IFAH-Europe meeting with CVMP and SAGAM

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Discussion on the reflection paper

"The use of Fluoroquinolones in Food-producing Animals in the European Union: Development of Resistance and Impact on Human and Animal Health"

(EMEA/CVMP/SAGAM/184651/2005-CONSULTATION)

Purpose

- To comment and discuss scientific sections of the Report (SAGAM)
- To propose and discuss prudent use wording and harmonisation actions (CVMP)
- Ultimate aim is to improve the rational and responsible use of fluoroquinolones (FQs) in the EU

General

- Appreciation for the well-balanced and constructive Report about the (fluoro)quinolone resistance status in Europe
- IFAH-Europe is grateful to get the opportunity to review the document and for the organisation of this meeting
- Agree to and strongly endorse the majority of statements and conclusions
- Some questions, however, need to be addressed, and a revised final paper published

General Comments (1)

- Considerable progress has been achieved regarding the prudent and responsible use of antimicrobial, including FQs,
  - e.g. introduction of Guideline CVMP/VICH/644/01-Final.
  - Animal Health Industry also contributed to prudent use strategies by establishing prudent use guidelines for FQs and conducting resistance monitoring and antibiotic consumption surveys.

- IFAH-Europe assumes that the Report refers to both quinolones and fluoroquinolones for food-producing animals

General Comments (2)

- One approach is to contain resistant pathogens. Another approach should be to reduce the occurrence of food-borne pathogens as such,
  - this will lower the transmission of FQ-resistant pathogens.
  - Hence, Good Agricultural Practice (GAP) must have the highest priority

- It might be beneficial to include which Qs/FQs are approved, when, where and for which indication/host species (e.g., on page 5 of the Report)

IFAH-Europe‘s major concerns

- Resistance mechanisms of FQs and breakpoint terminology (page 6 of Consultation Report)
- Potential public health effects of Salmonella infections with reduced susceptibility to FQs
- Fluoroquinolone-resistant Campylobacter infections
- Animal health consequences

Mechanisms of resistance to FQs and breakpoint terminology

- Resistance mechanisms should be slightly extended,
  - e.g. the activity of efflux pumps or changes in FQ entry could be addressed
- IFAH-Europe appreciates that new breakpoint terminology has been adopted.
  - It is particularly important to differentiate between epidemiological cut-off values and clinical breakpoint values (4th para.; p. 6).
- In this context, we request (in the same paragraph):
  - „resistance“ is replaced by „decreased susceptibility“
  - „Enterobactericeae“is replaced by „Salmonella“, as was correctly done in the conclusions

Decreased FQ susceptibility and Salmonella infections (1)

- **Interpretation of literature needs caution**
  - Only few controlled studies; usually case reports, mainly S. typhi
  - Seriously-ill patients with underlying diseases
  - Treatment information limited (e.g. pre-treatment isolates, treatment not according to label, travel information)

- **Helms studies**
  - Absence of medical treatment information
  - Long post-treatment study periods
  - Cause of death not available; n limited
  - Multiple-resistance not addressed

Decreased FQ susceptibility and Salmonella infections (2)

Duration of illness and lethality of patients of a German hospital with *Salmonella* infections caused by quinolone resistant and susceptible isolates (MICs in µg/ml)

						Duration (median days)	
Patients	n	Median Age	MIC_{90} nalidixic acid	MIC_{90} Cipro-floxacin	Mortality (%)	Disease	Medication
quinolone-resistant	40	53 (25 – 83)	> 128	0.25	0	11 (5-15)	7
quinolone-susceptible	40	48 (19 – 78)	4	0.015	0	10 (3-13)	7

Unpublished data, Schmitz & Werling, 2006

Conclusion: in this study quinolone resistance of *Salmonella* does not affect clinical outcome

Campylobacter Infections (1)

- Self-limiting disease; macrolides are the first choice drugs

- Nelson et al (2004) study contains various flaws such as limited data for FQ shortens diarrhoea by 4 days for resistant infections, but not in patients infected with susceptible strains

	Cip^R infections	Cip^S infections
Mean days of hospitalization	2	3
Mean days of missed work	3	4

Nelson et al., 2004

Campylobacter Infections (2)

Campylobacter Sentinel Surveillance Scheme, UK; 2000 – 2003. Data set refers to 10843 cases: 8746 domestic cases and 2097 patients with foreign travel history

Parameter	Domestic/ Travel	Ciprofloxacin-resistant cases	Ciprofloxacin-susceptible cases
Duration of disease (days)	d	11.1	11.4
	t	13.1	13.3
Hospital admission (%)	d	8.9	8.6
	t	3.5	4.6
Hospitalization (days)	d	4.6	5.1
	t	4.3	5.2

data submitted for publication

Campylobacter Infections (3)

- **Conclusions from Nelson study**
  This study failed to convincingly demonstrate an impact on public health related to FQ resistance. FQ-resistant Campylobacter infections are not more severe than susceptible infections.

- **Conclusions from the Sentinel study**
  FQ resistance does not affect the duration of illness. It also rejects the hypothesis that FQ-resistant Campylobacter display an increase in virulence.

Animal Health Consequences

- Target bacteria. Caution is needed to interpret Table 4; some figures may present an over-estimation of the resistance rates

- IFAH-Europe fully endorses investigation of novel PK/PD concepts.
  - *But, without data-protection there is little incentive*.
    - ➢ It is essential that significant investments in new data benefit from intellectual property protection

- For some diseases, no or few alternative antimicrobials are available. It is important to retain the efficacy of FQs

Conclusions

- Very valuable and constructive Report. Provides a well-balanced and comprehensive overview
- IFAH-Europe would appreciate it if CVMP/SAGAM could revise and republish the Consultation Report
- Particularly, we feel the need to adopt current breakpoint terminology (7th paragraph of conclusions) and the conclusions regarding salmonellosis and campylobacteriosis (4th paragraph)