutrient media that are inoculated with a bacterial suspension to determine the minimal inhibitory concentration of an antimicrobial agent.

**NOTE:** When this procedure is carried out in test tubes, it is referred to as broth macrodilution; when performed in microdilution plates, it is called broth microdilution.
Broth Dilution

microtitre plate

autoinoculator
Broth Dilution

Interpreting results
Broth Dilution

96 well microtiter plate

<table>
<thead>
<tr>
<th>ug/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>64</td>
</tr>
<tr>
<td>32</td>
</tr>
<tr>
<td>16</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>2</td>
</tr>
</tbody>
</table>
# Broth Dilution

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.03 0.06 0.12 0.25 0.5 1 2 4 8 16 32 64</td>
<td>2</td>
</tr>
<tr>
<td>B</td>
<td>Repeat (?)</td>
<td>Repeat</td>
</tr>
<tr>
<td>C</td>
<td>Repeat</td>
<td>8</td>
</tr>
<tr>
<td>D</td>
<td>≤0.03</td>
<td>&gt;64</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Controls</td>
<td></td>
</tr>
</tbody>
</table>

**Drug Concentration:***

- **A**: Concentrations tested from 0.03 to 64.
- **B**: Concentrations tested from 0.03 to 64, with a repeat at some concentrations.
- **C**: Concentrations tested from 0.03 to 64, with a repeat at some concentrations.
- **D**: Concentrations tested from 0.03 to 64, with a repeat at some concentrations.
- **E**: Concentrations tested from 0.03 to 64, with a repeat at some concentrations.
- **F**: Concentrations tested from 0.03 to 64, with a repeat at some concentrations.
- **G**: Concentrations tested from 0.03 to 64, with a repeat at some concentrations.
- **H**: Concentrations tested from 0.03 to 64, with a repeat at some concentrations.

**MIC Values:**

- **A**: MIC value is 2.
- **B**: MIC value is Repeat (?) or Repeat.
- **C**: MIC value is 8.
- **D**: MIC value is ≤0.03 or >64.
- **F**: MIC value is 0.06.

**Controls:**

- **H**: Controls value is 0.06.
Agar Disk Diffusion Susceptibility Test

An *in vitro* antimicrobial susceptibility test conducted using disks impregnated with a specified single concentration of an antimicrobial agent applied to the surface of an agar medium that has been inoculated with the test organism.

**NOTE:** The diameter of the zone of growth inhibition that results from the diffusion of an antimicrobial agent from the disks is measured with calipers or a ruler and recorded in millimeters.
Disk Diffusion

- Inoculate Agar plate
- Place disks on agar plate
Quality Control isolates tell me what is resistant and what is susceptible, correct?
Why use QC strains?

- QC = Quality Control strains, these can be considered ‘positive controls’

- QC are bacterial isolates that have undergone rigorous testing to ensure that under a standard test system they will always give the same MIC range with a given antibiotic

- If a QC is out of range it invalidates the AST and indicates there are problems in the method e.g. pH, ion concentrations, temperature etc
VET01-A4

Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals; Approved Standard—Fourth Edition

VET01-S2

Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals; Second Informational Supplement

This document provides the currently recommended techniques for antimicrobial agent disk and dilution susceptibility testing, criteria for quality control testing, and interpretive criteria for veterinary use.

This document provides updated tables for the CLSI antimicrobial susceptibility testing standard VET01-A4.
Table 5. Acceptable Quality Control Ranges of Minimal Inhibitory Concentrations for Broth Microdilution (μg/mL) for Reference Strains

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>Streptococcus agalactiae</th>
<th>Staphylococcus aureus</th>
<th>Escherichia coli</th>
<th>Providencia stuartii</th>
<th>Pseudomonas aeruginosa</th>
<th>Proteus mirabilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMBIC</td>
<td>0.16-0.60</td>
<td>0.1-0.4</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>0.16-0.25</td>
<td>0.1-0.25</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0.25-1.0</td>
<td>0.5-2</td>
<td>0.2-0.5</td>
<td>0.2-0.5</td>
<td>0.2-0.5</td>
<td>0.2-0.5</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>0.25-1.0</td>
<td>0.5-2</td>
<td>0.2-0.5</td>
<td>0.2-0.5</td>
<td>0.2-0.5</td>
<td>0.2-0.5</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>0.12-0.5</td>
<td>0.25-1</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.12-0.5</td>
<td>0.25-1</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0.12-0.5</td>
<td>0.25-1</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>0.12-0.5</td>
<td>0.25-1</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
</tr>
<tr>
<td>Ceftobiprole</td>
<td>0.12-0.5</td>
<td>0.25-1</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
</tr>
<tr>
<td>Ceftolozine</td>
<td>0.12-0.5</td>
<td>0.25-1</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
</tr>
<tr>
<td>Ceftazidime sodium</td>
<td>0.12-0.5</td>
<td>0.25-1</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
</tr>
<tr>
<td>Ceftazidime pamoate</td>
<td>0.12-0.5</td>
<td>0.25-1</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
</tr>
<tr>
<td>Ceftazidime sulbactam</td>
<td>0.12-0.5</td>
<td>0.25-1</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
</tr>
<tr>
<td>Ceftazidime thienamycin</td>
<td>0.12-0.5</td>
<td>0.25-1</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
</tr>
<tr>
<td>Ceftazidime xanabinol</td>
<td>0.12-0.5</td>
<td>0.25-1</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
</tr>
<tr>
<td>Ceftazidime zolidone</td>
<td>0.12-0.5</td>
<td>0.25-1</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
</tr>
<tr>
<td>Ceftazidime zoladromide</td>
<td>0.12-0.5</td>
<td>0.25-1</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
</tr>
<tr>
<td>Ceftazidime zoladromide</td>
<td>0.12-0.5</td>
<td>0.25-1</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
<td>0.03-0.12</td>
</tr>
</tbody>
</table>

Table 4. Acceptable Quality Control Ranges of Antimicrobial Disk Susceptibility Test Zone Diameters (mm) for Reference Strains on Mueller-Hinton Agar (Except Where Noted)

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>E. coli</th>
<th>ATCC 25922</th>
<th>S. aureus</th>
<th>ATCC 29213</th>
<th>P. aeruginosa</th>
<th>ATCC 27853</th>
<th>P. mirabilis</th>
<th>ATCC 32840</th>
</tr>
</thead>
</table>

*Clinical and Laboratory Standards Institute. All rights reserved.*
What does QC tell us……..

• As long as our QC strains are in range we have a valid test system

• It does NOT tell us if test bacteria are susceptible or resistant
What are interpretive criteria?

• These are commonly known as breakpoints; S, I, R (Susceptible, Intermediate, Resistant)

• **Susceptible**
  This category implies an infection due to the isolate may be appropriately treated with the dosage regimen of an antimicrobial agent recommended for that type of infection and infecting species, unless otherwise indicated.

• **Intermediate**
  This category implies an infection due to the isolate may be appropriately treated in body sites where the drug are physiologically concentrated or when a high dosage of drug can be used; also indicates a ‘buffer zone’ that should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretation.

• **Resistant**
  Resistant isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or fall in the range where specific microbial resistance mechanisms are likely, and clinical efficacy has not been reliable in treatment studies.
<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>Disk Content</th>
<th>Zone Diameter (mm)</th>
<th>MIC Breakpoint (µg/mL)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>S</td>
<td>I</td>
<td>R</td>
</tr>
<tr>
<td>Lincosamides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td></td>
<td>2 µg</td>
<td>≥24</td>
<td>15-20</td>
</tr>
</tbody>
</table>

Clindamycin is also used to test for susceptibility to lincomycin. Clindamycin is more active than lincomycin against most staphylococcal strains.

|                      |             |        |        |        |        |        |        |          |
| Pitnacycin           |             | 2 µg   | ≥13    | –      | ≤12    | ≤2     | –      | ≥4  |

| Macrolides           |             |        |        |        |        |        |        |          |
| Tilmicosin          |             | 15 µg  | ≥14    | 11-13  | ≤10    | ≤8     | 16     | ≥32 |

(24) For injectable product only.

| Bovine Respiratory Disease | Mannheimia haemolytica | 15 µg | ≥11    | –      | ≤10    | ≤16    | –      | ≥32 |
|                            | Pasturella multocida   |       |        |        |        |        |        |      |
|                            | Actinobacillus pleuropneumoniae |   |        |        |        |        |        |      |

| Tulasstramycin        |             | 30 µg  | ≥18    | 15-17  | ≤14    | ≤16    | 32     | ≥64 |

| Bovine Respiratory Disease | Mannheimia haemolytica | 30 µg | ≥18    | 15-17  | ≤14    | ≤16    | 32     | ≥64 |
|                            | Pasturella multocida   |       |        |        |        |        |        |      |
|                            | Helicobacter somni     |       |        |        |        |        |        |      |

| Swine Respiratory Disease | Pasturella multocida   | 30 µg | ≥18    | 15-17  | ≤14    | ≤16    | 32     | ≥64 |
|                            | Bordetella bronchiseptica |      |        |        |        |        |        |      |
|                            | Actinobacillus pleuropneumoniae | |        |        |        | ≤64    | –      |      |

(25) Hazy growth or double zones should be ignored. The outer, discrete zone of inhibition should be read. To detect isolates nonsusceptible to tulasstramycin, broth microdilution testing is required.
<table>
<thead>
<tr>
<th>Code</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M31-A3</td>
<td>VET01-A3</td>
<td>Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated From Animals; Approved Standard—Third Edition</td>
</tr>
<tr>
<td>M37-A3</td>
<td>VET02-A3</td>
<td>Development of <em>In Vitro</em> Susceptibility Testing Criteria and Quality Control Parameters for Veterinary Antimicrobial Agents; Approved Guideline—Third Edition</td>
</tr>
<tr>
<td>M42/M49-S1</td>
<td>VET03/VET04-S1</td>
<td>Performance Standards for Antimicrobial Susceptibility Testing of Bacteria Isolated From Aquatic Animals; First Informational Supplement</td>
</tr>
<tr>
<td>M42-A</td>
<td>VET03-A</td>
<td>Methods for Antimicrobial Disk Susceptibility Testing of Bacteria Isolated From Aquatic Animals; Approved Guideline</td>
</tr>
<tr>
<td>M49-A</td>
<td>VET04-A</td>
<td>Methods for Broth Dilution Susceptibility Testing of Bacteria Isolated From Aquatic Animals; Approved Guideline</td>
</tr>
<tr>
<td>X08-R</td>
<td>VET05-R</td>
<td>Generation, Presentation, and Application of Antimicrobial Susceptibility Test Data for Bacteria of Animal Origin; A Report</td>
</tr>
</tbody>
</table>
Need for Harmonisation

Franklin et al (2001) published a guideline on the harmonisation of surveillance programmes in animals on behalf of the Office International des Epizooties (OIE)

a) animal species/categories (including age) to be sampled
b) for food sampling, the relative merits of sampling at the abattoir and retail outlet should be considered. In addition to food of domestic origin, food of foreign origin may also be considered, possibly at the port of entry of the products
c) sampling strategy to be employed, for example: active or passive collection of samples; random, stratified or systematically collected samples; statistically based sampling or opportunistic sampling
d) samples to be collected (faeces, carcass, raw and/or processed food)
e) bacterial species to be isolated
f) antimicrobials to be used in susceptibility testing
g) standardised susceptibility testing
h) quality control – quality assurance
i) type of quantitative data to be reported
j) database design for appropriate data extraction

k) analysis and interpretation of data

l) reporting (consideration of transparency of reporting and interests of stakeholders)

Need for Harmonisation

At the outset it is important to emphasise that all of the reviewed surveillance systems have merit, especially when considering resistance trends within the countries in which the surveillance has been instigated.

The major challenge when analysing data across surveillance systems is a lack of harmonisation in sampling, susceptibility testing methods and in such basic terms as defining resistance.

All these factors can confound data interpretation even when analysing data vertically within a country but in horizontal analysis, across countries, it can be become almost impossible.
Definition of Resistance

National surveillance schemes do not all define resistance in the same way, there is considerable variability in what is defined as “resistant”

This means that it is not possible to simply compare resistant rates from different surveillance schemes as they are not measuring the same parameter

Indeed even within national surveillance schemes methods of analysis have changed over time such that % resistance values need to be viewed with caution
Clinical vs. Epidemiologic

- **Clinical Resistance**
  - Isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or fall in the range where specific microbial resistance mechanisms are likely (e.g. β-lactamases), and clinical efficacy has not been reliable in treatment studies

- **Epidemiological (Resistance)**
  - Isolate is defined as non-wild type (NWT) by the presence of an acquired or mutational resistance mechanism to the antibiotic. Isolates may or may not respond clinically to antimicrobial treatment
Question 4

Clinical Breakpoints and Epidemiological Cut-Off Values are both means of measuring prevalence of resistance
Clinical vs. Epidemiologic

Who said life was easy……..

MARAN (Netherlands) and SVARM (Sweden), as examples, use epidemiological cut-off values to determine resistance but VAV (Spain) use a combination of epidemiological cut-off values and clinical breakpoints.

Just to make sure you’re REALLY confused……..
MARAN and SVARM use epidemiological cut-off values BUT they do not use the same values in all cases.
### Table 10. MIC distribution (in %) for all salmonella’s (N = 2195) tested for antibiotic susceptibility in 2004.

<table>
<thead>
<tr>
<th>Total 2004</th>
<th>MIC distribution (µg/ml)</th>
<th>R%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.06 0.125 0.25 0.5 1 2 4 8 16 32 64 128 256 512 1024</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>21.2 62.0 1.7</td>
<td>15.1</td>
</tr>
<tr>
<td>Cefotaxim</td>
<td>90.3 8.3 1.0 0.05</td>
<td>0.1 0.2</td>
</tr>
<tr>
<td>Imipenem</td>
<td>84.1 14.9 0.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>32.1 56.8 10.0 0.7</td>
<td>0.2 0.1 0.1</td>
</tr>
<tr>
<td>Neomycin</td>
<td>90.2 8.2 0.6</td>
<td>0.1 0.1 0.5 0.3</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.1 17.6 62.5 3.8 0.3</td>
<td>0.3 4.9 3.1 7.3</td>
</tr>
<tr>
<td>Sulphameth.</td>
<td>85.6 5.7 1.0 0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>91.4 2.9 3.6 1.5 0.4</td>
<td>0.23 0.05</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>3.7 79.1 8.3 0.8</td>
<td>0.1 0.6 7.4</td>
</tr>
<tr>
<td>Nalidixic Acid</td>
<td>6.5 79.7 6.6 0.2</td>
<td>0.1 0.4 6.5</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>0.7 73.2 19.0 1.1</td>
<td>4.7 0.7 0.4 0.14</td>
</tr>
</tbody>
</table>
## Let's Compare Data within a Country

### Table 10. MIC distribution (in %) for all salmonella’s (N = 2238) tested for antibiotic susceptibility in 2005.

<table>
<thead>
<tr>
<th></th>
<th>MIC (%) distribution (mg/L)</th>
<th>R%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total 2005</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>0,04 0,1 0,1 0,4 15,8</td>
<td>16,0</td>
</tr>
<tr>
<td>Cefotaxim</td>
<td>0,1 0,4</td>
<td>0,0 0,7</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>0,2 0,3 0,1 0,7</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>0,7 0,4 0,1 0,3 0,0 0,0 0,0</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0,0 0,4 0,1 0,7</td>
<td>0,9</td>
</tr>
<tr>
<td>Neomycin</td>
<td>0,2 0,4 0,1 0,0 0,1 0,0 0,0</td>
<td>1,3</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0,8 0,1 0,4 0,0 0,0 0,0 0,0</td>
<td>17,7</td>
</tr>
<tr>
<td>Sulphamethoxazole</td>
<td>0,0 0,0 0,0 0,0 0,0 0,0 0,0</td>
<td>17,1</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>0,7 0,1 0,0 0,0 0,0 0,0 0,0</td>
<td>7,1</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0,0 0,0 0,0 0,0 0,0 0,0 0,0</td>
<td>10,1</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>0,9 0,7 0,5 0,1 0,1 0,1 0,1</td>
<td>8,7</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>0,5 0,6 0,7 0,8 0,9 0,7 0,8</td>
<td>8,4</td>
</tr>
<tr>
<td>Flornfenicol</td>
<td>2,1 2,9 0,9 0,8 0,6 0,4 0,4</td>
<td>6,6</td>
</tr>
</tbody>
</table>

### Notes:
- MIC stands for Minimum Inhibitory Concentration.
- R% represents the percentage of resistant strains.
- The values in the table indicate the proportion of strains resistant to each antibiotic at different concentrations.
What caused resistance to ciprofloxacin in Salmonella to jump so greatly in just one year?
In MARAN 2004, ciprofloxacin resistance in all *Salmonella* \((n = 2195)\) was reported to be 0.3\%, applying a clinical breakpoint of greater than 2 \(\mu g/ml\).

In MARAN 2005 ciprofloxacin resistance in all *Salmonella* \((n = 2238)\) was reported to be 10.1\%, as the epidemiological cut-off value of 0.06 \(\mu g/ml\) was used.
Ciprofloxacin resistance in *E. coli*

DANMAP (Denmark) uses $>0.03 \mu g/ml$

MARAN (Netherlands) and SVARM (Sweden) use $>0.06 \mu g/ml$

VAV (Spain) uses $>2 \mu g/ml$
SCIENTIFIC REPORT OF EFSA AND ECDC

The European Union Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in the European Union in 2009

European Food Safety Authority
European Centre for Disease Prevention and Control
ABSTRACT
The European Food Safety Authority and the European Centre for Disease Prevention and Control have analysed the information on antimicrobial resistance among zoonotic and indicator bacteria in 2009 submitted by 25 European Union Member States. This information covers antimicrobial resistance in *Salmonella* and *Campylobacter* isolates from humans, food and animals, and in indicator *Escherichia coli* and enterococci isolates from animals and food.

Page 17:
“The results must therefore be interpreted with care and no direct comparison between countries should be made. Where countries have used the same method over the time period covered by the report, then an evaluation of trends is likely to be valid, though may lack sensitivity dependent on the specific breakpoint used.”
CLSI Initiative on Harmonisation

Generation, Presentation and Application of Antimicrobial Susceptibility Test Data for Bacteria of Animal Origin; A Report

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CONCLUSIONS

- AST is the cornerstone of risk assessments and risk management

- Only 3 methods are globally approved for AST testing

- CLSI is the only organisation that has veterinary specific AST recommendations

- ALWAYS use appropriate QC otherwise AST data is meaningless

- Use clinical breakpoints to predict clinical outcomes

- Use epidemiological values to analyse shifts in susceptibility over time

“Responsible use does not simply equate to using fewer antimicrobials. Use the **right** drug in the **right** amount by the **right** route for the **right** period of time”

Jackie Atkinson, Director of Authorisations
Veterinary Medicines Directorate
United Kingdom
January 21, 2012
Questions?

Key Factors to Balance

- Science-based risk-benefit assessment vs. political decision
- Human health and food safety vs. animal health needs
  - Future animal protein availability and affordability
- Therapeutic use vs. performance use
- Veterinary oversight vs. lay person use
- Unintended consequences vs. desired outcome
  - Risk-risk analysis
  - Risk-benefit analysis

Clinical vs. Epidemiologic