



## Review

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



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## 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 quantify the effect of orally administered antimicrobials on AMR in swine.

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## 1. Introduction

Antimicrobials play an important role in animal and human health care. They are used for treatment and prevention of infectious diseases in livestock and to protect public health from food-borne diseases (Ungemach et al.,

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2006). Human population is growing (Koluman and Dikici, 2013) and, pork production has increased in the world (FAO, 2013). Large group sizes and limited space allowance in confined animals can cause an increased risk of injuries and diseases in pigs (Street and Gonyou, 2008; Salak-Johnson et al., 2007). These circumstances may enhance the need for antimicrobials in such intensive livestock farming. Oral administration is by far the most common route of administration for antimicrobials in pigs (Callens et al., 2012; Merle et al., 2012).

An inevitable side effect of the use of antimicrobials is the emergence and dissemination of resistant bacteria (van den Bogaard and Stobberingh, 2000). Moreover, the level of resistance increases not only in pathogenic bacteria, but also in commensal bacteria (e.g. *Escherichia coli*) after the introduction of a new antimicrobial as most retrospective and prospective studies show (van den Bogaard and Stobberingh, 2000).

In the last decade, antimicrobial usage in animal production systems has received a considerable public attention (Avgustin, 2012). The European Union (EU) restricted the use of antimicrobials as growth promoters in 1999 and banned it completely in 2006 (Avgustin, 2012). However, the EU ban of antimicrobial growth promoters resulted in a rise in antimicrobial use for therapeutic purposes which may have an adverse effect on the development of antimicrobial resistance (AMR) in humans (Cervantes, 2006). Therefore, antimicrobial use and its extent are important issues with regard to the occurrence of AMR and the protection of animal and human health.

Several studies report that oral administration of antimicrobials increases the risk of AMR (Taylor et al., 2009; Varga et al., 2009; Lutz et al., 2011). In food producing animals, oral administration is usually carried out in a large number of animals at the same time. If adequate application fails, treatment may happen for prolonged periods of time and may involve under dosing which might favour the selection of bacterial resistance (Ungemach et al., 2006). A recent study by Callens et al. (2012) has shown that under dosing is frequent with oral administration in pigs. Another important aspect of oral administration is the additional exposure of animals through dust containing antimicrobials or through contact with treated animals (Chen et al., 2008; Kietzmann et al., 1995; Sharma et al., 2008). Furthermore, the exposure to dust containing antimicrobial particles poses risk for the development of AMR not only for animals but also for humans since farmers and veterinarians are exposed as well (Armand-Lefevre et al., 2005; Meemken et al., 2008; Schwaber et al., 2013). Antimicrobials were detected in dust taken from the environment of chickens treated orally with antimicrobials (Richter et al., 2009). Untreated animals showed increased concentrations of antimicrobials in their blood when housed in pens that had previously been containing animals that were treated orally with antimicrobials (Kietzmann et al., 1995). Moreover, a certain part of the antimicrobials will not readily be absorbed but shed through faeces. Pig manure containing a high number of resistant bacteria could be a further risk factor for the spread of resistant bacteria in the environment (Hoelzel et al., 2010). These risk aspects indicate that animals could be exposed to a sub

therapeutic amount of antimicrobials in housing systems where antimicrobials are administered orally even if they are not treated themselves. Therefore, not only the amount of antimicrobials used could select for AMR, but also the administration route has to be considered.

Since oral administration of antimicrobials to swine appears a crucial factor for the risk of AMR development, we aimed to investigate to what extent commensal *E. coli*, a relevant bacterium to all animals and humans, is affected by this common application form in swine. Thus, the objective of this systematic literature review was to investigate the effect of orally administered antimicrobials on resistance development in *E. coli* of swine by reviewing the relevant scientific literature. The hypotheses of our study were

- (1) The risk of AMR to certain antimicrobials in *E. coli* increases with oral administration of this antimicrobial agent (group) compared to
  - (a) before the administration or
  - (b) no administration
 of antimicrobial agents in swine. (Overall resistance risk following antimicrobial administration)
- (2) The risk of AMR in *E. coli* differs between antimicrobial agent groups administered orally in swine. (Resistance risk and antimicrobial group)
- (3) Reduced dosing of orally administered antimicrobial agents in swine increases the AMR risk. (Resistance risk and antimicrobial dosage)

## 2. Materials and methods

### 2.1. Review question

The review question was to identify the rate of resistance in swine being treated with oral antimicrobials compared to the same swine before treatment or other swine not treated with antimicrobials.

The study population considered relevant for this review were swine in the farrow to finish phase in settings of commercial and research farms. The intervention of interest was use of antimicrobials in water and/or feed compared to before treatment or animals/groups not exposed to the intervention of interest. The outcome of interest was AMR in *E. coli* from pig faeces collected by rectal swabs or from the barn floor.

### 2.2. Identifying relevant literature

Literature on the effect of orally administered antimicrobials on the development of AMR in *E. coli* of swine was systematically reviewed. Relevant scientific papers published in peer-reviewed journals were identified using the keyword combinations (swine OR pig OR piglet OR farrow OR weaner OR sows) AND (resistance OR susceptibility) AND (antimicrobial OR antibiotic OR bacterial OR aminoglycoside OR cephalosporin OR macrolide OR penicillin OR quinolone OR tetracycline OR sulphonamide OR polypeptide) AND (administration OR application OR medication OR oral OR feed OR water) AND *E. coli*. All searches were performed during October and November 2012. The

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