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: Catry Boudewijn
CVMP/EMA Antimicrobials Working Party (AWP)

AMEG – European Commission Question 3: Call for information from the stakeholders

Background: Q3. Advice what the possible impact could be on the treatment of resistant bacteria in humans of **granting marketing authorisations for new classes of veterinary antibiotics**, and whether there is a need to restrict or ban the use in animals of certain new classes of antimicrobials or antibiotic substances (especially those that are important in human medicine) that are currently not authorised. It is stressed that the advice could discuss a **positive** impact (for example, better management of resistance in animals) **or** a **negative** impact (for example, increased risk of development of resistance in humans).

Target : Input should be sought from those **stakeholders most knowledgeable in the development of new antimicrobials** including, but not limited to, the animal health industry and clinical experts on animal health.

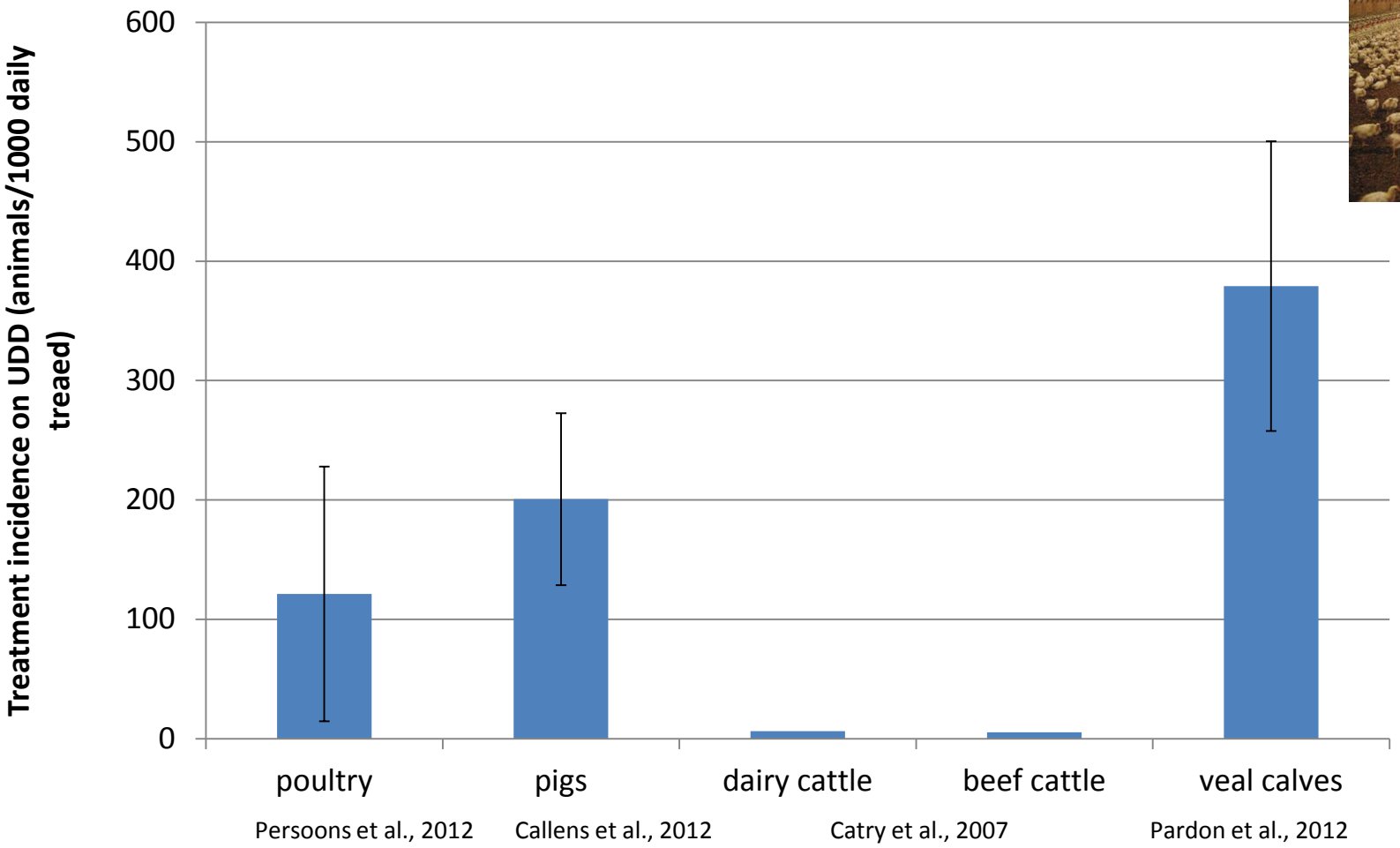
Reflections on interpretation of a ‘NEW’ antimicrobial

Existing antimicrobials for new indications/new species

New antimicrobials coming from human medicine not YET authorised for veterinary use

New compounds with new mechanism of action

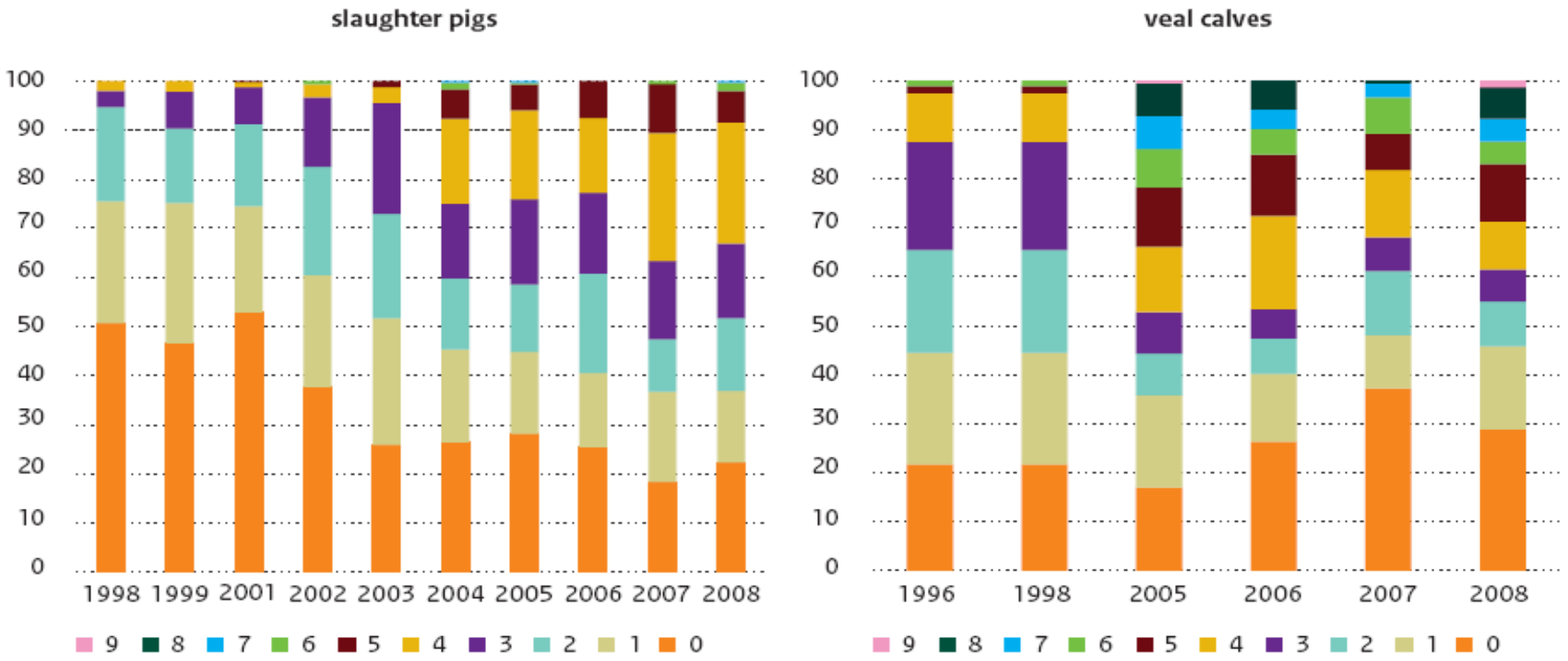
Consumption patterns across animal species



Courtesy: B. Pardon, Ghent University

Evolution *E. coli* multiresistant

Figure 25 Trends in percentages of *E. coli* strains fully susceptible, resistant to one to a maximum of nine antimicrobial classes in broiler chickens, slaughter pigs and veal calves in the Netherlands from 1996-2008 (MARAN-2008).



P.L. Geenen, M.G.J. Koene, H. Blaak,
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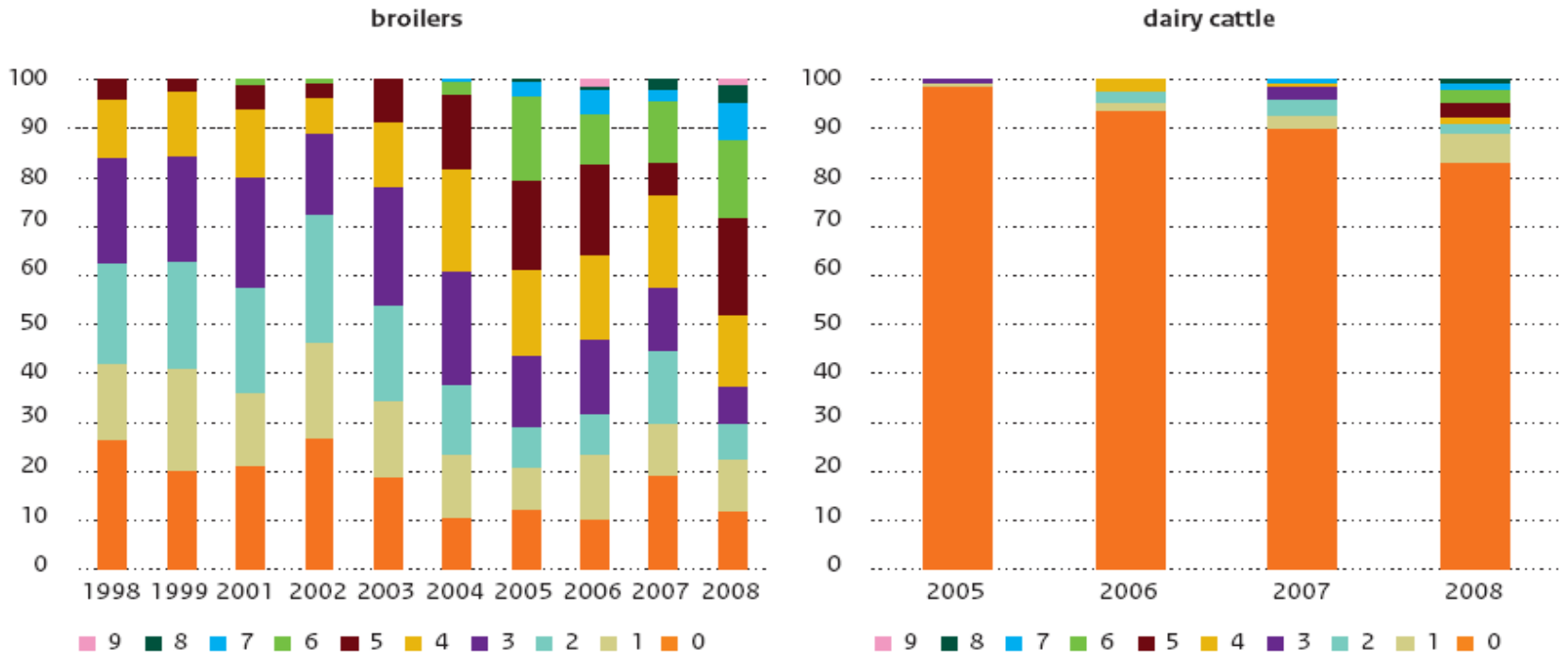
Evolution *E. coli* multiresistant



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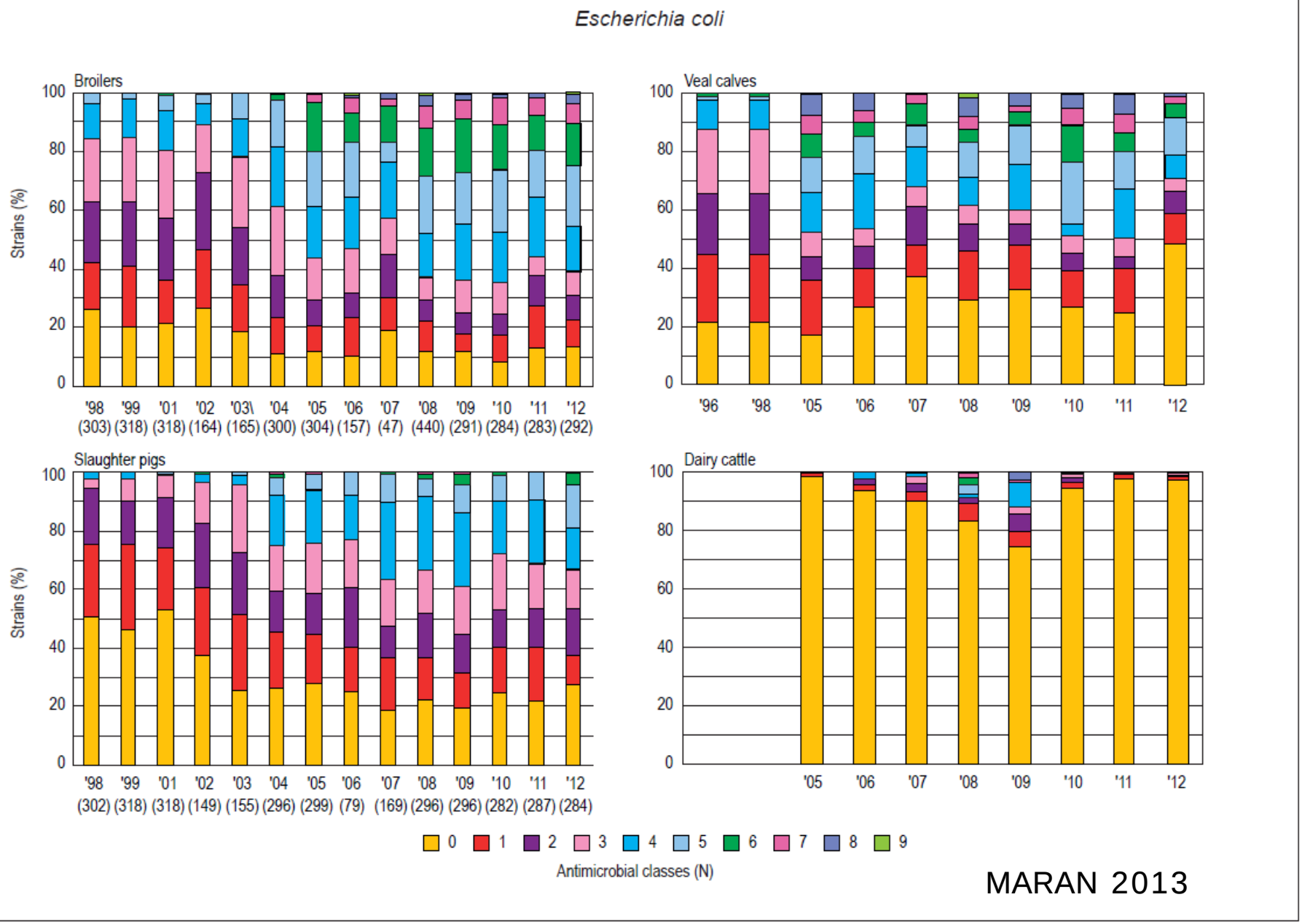


Figure Eco02. Resistance (%) to 0-9 antimicrobial classes among *E. coli* strains from broiler chickens, slaughter pigs, veal calves and dairy cattle in The Netherlands from 1998 - 2012.

Questions

1. In your estimation, is there a lack of veterinary antimicrobial medicines for the treatment of any specific important bacterial diseases in animals?

   If yes, please indicate for which animal species and therapeutic areas you consider this to be the case. In your answer please provide specific examples or any data or other evidence to support this and advise whether or not the current range of authorised antibiotics is adequate to meet animal health needs now and in the near future.

Questions (cont.)

2. Off-label use may result from either the use of antibiotics in animals for indications or therapy, other than those for which they have been approved (e.g. use for a different indication or in a different species) or from the use in animals of products authorised for use in humans.

   We would welcome any available information as to the extent of this use.

Questions (cont)

3. Are those antibiotics that to the knowledge of AMEG are authorised exclusively for use in humans (e.g. carbapenems, vancomycin, tigecycline, azithromycin, clarithromycin, mupirocin, ticarcillin, piperacillin/tazobactam, linezolid, rifamycins, monobactams, temocillin, cyclic esters, nitrofurans, etc…) used in veterinary medicine?

   If there is such information please specify which antimicrobials, indications and animal species and the extent of use.

Questions (cont.)

4. Are you aware of marketing authorisations/applications for antimicrobial veterinary medicinal products that have been refused or withdrawn solely or partly due to public health risks of antimicrobial resistance, please provide details.

Questions (cont.)

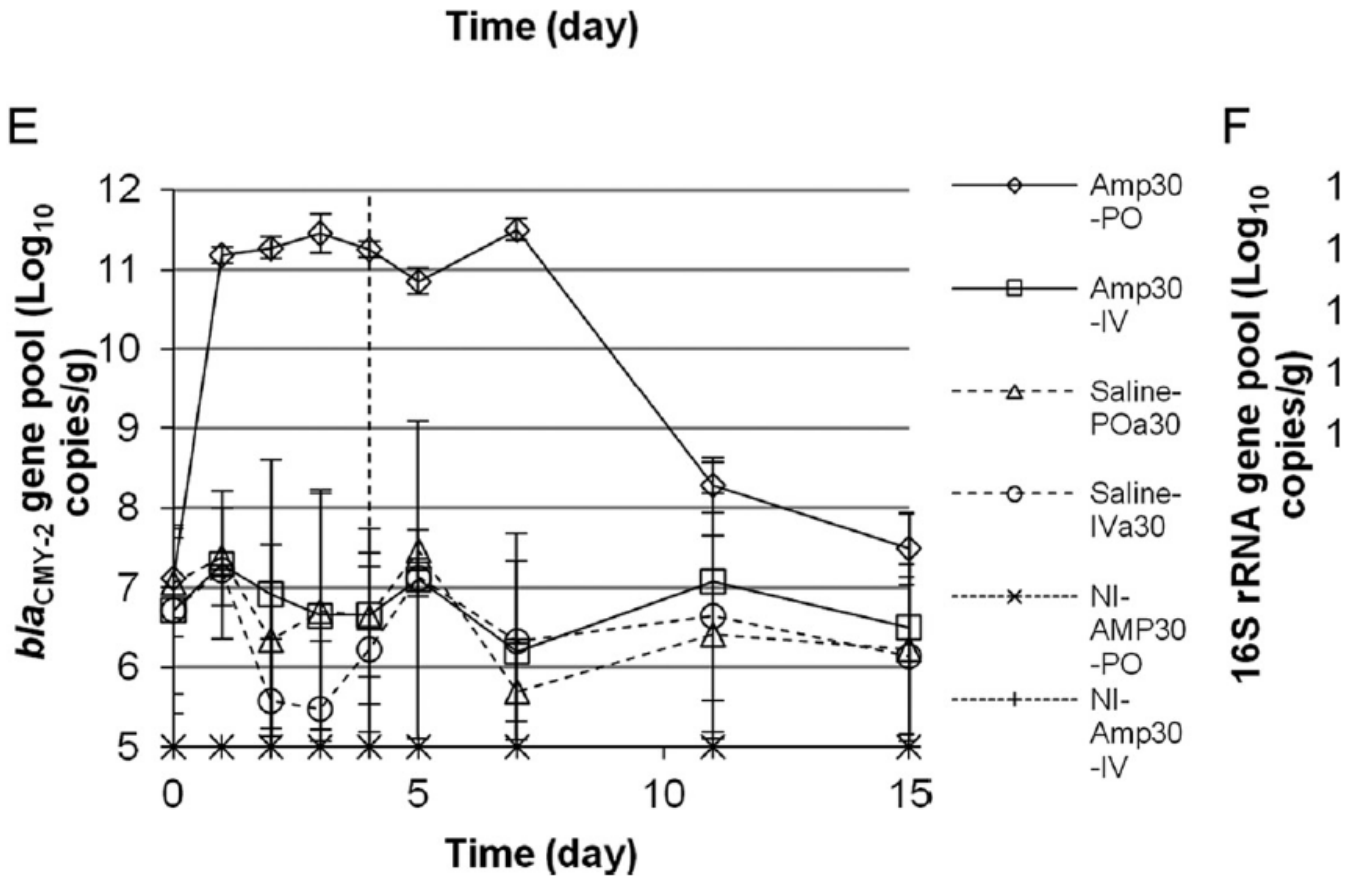
5. What impact do the data requirements in VICH GL27 and 36 have on the development of new veterinary medicinal products?

6. Are you aware of any modifications in the formulation, dose, duration, interval and route of administration of new compounds during research and development with a goal to reduce the risk for emergence of antimicrobial resistance?

   If yes, please provide examples of this.

Ampicillin IV vs PO vs CTR:

Evolution betalactamase resistance *E. coli*



Antibiotic Administration Routes Significantly Influence the Levels of Antibiotic Resistance in Gut Microbiota Lu Zhang et al. 2013, AAC

Oral antimicrobials increase antimicrobial resistance in porcine *E. coli* – A systematic review

E. Burow*, C. Simoneit, B.-A. Tenhagen, A. Käsbohrer

Federal Institute for Risk Assessment, Department of Biological Safety, Diedersdorfer Weg 1, 12277 Berlin, Germany

ARTICLE INFO

Article history:
Received 2 September 2013
Received in revised form 6 December 2013
Accepted 18 December 2013

Keywords:
Antimicrobials
E. coli
Oral
Porcine
Resistance
Swine

ABSTRACT

Administration of antimicrobials to livestock increases the risk of antimicrobial resistance (AMR) in commensal bacteria. Antimicrobials in pig production are usually administered per pen via feed which implies treatment of sick alongside with healthy animals. The objective of this systematic literature review was to investigate the effect of orally administered antimicrobials on AMR in *Escherichia coli* of swine.

Studies published in peer reviewed journals were retrieved from the international online databases ISI Web of Knowledge, PubMed, Scopus and the national electronic literature data base of Deutsches Institut für Medizinische Dokumentation und Information. The studies were assessed using the eligibility criteria English or German language, access to full paper version, defined treatment and control group (initial value or non-treatment) as well as administration and resistance testing of the same antimicrobial class. In the qualitative synthesis, only studies were included presenting the summary measures odds ratio or prevalence of resistance, the category of the applied antimicrobial and the dosage. An effect of the antimicrobial on AMR in *E. coli* was evaluated as an "increase", "no effect" or "decrease" if the odds or alternatively the prevalence ratio were >1.0, 1.0 or <1.0, respectively.

Eleven studies, describing 36 different trials, fulfilled the eligibility criteria and were finally assessed. An increase of AMR in *E. coli* was found in 10 out of 11 trials comparing AMR after with AMR prior to oral treatment and in 22 of the 25 trials comparing orally treated with untreated groups. Effects expressed as odds or prevalence ratios were highest for the use of aminoglycosides, quinolones and tetracycline. There was no clear association between the reported dosage and AMR towards tetracycline. Information on antimicrobial substance and dosage was missing in 4 and 5 of the 11 finally selected studies. The 36 identified trials were inhomogenous in usage and provision of information on sample size.

Oral administration of antimicrobials increases the risk of AMR in *E. coli* from swine. There is however a lack of studies on the impact of dosage and longitudinal effects of treatment. The published studies have a number of issues concerning their scientific quality. More high quality research is needed to better address and quantifiy the effect of orally administered antimicrobials on AMR in swine.