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**Focus Group Meeting on Fluoroquinolones:**

# **Use of Fluoroquinolones and Development of Resistance**

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## Proportion resistance (%) to quinolones among *Salmonella* and *Campylobacter* from food-producing animals

(Data from ARBAO II, Anon. 2004)

| Country           | Pathogen and percent reported resistance to quinolones |                                  |                |                  |         |
|-------------------|--------------------------------------------------------|----------------------------------|----------------|------------------|---------|
|                   | Salmonella                                             |                                  | <i>C. coli</i> | <i>C. jejuni</i> |         |
|                   | <i>S. Typhimurium</i><br>pigs                          | <i>S. Enteritidis</i><br>poultry | Pigs           | Cattle           | Poultry |
| Austria           | 0                                                      | 2                                |                |                  |         |
| Belgium           | 6                                                      | 0                                |                |                  |         |
| Denmark           | <1                                                     | 23                               | 8              | 11               | 0       |
| England and Wales | 8                                                      | 0                                | 17             | 0                |         |
| France            | 0                                                      |                                  | 20             |                  | 36      |
| Germany           | 4                                                      | 14                               |                |                  | 8       |
| Greece            |                                                        | 44                               |                |                  |         |
| Netherlands       | 3                                                      | 3                                | 11             |                  | 38      |
| Norway            |                                                        |                                  |                |                  | 0       |
| Poland            |                                                        | 8                                |                |                  |         |
| Sweden            |                                                        |                                  | 18             | 2                | 0       |
| Switzerland       | 0                                                      |                                  | 26             | 5                | 12      |



## Proportion resistance (%) to FQs and flumequine or nalidixic acid among *Escherichia coli* from pigs and broilers sampled at slaughter

| Origin and quinolone         | Break-point (mg/l) | Country and percent resistance |         |         |         |          |             |         |         |
|------------------------------|--------------------|--------------------------------|---------|---------|---------|----------|-------------|---------|---------|
|                              |                    | Austria                        | Denmark | Finland | France  | Italy    | Netherlands | Norway  | Sweden  |
| Pigs                         |                    | (n=134)                        | (n=317) | -       | (n=304) | (n=255)  | (n=155)     | (n=187) | (n=303) |
| FQ <sup>b</sup> ,            | >2                 | 2                              | 0       | -       | 0       | <1       | 0           | 0       | 0       |
| Nalidixic acid or flumequine | >16 or >4          | 8                              | 2       | -       | 3       | 9        | 0           | <1      | 1       |
| Broilers                     |                    | (n=140)                        | (n=138) | (n=300) | (n=308) | (n= 258) | (n=165)     | (n=141) | (n=306) |
| FQ <sup>b</sup> ,            | >2                 | 3                              | 0       | 0       | 3       | 11       | 3           | 0       | 0       |
| Nalidixic acid or flumequine | >16 or >4          | 54                             | 10      | 2       | 28      | 50       | 35          | 1       | 5       |

### Sources:

Austria (Steiermark): REMOST, France: AFSSA, Denmark: DANMAP 2003, Finland: FINRES, Italy: ITAVARM, The Netherlands: MARAN 2003, Norway: NORM/NORMVET, Sweden: SVARM 2003.



## Proportion resistance (%) to fluoroquinolones among animal pathogens from food-producing animals \*

| Country           | <i>A. pleuro-pneumoniae</i> | <i>E. coli</i> |         |      | <i>P. multocida</i> | <i>M. haemolytica</i> |
|-------------------|-----------------------------|----------------|---------|------|---------------------|-----------------------|
|                   | Pigs                        | Cattle         | Poultry | Pigs | Cattle              | Cattle                |
| Belgium           |                             | 35             |         | 3    |                     |                       |
| Denmark           | 0                           | 1              | 0       | 0    | 0                   |                       |
| England and Wales | 4                           | < 1            | 3       | 8    | 0                   | 0                     |
| Finland           |                             |                |         | 11   |                     |                       |
| France            | 0                           | 31             | 5       | 5    | 5                   | 5                     |
| Germany           |                             | 2              |         |      | 1                   | 2                     |
| Italy             |                             | 22             | 4       |      |                     |                       |
| Latvia            |                             |                |         | 44   |                     |                       |
| Netherlands       |                             |                |         |      | 0-1                 | 2-6                   |
| Norway            |                             |                | 2       | 0    |                     |                       |
| Poland            | 1                           |                |         |      |                     | 0                     |
| Portugal          |                             |                |         | 76   |                     |                       |
| Spain             |                             | 12             |         | 16   |                     |                       |
| Sweden            | 0                           | 1              |         | 3    | < 1                 |                       |

\* data from ARBAO II (Anon. 2004)

# Selection for FQ resistance

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- Mechanism of action
    - Inhibition of DNA gyrase activity
    - Concentration-dependent drugs
    - Bactericidal : rapid reduction of susceptible bacterial population
  - Pharmacokinetics
    - Good oral bioavailability of FQs
    - Excretion as active drugs in intestinal lumen

## Mechanisms of resistance

| <i>Mutation</i>                                 | <i>Enterobacteriaceae</i>                                | <i>Campylobacter</i>                        |
|-------------------------------------------------|----------------------------------------------------------|---------------------------------------------|
| 1 <sup>st</sup><br><i>GyrA</i> ,<br><i>GyrB</i> | DNA gyrase<br>Quinolone R<br>Reduced (F)Q susceptibility | DNA gyrase<br>Quinolone R<br>(F)Quinolone R |
| 2 <sup>nd</sup><br><i>ParE</i> ,<br><i>ParC</i> | Topoisomerase IV<br>(F)Quinolone R                       | Lack of<br>topoisomerase IV                 |

- + Decreased uptake or efflux – Not specific
- + *qnr*, plasmid mediated gene

# Monitoring of resistance

## Epidemiological cut-off value

### *Salmonella*

*Ciprofloxacin* WT  $\leq 0.064 \mu\text{g/ml}$

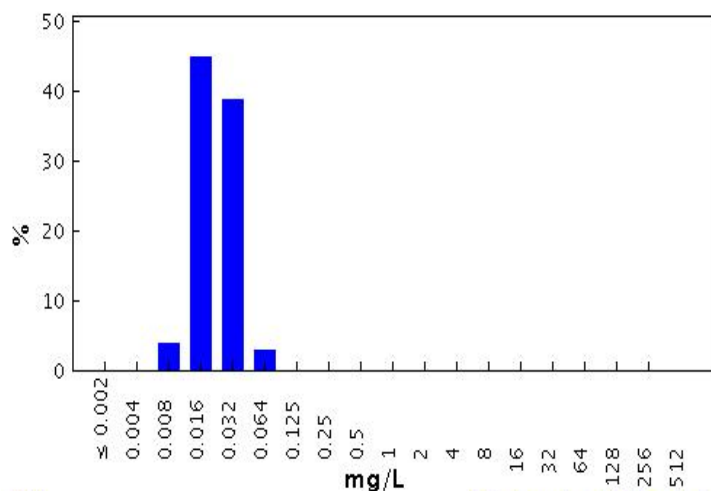
*Nalidixic acid* WT  $\leq 16 \mu\text{g/ml}$

### *Campylobacter*

*Ciprofloxacin* WT  $\leq 1 \mu\text{g/ml}$

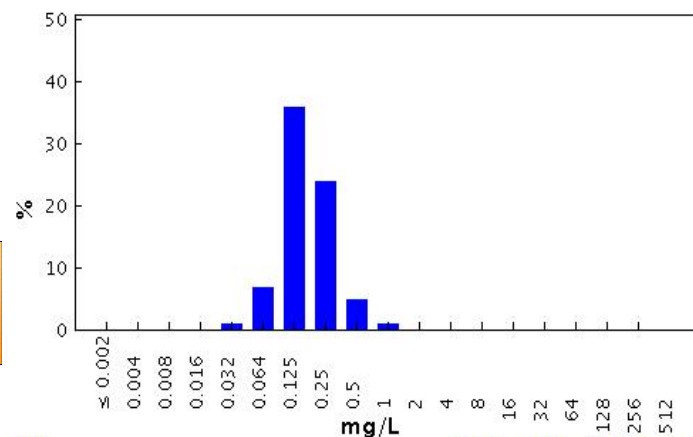
*Nalidixic acid* WT  $\leq 16 \mu\text{g/ml}$

Ciprofloxacin / *Salmonella* spp  
Antimicrobial wild type distributions of microorganisms – reference database  
EUCAST



MIC  
Epidemiological cut-off: WT  $\leq 0.064 \text{ mg/L}$   
1733 observations (3 data sources)  
Clinical breakpoints: S  $\leq 0.5 \text{ mg/L}$ , R  $> 1 \text{ mg/L}$

Ciprofloxacin / *Campylobacter jejuni*  
Antimicrobial wild type distributions of microorganisms – reference database  
EUCAST



MIC  
Epidemiological cut-off: WT  $\leq 1 \text{ mg/L}$   
1023 observations (16 data sources)  
Clinical breakpoints: S  $\leq 0.5 \text{ mg/L}$ , R  $> 1 \text{ mg/L}$





*Thank you!*