EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Consultation meeting with stakeholders

Request from the European Commission for advice on the impact on public and animal health of the use of antibiotics in animals

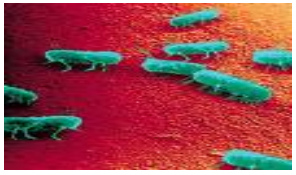
Presented by: Dr John Threlfall
Member:EFSA Panel on Biological Hazards (BIOHAZ); EMA Antibiotics Working Party (AWP)

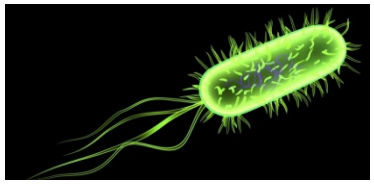
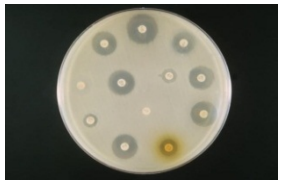
Human health consequences of antibiotic resistance transmitted through the food chain

- **Increased number of infections**
- **Increased frequency of treatment failures**
- **Increased severity of infections**
- **Prolonged duration of illness**
- **Increased frequency of bloodstream infections**
  - **Increased hospitalization**
  - **Increased mortality**
- **Increased costs to society**

Food-borne antimicrobial resistance: areas of international concern

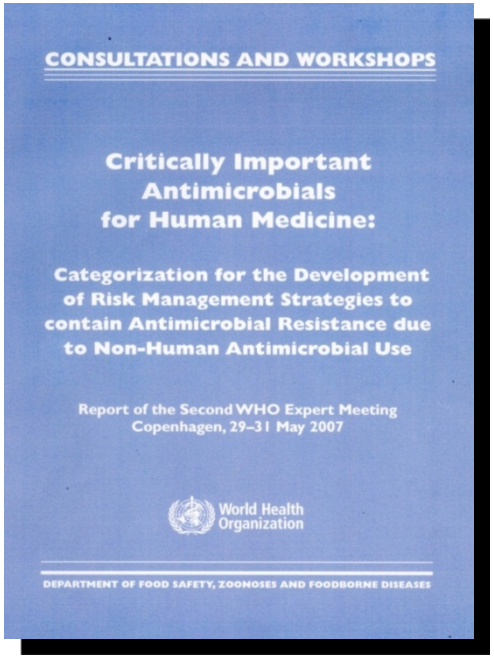
- International spread of *(*multi)-resistant *Salmonella* organisms;
- *Campylobacter* : resistance to fluoroquinolones, (macrolides);
- Epidemics of ESBL/ AmpC–producing *E. coli*;
- Increasing resistance to CIAs:
  - **Quinolones / fluoroquinolones (and plasmid-mediated resistance)**
  - **3 /4th generation cephalosporins**
  - **Carbapenams**

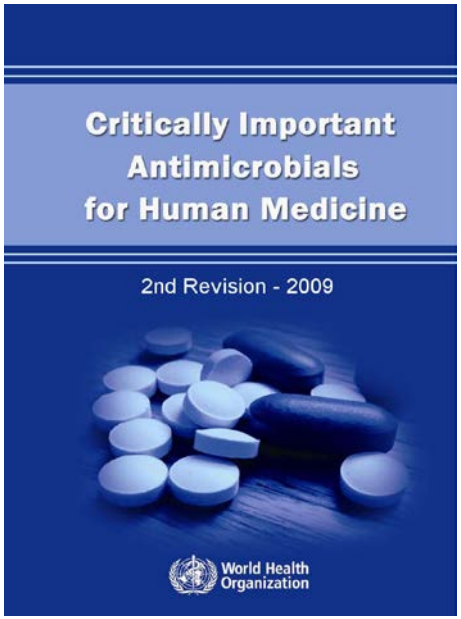


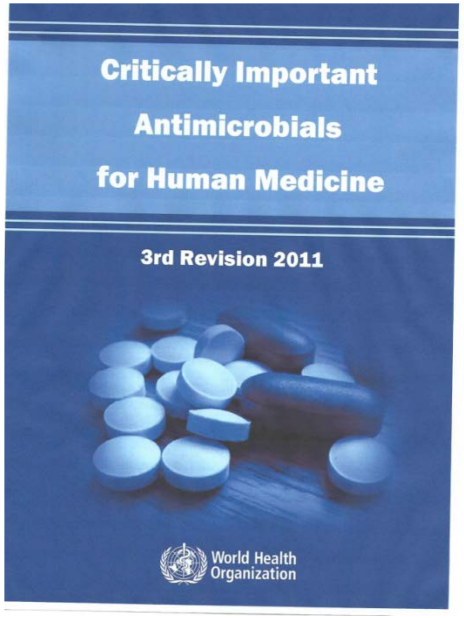



Critically-Important Antimicrobials (CIAs)

WHO: 2007, 2009, 2011



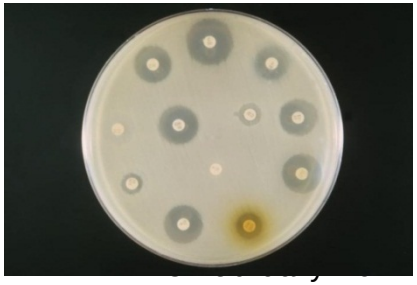




e.g. Quinolones / fluoroquinolones
3rd / 4th-generation cephalosporins
Macrolides
Carbapenams

Question 4 from the EC

Advice on the risk mitigation options [alternatives], including an assessment of costs and benefits, related with the use of certain classes of antibiotics or antibiotic substances that are critically-important in human medicine and are currently authorised as veterinary medicinal products



Q4 – CIAs to be considered

- 3rd / 4th–generation cephalosporins

- Fluoroquinolones

Question / point to be clarified	Comment
1. Could you provide examples of animal diseases for which the use of Critically Important Antimicrobials for human use (see WHO list of CIA) is essential?	

Question / point to be clarified
2. Do you have examples of situations where risk mitigation measures on use of antimicrobials in animals have led to a positive or negative impact on animal health and welfare, an economic impact or a practical impact on animal husbandry? Could you please indicate, if known, whether such measures were voluntary or compulsory. Please also provide details of the duration over which the measures have been in place and difficulty and timing of implementation. In order to facilitate the presentation of your answer, you might wish to fill in the next table.

Antimicrobial (or class of)	Risk mitigation measures	Costs	Benefits	Reference

General question

3. Do you have examples of situations where risk mitigation measures on use of antimicrobials in animals have led to a positive outcome on public health such as decrease in resistance in animals (and food derived thereof) or humans, or negative such as increased bacterial contamination of food.

In order to facilitate the presentation of your answer, you might wish to fill in the table below.

Antimicrobial (or class of)	Risk mitigation measures	Costs	Outcome	Reference

General comment
4. Could you provide input on the possible need of further future risk mitigation measures in relation to the use of certain classes of antibiotics or antibiotic substances that are currently authorised as veterinary medicinal products. If possible, this should include an estimate of the cost and benefits of such measures. In order to facilitate the presentation of your answer, you might wish to fill in the table below for question 4

Antimicrobial (or class of)	Risk mitigation measures	Costs	Possible benefits	Reference

General question	Comment / Answer
5. To allow the assessment of measures to promote responsible use of CIAs in animals, could you provide any data to assess the impact of expiry of marketing exclusivity of CIAs used in animals on sales and usage patterns.	

Some key documents

- Reflection paper on the use of third and fourth generation cephalosporins in food producing animals in the European Union: development of resistance and impact on human and animal health J. vet. Pharmacol. Therap. 32, 515–533, doi: 10.1111/j.1365-2885.2009.01075.x.
- CVMP Reflection paper on the use of fluoroquinolones in food-producing animals in the European Union: Development of resistance and impact on human and animal (EMEA/CVMP/SAGAM/184651/2005).
- Scientific Opinion on the public health risks of bacterial strains producing extended-spectrum β-lactamases and/or AmpC β-lactamases in food and food-producing animals. EFSA Panel on Biological Hazards (BIOHAZ). EFSA Journal 2011;9(8):2322

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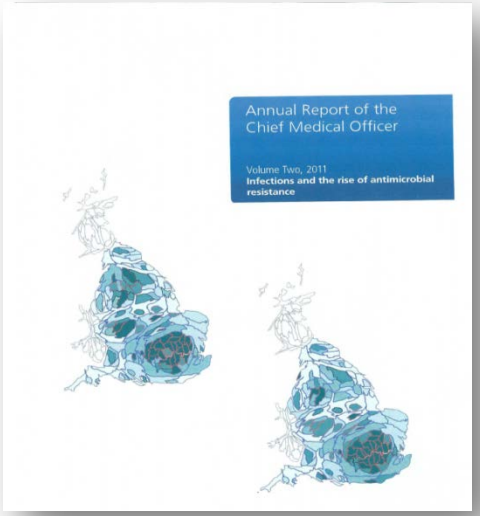
efsa
European Food Safety Authority

UK Chief Medical Officer Reports 2009, 2011

There should be a ban on the use of certain types of antibiotics (quinolones and cephalosporins) in animals, in order to protect their activity in humans'

Sir Liam Donaldson, CMO, 2009



National approach to tackling antimicrobial resistance should be managed jointly between DH and Defra to ensure that a comprehensive integrated programme is developed'.

Dame Sally Davies, CMO, 2013

General mitigation measures (1)

Guidance on prudent use of antimicrobials for animals published in many EU countries but most on a general level. Some specific examples: -

Germany (2000): Mandatory that reserve antimicrobials with last resort character in human medicine used restrictively in individual animals on a short-term basis and only in cases where e strictly indicated.

The Netherlands (2007): Drugs of 'eminent importance to public health' considered third choice drugs for treatment of infections in food animals. Third choice means: only to be used if no alternative therapy is possible, based on susceptibility test of target pathogens. For individual animals with severe invasive infections, third choice drugs may be used for empiric first choice

General mitigation measures (2)

Netherlands, August 2011. Dutch Health Council advised Dutch government to limit the use of antibiotics i that are of PH-concern n food-producing animals. Advice mainly based on the ESBL-threat .

Advice included:

1. Short term measures:

a. Do not allow the current and future last resort drugs to be used in food animals. Included carbapenems, tigecycline, glycopetides, daptomycin, oxazolidones, and mupirocin, and also new ones to be developed.

b. Antibiotic use on farms should be transparent and a control institute is necessary

c. Use of cephalosporins to be limited as much as possible to individual animals based on appropriate diagnostics

d. Coilistin use should be limited and if possible phased out

2. Long term measures:

a. Restrict/phase out the use of beta-lactams, fluoroquinolones and aminoglycosides in animals

i. Limited use for individual animals based on appropriate diagnostics

Specific mitigation measures –cephalosporins (1)

No harmonized approach on prudent use of cephalosporins in animals in different MSs.

Finland (2003)

- National legislation prohibits use of 3rd and 4th generation cephalosporins for animals unless a VMP containing these substances has marketing authorization.
- Off-label use of 3rd- generation cephalosporins prohibited.
- Recommendations given for specific indications in different animal species. e.g 3rd-generation cephalosporins advised only for treatment of foal septicaemia.

EFSA (2011)

- 'Highly effective control option would be to stop all uses of cephalosporins/systemically active 3rd/4th generation cephalosporins, or to restrict their use (use only to be allowed under specific circumstances).

Specific mitigation measures – fluoroquinolones (1)

All fluoroquinolone products (EMEA/CVMP 2005)

- Official and local antimicrobial policies should be taken into account when product is used.
- Should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials."
- "Whenever possible, should only be used based on susceptibility testing."
- "Use of e product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to fluoroquinolones and may decrease e effectiveness of treatment with other quinolones due to the potential for cross resistance."

Specific mitigation measures – fluoroquinolones (2)

Australia: Has never permitted the use of fluoroquinolones in any farm animals

Finland: Use of fluoroquinolones in poultry not permitted

USA: 2005: Withdrawal of Approval of use of (Baytril for use in poultry on basis that 'use of fluoroquinolones in poultry caused the development of fluoroquinolone-resistant *Campylobacter* species in poultry, and that these fluoroquinolone-resistant organisms are transferred to humans and cause the development of fluoroquinolone-resistant Campylobacter in humans, and that fluoroquinolone-resistant Campylobacter infections in humans are a health hazard.'

Potential legislative controls

European Union, October 2011

'European Parliament calls upon the European Commission to make legislative proposals to phase out the prophylactic use of antibiotics in livestock farming in the EU'

(European Parliament, 27 October 2011)

UK, 9th January 2013

Similar proposal made during House of Commons debate on antibiotic use on intensive farms

(House of Commons, 9 January 2013)

Q4 – Final general question

Finally, to allow the assessment of measures to promote responsible use of CIAs in animals, could you provide any data to assess the impact of expiry of marketing exclusivity of CIAs used in animals on sales and usage patterns.

- Voluntary withdrawal examples to be provided whenever possible
- Treatment guidelines to be reported where relevant

Difficulties in answering Q4

- Complexity in link usage to resistance.
- Often several actions implemented at the same time. difficult to identify the effect of each.
- Defining key ‘measurements’ of success ‘.
- Risk to risk: Difficult to evaluate the consequence of a specific action, e.g. replacement by other antibiotics and other practices what impact finally on resistance.
- When use maybe acceptable.
- Use for different animal species may be different.
- Control of extra-label use.
- Cost: important to clarify for whom - e.g; authorities, industry, veterinarians ,farmers, consumers; cost for industry following change in SPC labelling; cost of referral procedures.

Thank you!

Please provide your answers by.....