

Assistance in the Update of the Systematic Literature Review (SLR): “Influence of Copper on Antibiotic Resistance of Gut Microbiota on Pigs (including Piglets)”

Corporate authors

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Abstract

A total of 901 references were examined to assess the influence of copper supplemented diets on copper and antibiotic resistance of gut microbiota in pigs (including piglets). Merely 33 references were found eligible to answer this review question. From these 33 references, eleven references were assigned as experimental field studies, ten references were experimental environmentally controlled studies, and twelve references were assigned as cross-sectional studies. The references assigned as experimental field studies provided the most suitable information for the review question. The other studies gave useful information concerning the mechanism of resistance or prevalence of resistant isolates. The overall methodological quality of the field studies was rather poor. Only three of the eleven field studies had a methodological quality that was considered acceptable for the present review question. Therefore, the restricted number of studies available from the SLR, and the limitations in terms of results and methodological quality do not allow excluding the possibility of a positive correlation between copper supplementation above requirements and development of antibiotic resistance.

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Key words: Pigs, gut microbiota, copper, antibiotics, resistance, antimicrobial, feed

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1. Introduction

1.1. Background and Terms of Reference as provided by EFSA

1.1.1. Background

In the context of the mandate on maximum copper content in complete feed the working group on "Revision of maximum content of copper in feed" of the FEEDAP Panel considered it necessary to conduct a systematic literature review (SLR) on the influence of copper on antibiotic resistance of gut microbiota in pigs (including piglets). The review was started in October 2015 as an update of the previous SLR performed in 2012 in the context of the mandate on the re-evaluation of copper as a feed additive. The current SLR considered the period since 2012, additional grey literature and reports sent by European countries. Articles already identified during the SLR of 2012 were not reviewed again, but are still reported here to make a complete overview of the available relevant literature.

1.1.2. Terms of Reference

The purpose of the contract was to provide scientific assistance to the FEED Unit of EFSA in the completion of a systematic review of existing evidence of the influence of copper on antibiotic resistance of gut microbiota on pigs (including piglets). The specific objectives are the following:

- Objective 1: Finalise, especially by adding the approach to assessing the methodological quality of the included studies, the draft protocol provided by EFSA. If necessary, after piloting the selection criteria and the data extraction proposed in the protocol, amend it accordingly;
- Objective 2: Gather and select the relevant papers according to the protocol;
- Objective 3: Perform the data collection/extraction of the selected papers. EFSA might provide a specific IT tool;
- Objective 4: Assess the methodological quality of the included studies (according to the pre-established protocol);
- Objective 5: Provide a report with the synthesis of the data from the included studies.

This contract/grant was awarded by EFSA to:

Contractor: Ghent University. Department of Animal Production. Proefhoevestraat 10, 9090 Melle, Belgium

Contract title: Service Contract

Contract number: NP/EFSA/FEED/2015/01

2. Data and Methodologies

The systematic literature review comprised six steps (Figure 1) and was conducted according to the protocol which can be found in Annex A.

2.1. Data

The first step comprised the data search and was conducted by EFSA. The search strategies are specified in the protocol. The concepts that were captured for this search strategy were population (pig and gut flora), intervention/exposure (copper and diet), and outcome (copper and/or antibiotic resistance). The limits were publication year >1980, no reviews and title and abstract in English. During the data search of the update also abstracts in French, Italian, Spanish and German were allowed for the published records and all EU languages were allowed for non-published papers

received from EU countries. A combination of keywords with boolean operators and strings was piloted.

The search strategy was applied to different information sources. Published scientific literature was searched using five bibliographic databases: Web of Science, CCC, CABI and FSTA and Medline. A total of 540 references could be retrieved using these databases: 270 references from each, the SLR of 2012 and the updated SLR.

The following five databases were searched for grey literature: Système Universitaire de Documentation (SUDOC), Trove, International information system for the Agricultural Sciences and Technology (AGRIS), Global ETD search and OpenGREY. Grey literature was only searched during the update, not during the SLR of 2012. A total of 336 references were found.

In addition non-published studies were requested to the European countries (including European Union (EU) Member States and EEA/EFTA countries) through a call for data that was managed by EFSA. Four countries responded to the request, yielding eleven records: France (n=4), Czech Republic (n=5), Slovakia (n=1) and Norway (n=1).

2.2. Methodologies

2.2.1. Selection of the studies and data collection

The query of the current update yielded 617 records, of which 270 were scientific reports and 336 grey literatures, in addition to the 270 scientific reports from the previous SLR. The data from European countries resulted in 11 extra records.

A flow chart of the different steps performed during this update of the SLR are displayed in Figure 1. Steps two, four and five were performed in parallel by two mutually independent reviewers (the contractor of Ghent University and one of three members of the EFSA FEED Unit, who reviewed an equal number of references each). Discrepancies were discussed and agreements were reached. Step three was exclusively conducted by EFSA staff. Step six was conducted by all four reviewers.

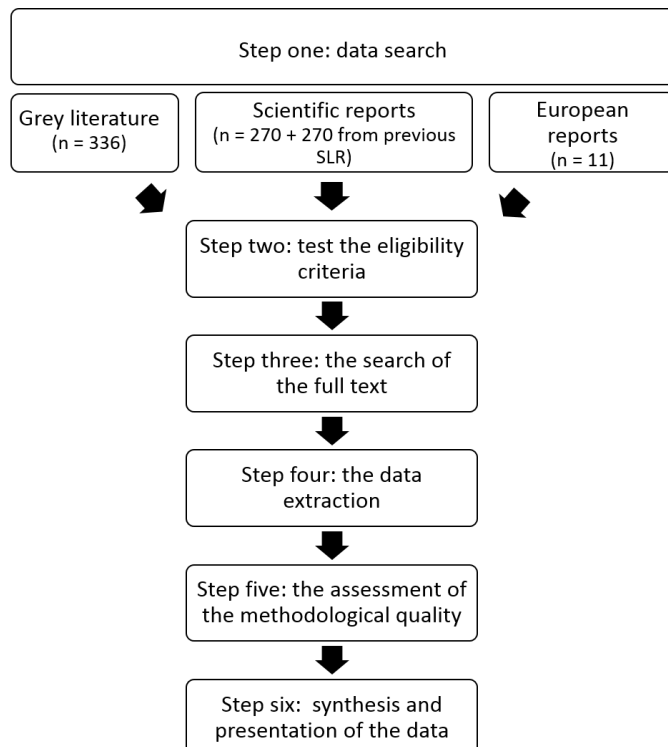


Figure 1 Various steps from the SLR update

2.2.2. Pilot study

A pilot study (Appendix A) was performed during the first SLR by the contractor of Ghent University to test the eligibility criteria listed in the protocol on 19 references. Also, the table for data extraction (Table 4 in the protocol) was amended and tables for the assessment of the methodological quality (Table 5 and 6 in the protocol) were constructed. A preliminary screening of the 227 studies suitable for the first SLR (after removal of the duplicates), based on these eligibility criteria, was performed by the contractor of Ghent University. This was performed to estimate how many references would remain in order to plan the further steps in the SLR. The final study selection was performed using the web-based software DistillerSR.

2.2.3. Software

All search results, including studies retrieved from grey literature or received from European countries, were merged by EFSA staff (FEED Unit) using the reference management software from EndNote and duplicate records were removed. The new information retrieved was then uploaded by EFSA staff (AMU unit) into the systematic review system Distiller SR (Evidence Partners, Ottawa, Canada). This web-based software was used for steps two, four and five. An additional check for duplicate records was performed by EFSA staff (AMU unit) in order to upload only studies that were not considered in the previous SLR. The evaluation of the retrieved references was performed using the forms constructed during the previous SLR. These forms were based on the tables provided in the protocol.

2.2.4. Limitations

The findings of this report may be limited due to the following issues:

- The studies were retrieved mainly in English language, with limited other languages. During the update of 2015 this limitation was encountered by allowing also French, Italian, Spanish and German papers. For the non-published papers received from the EU countries even all EU languages were accepted;
- Although the intention to be comprehensive in the search process, the search may have missed some publications;
- During the whole selection process some valuable information might have been lost, because no other animal species than pigs were considered and only primary research publications included;
- Different study designs were eventually selected following the eligibility criteria of the protocol: experimental studies and observational studies (cross-sectional). This represented a challenge for the synthesis of results and for drawing the conclusions.

3. Results

3.1. Pilot study

The major results from the pilot study (Appendix A) were that the eligibility criteria are specific and precise for selection of appropriate studies for this SLR. However, it became clear that based on title and abstract it was difficult to test all eligibility criteria on the references. It remains necessary to examine full-text documents as well to assess if studies can be included for SLR, although this is laborious. Also, availability of these full-text documents became an important issue.

The table for data extraction was adjusted based on comments of the contractor of Ghent University after assessing this table on the 19 references. Checklists to assess the methodological quality, based on the individual aspects of study design (objectives, population, intervention, outcome assessment, withdrawals and data analysis), were constructed by the contractor of Ghent University. Individual criteria within each checklist were evaluated by using 'yes', 'no', 'partial' or 'unclear'. Critical aspects of the methodological quality assessment that would lead to the consideration of a study as of "bad quality" appeared in 'bold' in the checklists.

During the SLR of 2012 a preliminary study selection (Appendix A) was performed by the contractor of Ghent University and after consulting with two scientific officers of the EFSA FEED Unit, it was decided that all references, would first be screened on title and abstract by the contractor of Ghent University and to be assigned to group YES (suitable for SLR), NO (not suitable for SLR), or DOUBTFUL (the lists of the references belonging to each group are provided in Appendix A). For references in the latter group, full-texts would be examined to assess if they are suitable for SLR. In conclusion, only for a very limited amount of articles (19) it was certain that they could be included for systematic review. For a relative large number of references (8) in comparison to the number of included articles, the full-text documents could not be retrieved by the contractor of Ghent University. Some of these references were book chapters or proceedings of congresses. However, they could contain useful information regarding the review question and therefore, it seems necessary to obtain full-text of these references as well.

During the update of the SLR no preliminary study was carried out.

3.2. Study selection

The second step of the flow chart (Figure 1) consisted of testing the eligibility criteria to select the relevant studies. For the selection of the studies the web-based software DistillerSR was used. The flow diagram of this study selection is represented in Figure 2. The ID of the reference is the number of this record in the list of all 944 records uploaded in DistillerSR (these also include the references from the previous SLR and references afterwards marked as duplicates).

During the first SLR 270 references were retrieved of which 43 were identified as duplicates. The remaining 227 references were screened by title and abstract by two reviewers, i.e. the contractor of Ghent University and one scientific officer of the EFSA FEED Unit. After this screening, both reviewers included 28 references and excluded 193 references. There was an inclusion/exclusion conflict about 6 references. After careful examination and communication between both reviewers, it was concluded that 3 references were included and 3 references excluded.

These results on inclusion of references were compared with the results of the preliminary study selection performed by contractor of Ghent University. In this preliminary test, 19 references were included, whereas now 31 references remained included. To explain the differences, full-text documents were retrieved and assessed by both reviewers. After this assessment, another 9 references from the 31 references could be excluded for SLR, because they were deemed not eligible or full-text could not be retrieved. In conclusion, after thorough examination 22 references were appropriate to answer the review question and are included for data extraction.

The 270 new scientific reports and 336 records from grey literature gathered during the update of 2015 were also screened by title and abstract. This was performed by two reviewers, i.e. the contractor from Ghent University and three EFSA staff members (FEED Unit) who reviewed an equal

number of records each. Forteen of them were identified as duplicates. There was an inclusion/exclusion conflict in 9 of them. After discussion it was decided that all references in conflict were to be excluded. The screening resulted in the inclusion of 7 scientific reports and 3 grey literature records. One record of the latter category, i.e. reference number 785 (PhD dissertation) was split in two because it contained two relevant chapters concerning distinctive trials, resulting in an extra reference (number 937).

Eleven articles were received from the European countries: 4 from France, 5 from Czech Republic, 1 from Slovakia and 1 from Norway. Two references received from France (number 933 and 935) were marked as duplicates from another study (number 295). After screening of title and abstract all of these references were excluded.

In conclusion 33 records were considered appropriate and were retained to the data extraction level. Lists of the references that are included or excluded are provided in Appendix B.

A relative higher number of relevant scientific studies were identified during the more recent years: 22 studies from the period 1980-2012 identified during the previous SLR, compared to 7 reports from the much shorter period 2012-2015 during the update. This increase was not due to the extension of the searched sources in the update as only 4 studies originated from the new sources explored (i.e. grey literature and call for data from European countries) and all were published before 2012. This demonstrates an increasing concern about the effect of copper in pig nutrition and development of antibiotic resistance.

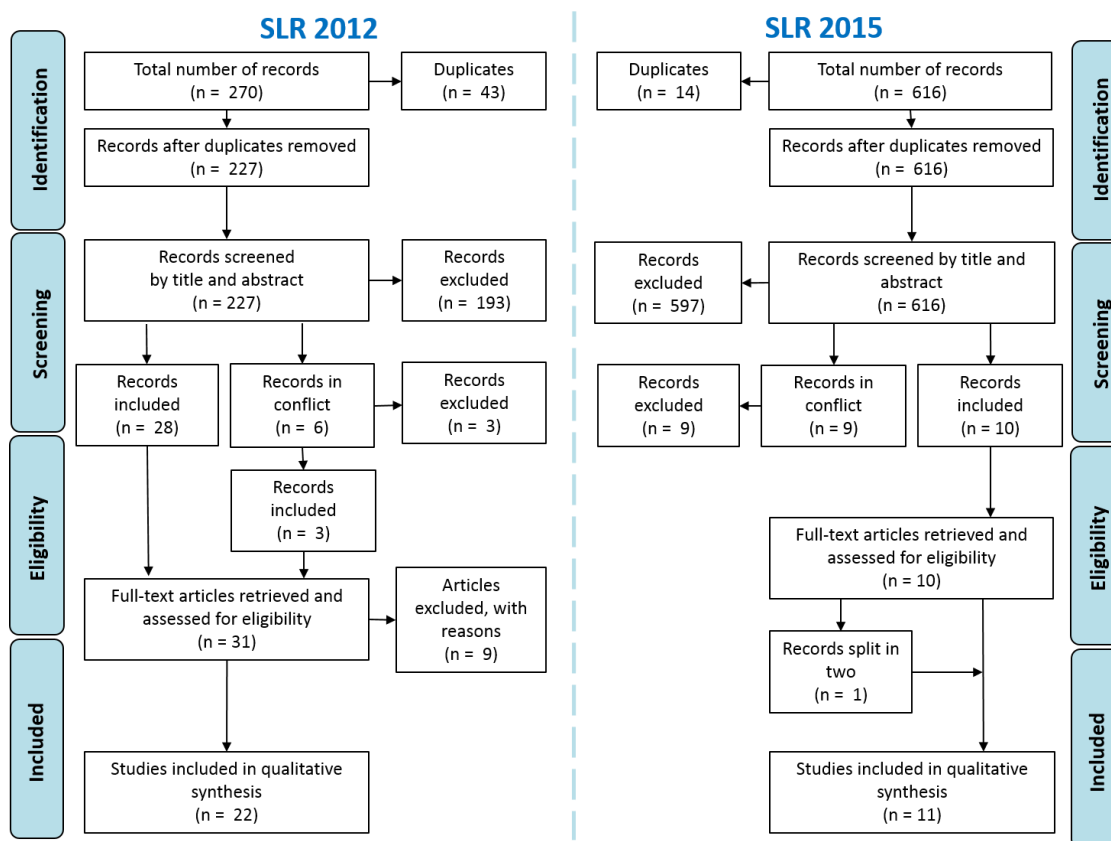


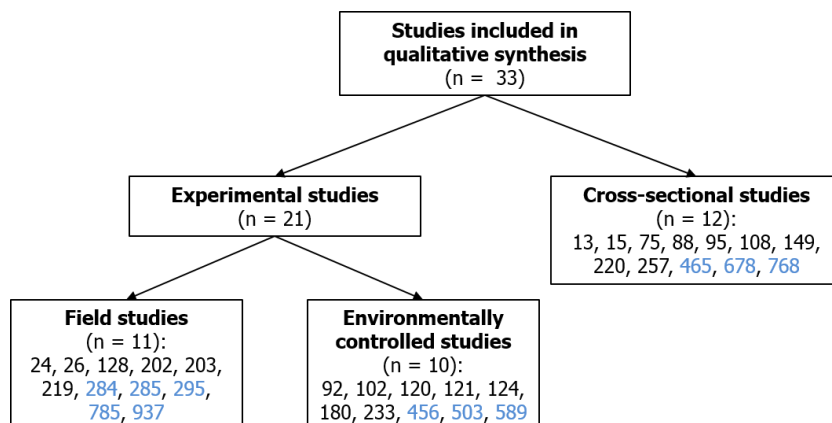
Figure 2 Flow diagram of the study selection using the DistillerSR software

3.3. Data synthesis

During the study selection process, it was found that the study type and study design of the included studies were very diverse. Two major groups of studies could be made, i.e. “Cross-sectional studies” (observational studies which report on the prevalence of copper and/or antibiotic resistant gut microbiota originating from exposed pigs) and “Experimental studies”. The group of experimental

studies could be further divided in “Field studies” (in which the effect of supplementation of copper in the diet of piglets/pigs on copper and/or antibiotic resistance of gut microbiota is investigated) and “Environmentally controlled studies” (which try to ascertain the mechanism of resistance, e.g. studies on the resistance gene and the operon, etc.). Figure 3 summarises the classification of the selected studies. Additionally, in each group, there were many differences in study design (e.g. treatments, sampling, duration, antibiotics tested, microbial species tested, etc.) and in the methodological quality of the studies. Therefore, it was agreed to synthesise the data in a narrative approach for each group rather than conducting a meta-analysis.

Two different checklists (one for experimental studies and another for cross-sectional studies) were constructed to assess the methodological quality of each study type. These checklists are represented as Table 5 (methodological quality for experimental studies) and Table 6 (methodological quality for cross-sectional studies) in the protocol.



References from the update of 2012 until 2015 are marked in blue

Figure 3 Classification of the selected studies

3.3.1. Experimental studies

Field studies

This group of studies is the one that provides the most useful information for answering this review question. This group consists of studies conducted with pigs that received an intervention (experimental diets) and that are followed for several weeks to assess the appearance of resistant isolates to copper and/or antibiotics, regardless if the study was carried out in a commercial farm or in the farming facilities of a university.

A total of 11 out of 33 references were assigned to this group: six derived from the previous SLR and five from the update. These references had the following identification numbers: 24 (Amachawadi *et al.*, 2010), 26 (Amachawadi *et al.*, 2011), 128 (Hasman *et al.*, 2006), 202 (Pupavac *et al.*, 1996), 203 (Ragland *et al.*, 2006), 219 (Shelton *et al.*, 2009), 284 (Agga *et al.*, 2014), 285 (Agga *et al.*, 2015), 295 (Amachawadi *et al.*, 2015), 785 (Holt *et al.*, 2008a) and 937 (Holt *et al.*, 2008b). The last two correspond to different chapters from the same thesis, as explained above.

Characteristics of the field studies

The main characteristics of the field studies are represented in Table 1.

Table 1: Characteristics of the field studies

ID	Year	Country	Number of Pigs	Age	Duration	Numb. treatments relevant for SLR	Animals / Treatment	Animals / pen	Repetitions / blocking	Basal diet (content of Cu/Zn) = control group	CuSO ₄ treatment	Treatment 2	Treatment 3	Confirmatory analysis of Cu content diet?	Parameters analysed	Any zootechnical parameter	Sampling schedule	Withdrawn / missing data	Statistics	Statist. unit	Comment
24	2010	Kansas, USA	150	21 days	5 weeks	3 (out of 5 treatments)	30	5	Not indicated	Basal diet (corn, soybean meal, vitamins, amino acids, trace mineral supplements) containing 16.5 ppm copper as CuSO ₄ and 125 ppm zinc as ZnO	Basal diet with 125 ppm copper as CuSO ₄	Basal diet with 125 ppm copper as CuSO ₄ and 3000 ppm zinc as ZnO (ZnO reduced to 2000 ppm after the 2nd week)	NA	No	Species identification of enterococcal isolates, tcrB gene (Cu resistance), antibiotic resistance genes (<i>ermB</i> , <i>tetM</i> , <i>varA</i> , <i>vanB</i>), copper susceptibility, antibiotic susceptibility, transferability of <i>tcrB</i> gene	No	Faecal samples of three randomly selected piglets per pen and per week	The total number of isolates tested varies between treatment groups and through the different weeks. This is not discussed in the paper	Generalised mixed model (tcrB gen), analysis of variance (MIC values transformed based on rank)	Not specified Isolate	Prevalence of tcrB gene has low internal validity due to the different number of total isolates in different groups through the different weeks. Uncertainty on the independency of the samples (the same piglet could be sampled at different weeks). Low external validity.
26	2011	Kansas, USA	60	21 days	6 weeks	2	30	6	not indicated	Basal diet (corn, soybean meal, vitamins, amino acids, trace mineral supplements) containing 16.5 ppm copper as CuSO ₄	Basal diet with 125 ppm copper as CuSO ₄	NA	NA	No	Species identification of enterococcal isolates, tcrB gene (Cu resistance), antibiotic resistance genes (<i>ermB</i> , <i>varA</i>), copper susceptibility, antibiotic susceptibility, clonal relationship, inter-species transferability of <i>tcrB</i> gene	No	Faecal samples of three randomly selected piglets per pen on days 0, 14, 28 and 42	No	Generalised mixed model (tcrB gen), analysis of variance (MIC values transformed based on rank)	Not specified Isolate	Uncertainty on the independence of the samples (the same piglet could have been sampled at different weeks)
128	2005 (isolates inoculated to pigs from 2002)	Denmark	24 pigs inoculated at day 0 with 10 copper sensitive and 10 copper resistant <i>E. faecium</i> strains (10 ⁹ bacteria of each strain)	8 weeks	7 weeks	2	12	6	2 pens /treatment	No CONTROL group	Low Copper (it can be also considered the Control) 6.4 mg/kg feed	High Copper: 208 mg/kg feed	NA	Yes	- Culture and isolation of 15 <i>E. faecium</i> -like isolates - Identification of <i>E. faecium</i> strains - Detection of <i>tcrB</i> gene - Detection of macrolide (Erythromycin) and glycopeptide (Vancomycin) resistance - Phenotypic detection of copper resistance	-Body weight -Average Daily Gain (ADG)	Faecal samples at d0, 7, 14, 21 and 28. From each pig	No	Yes		

ID	Year	Country	Numb. pigs	Age	Duration	Numb. treatments relevant for SLR	Animals /treatment	Animals /pen	Repetitions /blocking	Basal diet (content of Cu/Zn) = control group	CuSO ₄ treatment	Treatment 2	Treatment 3	Confirmatory analysis of Cu content of each diet?	Parameters analysed	Any zootechnical parameter?	Sampling schedule	Withdrawn /missing data	Statistics	Statist. unit
202	1996	Serbia	60	Not Specified	Not Specified	4 (out of 6 treatments)	10	NA	NA	I: Basal diet not described	II: Basal diet with 200 ppm copper	IV: Basal diet with 200 ppm copper and 20 ppm flavomycin	VI: Basal diet with 200 ppm copper and 20 ppm salocin	No	- Total <i>E. coli</i> count - Representative <i>E. coli</i> isolates selected for susceptibility to (antibiotics and sulfapreparations) Gentamycin, Penicillim, streptomycin, Amoxicilin, Trofurantain, Lincomycin, Cefalosporin and Trimethosul	No	Samples of intestines, sown up to 10 hrs. after slaughter, only once at the end of the treatments, one per pig.	No		
203	2004	USA	96	17 to 20 days old	35 days	2 (out of 6 treatments)	16	4	4 replicate/bl ocks	Phase 1 basal diet (for 3 weeks) containing 20 ppm Cu and 152 ppm Zn Phase 2 basal diet (for 2 weeks) containing 16.5 ppm 18.7 Cu and 147 ppm Zn	192.4 ppm copper as CuSO ₄	No	No	No	Samples of rectal swabs - MIC (resistance to Vancomycin) for enterococcal isolates from Day 0 and Day 21+Day 35 (pooled) - Identification of Enterococcal species	- Weight - Average Daily Gain - Feed intake -Feed:Gain	Samples of rectal swabs 3 samples on Day 0, Day 21 and Day 35	- 9 removed for welfare issues (without specifying from which) - 7 removed for exudative epidermitis: 1 in Control, 1 in Copper diet, 4 Zinc diet (1 in another treatment not relevant to the SLR) - 2 from Cu treatment removed because they failed to make productive traits		
219	2009	USA	180	21 days	42 days	3 (out of 5 treatments)	30	5	6 pens/treatment, blocking by weight and location in nursery	Basal diet (corn, soybean meal, vitamins, amino acids, trace mineral supplements) containing 16.5 ppm Cu and 165 ppm Zn	Basal diet with 125 ppm CuSO ₄	Basal diet with 125 ppm CuSO ₄ and 3000 ppm ZnO	No	No	Fecal samples - Counts (CFU) of <i>E. coli</i> and total coliforms (One colony per sample was used for isolates) - MIC on each isolate for: Chlorotetracycline, Neomycin, Oxytetracycline and Tiamulin	- Average Daily Gain - Average Daily Feed intake -Feed:Gain	Fecal samples collected at d14 and d42 from 3 pigs per pen, i.e. 18 samples per treatment.	Not reported	Yes	Not indicated. Isolate

ID	Year	Country	Numb. pigs	Age	Duration	Numb. Treatments relevant for SLR	Animals /treatment	Animals /pen	Repetitions /blocking	Basal diet (content of Cu/Zn) = control group	CuSO ₄ treatment	Treatment 2	Treatment 3	Confirmatory analysis of Cu content of each diet?	Parameters analysed	Any zootechnical parameter?	Sampling schedule	Withdrawn /missing data	Statistics	Statist. unit	Comment
284	2014	Kansas, USA	160	3 weeks	-Adaptation period: 2 weeks -Experimental diets: 21 days -Wash out period: 2 weeks	3 (out of 4 treatments)	40	5	8 pens /treatment blocked by barn (n=2) and by weight at arrival	Basal diet (corn, soybean meal, vitamins, amino acids, trace mineral supplements) containing 16.5 ppm CuSO ₄	Basal diet with 125 ppm CuSO ₄	Basal diet with 125 ppm CuSO ₄ and 550 ppm chlortetracycline	NA	No	- Culture and isolation of <i>E. coli</i> - <i>pcoD</i> gene (copper resistance) - antibiotic resistance genes (<i>tet(A,B,C,E)</i> and <i>blaCMY-2</i>) - copper susceptibility - antibiotic susceptibility	No	Faecal samples of three randomly selected piglets per pen on days 0, 7, 14, 21, 28 and 35 (total 72 relevant samples/sampling day)	No	Three-level mixed effects logistic regression model to model the fixed effects of 2 treatments and 3 treatment periods, with pen and faecal sample as random effects	<i>E. coli</i> isolate	Study focusses mainly on antibiotic resistance (genes), less conclusions about the relation to copper. Similar study design as reference 285, but different analyses. Uncertainty on the independence of the samples (the same piglet could have been sampled at different weeks)
285	2015	Kansas, USA	160	3 weeks	Adaptation period: 2 weeks, Experimental diets: 21 days, Wash out period: 2 weeks	3 (out of 4 treatments)	40	5	8 pens /treatment blocked by barn (n=2) and by weight at arrival	Basal diet (corn, soybean meal, vitamins, amino acids, trace mineral supplements) containing 16.5 ppm CuSO ₄	Basal diet with 125 ppm CuSO ₄	Basal diet with 125 ppm CuSO ₄ and 550 ppm chlortetracycline	NA	No	Total DNA extraction: - Detection of 14 antibiotic resistance genes (<i>tet(A,B,C,D,E,G,K,L,M,O,S,P,Q,X)</i>) - Quantification of 3 antibiotic resistance genes (<i>tetA</i> , <i>tetB</i> and <i>blaCMY-2</i>) - Quantification of <i>pcoD</i> gene (copper resistance)	No	Faecal samples of three randomly selected piglets per pen on days 0, 7, 14, 21, 28 and 35 (total 72 relevant samples/sampling day)	- 7 faecal samples were not sufficient for total DNA extraction and were excluded from analysis	Yes	-Detection: binary outcome (presence/absence of <i>tet</i> genes) -Quantification: reaction reading from qPCR	Uncertainty on the independence of the samples (the same piglet could have been sampled at different weeks).
295	2015	Kansas, USA	240	34 days	Adaptation period: 1 week, Experimental diets: 3 weeks, Wash out period: 2 weeks	4 (out of 6 treatments)	40	5	8 pens /treatment blocked by barn (n=2)	Basal diet (corn, soybean meal, vitamins, amino acids, trace mineral supplements) containing 16.5 ppm CuSO ₄	Basal diet with 125 ppm copper as CuSO ₄	Basal diet with 125 ppm copper as CuSO ₄ and 22 mg/kg BW chlortetracycline	Basal diet with 125 ppm copper as CuSO ₄ and 22 mg/kg BW tylosin	No	- Species identification of enterococcal isolates - <i>trb</i> gene (copper resistance) - antibiotic resistance genes (<i>ermB</i> , <i>tetM</i>) - copper susceptibility - antibiotic susceptibility and profiling	No	Faecal samples of three randomly selected piglets per pen on days 0, 7, 14, 21, 28 and 35 (total 96 relevant samples/sampling day)	No	Yes	Not specified. Isolate	Uncertainty on the independence of the samples (the same piglet could have been sampled at different weeks).

ID	Year	Country	Numb. pigs	Age	Duration	Numb. Treatments relevant for the SLR	Animals / Treatment	Animals / pen	Repetitions / blocking	Basal diet (content of Cu/Zn) = control group	CuSO ₄ treatment	Treatment 2	Treatment 3	Confirmatory analysis of Cu content of each diet?	Parameters analysed	Any zootechnical parameter?	Sampling schedule	Withdrawn / missing data	Statistics	Statist. unit	Comment
785	2008	North Carolina, USA	16	No details; weaned; BW ≈ 5kg	5 weeks	2 (out of 4 treatments)	4	1	4 pens /treatment blocked by weight	Basal diet (corn, soybean meal, whey, vitamins, amino acids, trace mineral supplements) containing 15 ppm copper as CuSO ₄ , and 125 ppm zinc	Basal diet with 240 ppm copper as CuSO ₄	NA	NA	No	- Culture and isolation of <i>E. coli</i> and Enterococci - antibiotic susceptibility	Yes	Faecal samples: - <i>E. coli</i> : daily from days 0 to 7, on days 14, 24, 31 and 38; - Enterococcus: days 0, 7, 14, 24, 31, 38 (total 8 relevant samples/ sampling day)	Clearly stated when only very few or no isolates could be isolated and when excluded from analysis	Mixed model that includes treatment, time, level of antibiotic in culture medium and interactions	Not specified. Isolate	Dose of supplemental copper is in the therapeutic range. Very small trial with only 4 piglets per treatment. No clear conclusions are made.
937	2008	North Carolina, USA	232 (only barrows)	No details; weaned; BW ≈ 7kg	5 weeks	2 (out of 4 treatments)	58 (not sure if all treatments consider an equal number of animals)	4 or 5	12 pens /treatment blocked by weight	Basal diet (corn, soybean meal, whey, vitamins, amino acids, trace mineral supplements) containing 14.4 ppm copper as CuSO ₄ , and 120 ppm zinc	Basal diet with 240 ppm copper as CuSO ₄	NA	NA	No	- Culture and isolation of <i>E. coli</i> and Enterococci - copper susceptibility - antibiotic susceptibility	Yes	Faecal samples on days 0, 7, 21, 28 and 35 (no clarity about number of relevant samples/ sampling day)	No	Mixed model that includes treatment, time, level of antibiotic in culture medium and interactions	Not specified. Isolate	Uncertainty on the independence of the samples (all isolates available were used for analysis, as a consequence from some pigs more isolates count than from others). Dose of supplemental copper is in the therapeutic range.

NA: not applicable; BW: body weight

Results of the field studies

A summary of the most important results of the field studies is represented in Table 2. All field studies considered were relatively recent (2004-2015), except for study 202 dating from 1996.

Relation feeding copper – copper resistance: Five studies investigated the effect of feeding copper on the copper resistance of enterococcal isolates in pigs (24, 26, 128, 295, 937).

In studies 24 and 295 no relationship between feeding weaned piglets with elevated copper (125 ppm copper as CuSO₄) compared to the control diet (16.5 ppm) and the increased prevalence of copper resistant enterococci could be found. Likewise study 937 could not demonstrate a higher prevalence of copper resistance when increasing the copper level in the diet (240 ppm compared to 15 ppm). This relationship was confirmed, however, in study 26 (similar trial as 24 and 295). In addition, in study 128, the increased supplementation of copper (208 ppm compared to 6.4 ppm) lead to an increase in copper resistant *Enterococcus faecium* isolates. Study 295 however pointed at an increased prevalence of transferable copper resistance gene among fecal enterococci when supplementing copper in combination with antibiotics. From studies 24, 26 and 295 it appeared that there is a positive correlation between the presence of *tcrB* gene and resistance to copper. Also, *E. faecium* isolates have a higher prevalence of *tcrB*-positive isolates compared with *Enterococcus faecalis* isolates. In study 295 the prevalence returned to the baseline after the withdrawal of antimicrobials from the feed, suggesting that a withdrawal period prior to harvest may reduce the prevalence of antimicrobial resistance enterococci, thereby reducing the risk of potential transfer. This possibility of transferring the *tcrB* to enterococci from the same and from different species was demonstrated in studies 24 and 26.

Merely three studies investigated the influence of feeding copper on the copper resistance of coliforms (284, 285, 937) and none could confirm this relation. Two of these studies, 284 and 285, are related in that they used samples from the same trial, but analysed different parameters. The first study (284) found that copper minimum inhibitory concentration (MIC) was not affected by copper supplementation or by *pcoD* gene carriage. The second study (285) reported that copper supplementation was not associated with an increased *pcoD* gene quantity. The third study could also not confirm any increase in copper resistance after feeding an elevated level of copper (240 ppm compared to 14.4 ppm in control diet).

Relation feeding copper – antibiotic resistance: Seven studies investigated the effect of feeding copper on the antibiotic resistance of enterococcal isolates in pigs (24, 26, 128, 203, 295, 785, 937).

Study 128 showed a co-selection between copper and erythromycin (macrolide) resistance. In addition, in two other studies (785 and 937) feeding elevated levels of copper in the diet increased the macrolide (erythromycin and tylosin) and aminoglycoside (neomycin) resistance. This increase in antibiotic resistance in study 937 was however not accompanied by an elevated resistance for copper.

Conjugation assays in studies 24 and 26 showed that the transfer of the *tcrB* gene was accompanied by a transfer of the tetracycline (*tetM*) and the erythromycin (*ermB*) resistance genes. All *tcrB* positive isolates from studies 24, 26 and 295 were positive for *tetM* and *ermB*. It should, however, be remarked that these two antibiotic resistance genes were also found in all *tcrB* negative isolates.

A co-selection between resistance in copper and resistance to vancomycin (glycopeptides) is less or not appearing. Only one study (128) could clearly demonstrate a co-selection for glycopeptides. Three studies (24, 26, 295) found that copper resistance was accompanied by an increase in vancomycin MIC, but all isolates were still considered susceptible. Additionally, in study 203 there was no increase reported in vancomycin resistant isolates between the control group (11.2 ppm) and the group receiving an increased copper supplementation (192.4 ppm).

Six studies investigated the influence of feeding copper on the antibiotic resistance of coliforms/*Escherichia coli* (202, 219, 284, 285, 785, 937).

Three studies (202, 785, 937) evidenced that copper supplementation influences the appearance and degree of antibiotic resistance of *E. coli* isolates, although the affected antibiotics differ.

Study 219 showed that a copper supplemented diet did not select for higher resistance of *E. coli* isolates to certain antibiotics compared to the control. On the contrary, at a certain time point the percentage of resistant isolates to chlortetracycline and neomycin is less in the copper supplemented group than in the control. In line with this, two more recent studies based on the same data (284, 285) showed that copper supplementation was associated with lowered *bla_{CMY-2}* gene copies, without an increase in *pcoD* gene quantity. According to their results *tetA* and *bla_{CMY-2}* are positively associated with each other and negatively associated with both *pcoD* and *tetB*. This points at the potential opportunity to select for a less harmful tetracycline resistance profile in *E. coli* by replacing in feed antibiotics by copper.

In the study 284 a general remark was made that the prevalence of antibiotic resistance in *E. coli* from swine production is very high and a big variation in resistance patterns can be identified. In addition, study 785 confirmed that resistance develops and persists in nursery facilities regardless of the use of antimicrobial growth promoters. In the study 937 it was concluded that antibiotic resistance will not be easily reversed by removal of antimicrobial growth promoters from swine feeds. Authors of study 785 warranted further research on the use copper supplementation and its role in the development of antibiotic and the *pco*-mediated copper resistance.

Table 2: Results of the field studies

ID	Treatment	<i>tcrB</i> gene positive isolates (%)	Species identification	Antibiotic resistance genes	Copper susceptibility	Antibiotic susceptibility	Transferability of <i>tcrB</i> gene	Clonal relationship
24	Control	1 out of 67 (1.5)	<i>tcrB</i> positive: 14 <i>E. faecium</i> and 1 <i>E. faecalis</i>	15 isolates <i>tcrB</i> positive and 15 isolates <i>tcrB</i> negative : all them positive for <i>erm</i> (B) and <i>tet</i> (M) genes and negative for the <i>vanA</i> and <i>vanB</i> genes	Mean MIC of copper for <i>tcrB</i> positive was 21.1 mM and for <i>tcrB</i> negative 6.1 mM (p<0.001)	All isolates (15 <i>tcrB</i> positive and 15 <i>tcrB</i> negative) were resistant to tetracycline, chlortetracycline, erythromycin and oxytetracycline with MIC > 100 µg/mL; and susceptible to vancomycin (MIC vancomycin higher for <i>tcrB</i> positive than for <i>tcrB</i> negative p<0.001)	Mean transfer frequency for <i>tcrB</i> -positive <i>E. faecium</i> (14 isolates) was 1.01x10 ⁻⁵ . The <i>E. faecalis</i> isolate had a transfer frequency of 1.16x10 ⁻⁵	Six patterns were observed among the 14 <i>tcrB</i> positive <i>E. faecium</i> isolates
	CuSO ₄	2 out of 57 (3.5)						
	CuSO ₄ +ZnO	5 out of 52 (9.6)						
	ZnO	5 out of 69 (7.2)						
	Neomycin + oxytetracycline	2 out of 78 (2.6)						

The number of *tcrB*-positive enterococci isolated was not different among the five dietary treatment groups

ID	Treatment	<i>tcrB</i> gene positive isolates (%)	Species identification	Antibiotic resistance genes	Copper susceptibility	Antibiotic susceptibility	Transferability of <i>tcrB</i> gene	Clonal relationship
26	Control	5 out of 180 (2.8)	43 <i>tcrB</i> positive isolates: 35 <i>E. faecium</i> and 8 <i>E. faecalis</i> ; 44 (randomly chosen) <i>tcrB</i> negative isolates: 25 <i>E. faecium</i> and 19 <i>E. faecalis</i>	All (43 <i>tcrB</i> positive and 44 <i>tcrB</i> negative) isolates were positive for <i>ermB</i> gene and negative for <i>vanA</i> gene	Mean MIC of copper for <i>tcrB</i> positive was 22.2 mM and for <i>tcrB</i> negative 6.2 mM (p<0.001)	All (<i>tcrB</i> positive and negative) isolates were resistant to erythromycin (MIC>100 µg/mL) and susceptible to vancomycin. Vancomycin values significantly differed (0.42 for <i>tcrB</i> positive versus 0.22 µg/mL for <i>tcrB</i> negative, p<0.001)	Mean transfer frequency for <i>tcrB</i> -positive <i>E. faecium</i> (5 isolates) and <i>E. faecalis</i> (5 isolates) were 9.3x10 ⁻⁶ and 8.2x10 ⁻⁶	17 patterns were observed among the 35 <i>E. faecium tcrB</i> positive isolates; and four patterns between the eight <i>E. faecalis</i> isolates.
	CuSO ₄	38 out of 180 (21.1)						

Statistically significant difference between treatment groups (p<0.05). It was affected by sampling day (p<0.05). Interaction treatment / sampling time significant (p<0.05)

ID	Resistance to Copper	Resistance to Antibiotics	OTHER results	Zootechnical Parameters	COMMENTS
128	Background level of <i>tcxB</i> positive isolates before inoculation was 35-40% for both treatments. No significant increase in low-Cu diet; at day 7 increase to 94% in treatment high-Cu, then remained constant	Macrolide resistance: 20% of isolates from low copper group, 80% of isolates from high copper group, all these also resistant to copper. Glycopeptide resistance: none from low copper group, 24 isolates from high copper group.	38 selected Cu-resistant and/or <i>tcxB</i> -positive isolates were submitted to PFGE and compared to profile of the 20 original inoculated strains: - 33 isolates were identified to be same as original inoculum and all had <i>erm(B)</i> gene. - 5 remaining isolates did not show PFGE comparable profile to those of original inoculum; they were not resistant to macrolides and were <i>erm(B)</i> negative. <i>tcxB</i> gene present in enterococcal species other than <i>E. faecium</i> : <i>E. gallinarum</i> , <i>E. casseliflavus</i> , <i>E. mundtii</i> . Phenotypic resistance to copper determined in these bacteria. Isolates were sensitive to macrolides and glycopeptides and negative for the presence of the <i>erm(B)</i> gene.	No significant differences in ADG from day 0 to day 35 in pigs fed the two diets	High levels of copper given to piglets do select for copper resistant <i>E. faecium</i> . Macrolide and glycopeptide-resistant bacteria are co-selected under the experimental settings of the study.

ID	Resistance to Antibiotics	OTHER results	COMMENTS
202	Resistance/Susceptibility reported together. Strains isolated from all groups resistant to Penicillin, Amoxicilin and Lincomycin. All susceptible to Trofurantoin. To Streptomycin and Gentamycin all groups were susceptible, except VI that was identified as resistant. Resistance to Cefalosporin only in VI. Resistance to Trimethosul was identified in II and VI.	- Numbers of <i>E. coli</i> per gram sample: Treatment I: x10*7 Treatment II: x10*5 Treatment IV: x10*3 Treatment VI: x10*4 - Characteristics of Strains from different groups: I and V fermented Glucose I and II fermented Sucrose IV less expressed hemolysis	Results show that the doses of antibiotics and copper influenced the appearance and degree of resistance of <i>E. coli</i> to antibiotics (when permanently added to the feed)

ID	Resistance to Antibiotics	Other results	Zootechanical Parameters	COMMENTS
203	Resistance/Susceptibility to Vancomycin reported together [MIC \geq 32 mg/L were considered evidence of resistance]: Isolates from all treatments found sensitive to Vancomycin	Enterococci were identified to the species level and in rank order, isolates consisted of <i>Enterococcus faecium</i> (69), <i>Enterococcus faecalis</i> (33), <i>Enterococcus avium</i> (27), <i>Enterococcus durans</i> (20), and <i>Enterococcus gallinarum</i> (1), respectively.	- ADF at the end of experiment was significantly higher in the zinc (0.352 kg/d) than in the copper (0.297 kg/d) treatment, the latter not differing from control. - Feed:Gain was significantly higher in the copper and zinc treatments (1.58 and 1.59 respect) than in the control (1.53)	In this study, the young pigs did not represent a significant reservoir of vancomycin-resistant enterococci

ID	Resistance to Antibiotics	OTHER results	Zootechanical Parameters	COMMENTS
219	Resistance/Susceptibility to the tested antibiotics reported together [MIC \geq 16 mg/L were considered evidence of resistance for Chlortetracycline, Neomycin and Oxytetracycline], [MIC \geq 32 mg/L were considered evidence of resistance for Tiamulin]: - At d14 the % of <i>E. coli</i> isolates resistant to chlortetracycline and oxytetracycline tended (p<0.10) to be increased by CuSO ₄ addition. - At d42 the % of <i>E. coli</i> isolates resistant to chlortetracycline and neomycin was significantly lower in the Cu treatment compared to the other treatments.	- Coliform and <i>E. coli</i> counts at d14 and d42 did not differ between treatments.	- ADG was different and higher in Cu and Zn treatments from control, but no different from the Cu+Zn and the Abtics treatments - ADG was different and higher in Zn and Cu+Zn treatments from control, but no different from the Cu and the Abtics treatments	The copper \times zinc interaction for <i>E. coli</i> resistance to chlortetracycline and neomycin from isolates on d42 is an interesting observation from this study

ID	Treatment	<i>pcoD</i> gene positive isolates (%)	Prevalence <i>pcoD</i> in different treatment periods	Copper resistance (MIC ≥ 20 mM; %)	Copper resistance in different treatment groups	Antibiotic resistance genes	Antibiotic resistance	Comment
284	Control	46 out of 288 (16.0)	prevalence of <i>pcoD</i> is lower among isolates during treatment (OR=0.38) and post-treatment (OR=0.34) compared with pre-treatment levels, but this presence of <i>pcoD</i> was not associated with a shift in copper MIC distribution	264 out of 288 (91.7)	Control group more resistant to Cu than treatment groups (p=0,027) across all periods	<i>bla</i> _{CMY-2} : 72% <i>tetA</i> : 66%, <i>tetB</i> : 48%, <i>tetC</i> : 2.1%, <i>tetE</i> : 1.6%	Percentage of isolates resistant to antimicrobials: amikacin 0.0%, azithromycin 6.3%, ampicillin 74.6%, amoxicillin 70.2%, ceftriaxone 68.9%, chloramphenicol 38.5%, ciprofloxacin 0.0%, trimethoprim 4.1%, ceftiofur 66.9%, gentamicin 42.3%, kanamycin 23.5%, nalidixic acid 0.0%, sulfisoxazole 82.3%, streptomycin 71.0%, tetracycline 97.1%, ceftiofur 64.8%. The antibiotic resistance differs between sampling times and treatment groups.	Resistance to most antibiotics tested decreased over time when CTC and copper were supplemented (alone or in combination) compared with the control group. Copper supplementation was significantly associated with reduced resistance to most of the antibiotics tested.
	CuSO ₄	43 out of 288 (14.9)		266 out of 288 (92.4)				
	CuSO ₄ + CTC	49 out of 288 (17.0)		278 out of 288 (96.5)				

ID	Treatment	Prevalence <i>pcoD</i>	Copper resistance in different treatment periods	Mechanism of copper resistance	Antibiotic resistance genes (%)	Comment
285	Control	Mean log 10 copies of <i>pcoD</i> /gram faeces are determined, but unclearly reported in a graph	pcoD gene quantities increased at first during treatment, followed by a gradual decrease through the remaining sampling days; yet poorly described	<i>pco</i> -mediated copper resistance is an auxiliary mechanism that cooperates with the host bacterial cell copper management systems. It can modestly extend the range of environmental copper concentrations over which the bacterial cell can survive but does not provide a large leap in MIC with its presence	Prevalence of <i>tetA</i> and <i>tetB</i> across all treatment groups and sampling days: 77% and 57% respectively. The median number of <i>tet</i> -genes detected per sample did not significantly differ among treatment groups. Detection of both <i>tetA</i> and <i>tetB</i> decreased from pre-treatment to treatment phase	The major drawback of the total community approach is that it is impossible to attribute the resistance genes to particular bacteria. Thus the approach is subjected to a unique form of bias known as the "ecological fallacy".
	CuSO ₄					
	CuSO ₄ + CTC					

ID	Treatment	<i>tcrB</i> gene positive isolates (%)	Copper resistance	Species identification	Antibiotic resistance genes	Antibiotic susceptibility	Comment
295	Control	- pre-treatment: 3 out of 72 (4.2) - treatment: 33 out of 216 (15.3) - post-treatment: 11 out of 144 (7.6)	All 372 <i>tcrB</i> positive isolates were resistant to copper, with an MIC between 12 and 24mM. All 372 <i>tcrB</i> negative isolates were susceptible to copper, with an MIC between 4 and 8mM.	Across all treatments 372 <i>tcrB</i> positive isolates: 331 <i>E. faecium</i> and 41 <i>E. faecalis</i>	All (372 <i>tcrB</i> positive and 372 <i>tcrB</i> negative) isolates were positive for both <i>ermB</i> and <i>tetM</i> .	- All (372 <i>tcrB</i> positive and 372 <i>tcrB</i> negative) isolates were resistant to tetracycline (MIC $\geq 16\mu\text{g/ml}$) and tylosin (MIC $\geq 8\mu\text{g/ml}$), and susceptible to vancomycin (MIC $\leq 4\mu\text{g/ml}$). Vancomycin values significantly differed (0.78 for <i>tcrB</i> positive versus 0.39 $\mu\text{g/mL}$ for <i>tcrB</i> negative, $p < 0.0001$) - Frequency of resistant isolates (n=50 <i>tcrB</i> positive and n= 50 <i>tcrB</i> negative; %): Lincomycin: 100, tetracycline: 95, kanamycin: 76, tylosin: 71, erythromycin: 69, quinupristin/dalfopristin: 61, streptomycin: 53, gentamicin: 14, chloramphenicol: 0, linezolid: 0 and vancomycin: 0	It is possible that 3 weeks of treatment duration were not sufficient for copper to exert a major selection pressure on <i>tcrB</i> positive enterococci, as the prevalence of <i>tcrB</i> was low (17.1%) in piglets fed diets supplemented with copper alone or in combination with antibiotics.
	CuSO ₄	- pre-treatment: 4 out of 72 (5.6) - treatment: 37 out of 216 (17.1) - post-treatment: 11 out of 144 (7.6)					
	CuSO ₄ + CTC	- pre-treatment: 11 out of 72 (15.3) - treatment: 50 out of 216 (23.2) - post-treatment: 14 out of 144 (9.7)					
	CuSO ₄ + tylosin	- pre-treatment: 3 out of 72 (4.2) - treatment: 62 out of 216 (28.7) - post-treatment: 3 out of 144 (2.1)					

The overall prevalence of the *tcrB* gene among fecal enterococci was significantly ($p < 0.05$) affected by treatment, day of sampling and interaction terms between treatments and sampling periods. The prevalence is higher if copper is combined with antibiotics. The proportion of isolates resistant to each antimicrobial did not differ between *tcrB* positive and *tcrB* negative isolates ($p > 0.05$).

ID	Treatment	Total number of bacteria (x 10 ⁶)	Antibiotic resistance in <i>E. coli</i> (%; only statistically different displayed)	Antibiotic resistance in <i>enterococci</i> (%; only statistically different displayed)	Average daily gain (kg/d)	Gain/feed	Comment
785	Control	<i>E. coli</i> : 61.5 <i>Enterococci</i> : 16.6	- tylosin: d14: 23.8; d31: 23.3; d38: 33.7 - sulfamethazine: d14: 16.7 (erythromycin, neomycin: no difference)	- tylosin: d14: 4.7; d31: 10.5 - erythromycin: d14: 6.6; d31: 11.4 - neomycin: d14:5.3 (sulfamethazine: no difference)	0.43	0.60	Piglets were progeny of sows of a farm from which the use of subtherapeutic antibiotics had been discontinued since 1972
	CuSO ₄	<i>E. coli</i> : 30.8 <i>Enterococci</i> : 6.9	- tylosin: d14: 50.3 ; d31: 53.5; d38: 60.0; -sulfamethazine: d14: 44.2	- tylosin: d14: 50.0 ; d31: 58.6 - erythromycin: d14: 50.0; d31: 54.3 - neomycin: d14:50.4	0.45	0.64	

No statistically significant differences among treatments in total number of bacteria isolated or in performance

ID	Treatment	Total number of bacteria (x 10 ³)	Copper resistance (%)	Antibiotic resistance in Faecal coliforms (%; only statistically different displayed)	Antibiotic resistance in <i>enterococci</i> (%; only statistically different displayed)	Average daily gain (kg/d)	Gain/feed	Comment
937	Control	Faecal coliforms: 2.449 <i>Enterococci</i> : 17.5	Faecal coliforms: 52.6%, <i>Enterococci</i> : 24.1%	- erythromycin: 25.7 (tylosin, sulfamethazine, neomycin: no difference)	- erythromycin: 27.5 - tylosin: 30.9 - Neomycin: 9.7 (sulfamethazine: no difference)	0.39	0.56	Isolates that were selected from the MacConkey's agar and thought to be <i>E. coli</i> did not always fluoresce under UV light after incubation in Colilert. We could not be sure that every isolate was <i>E. coli</i> therefore data were reported as faecal coliforms
	CuSO ₄	Faecal coliforms: 2.887 <i>Enterococci</i> : 16.1	Faecal coliforms: 56.0% <i>Enterococci</i> : 20.5%	- erythromycin: 36.9	- erythromycin: 44.3 - tylosin: 46.7 - Neomycin: 18.3	0.38	0.59	

No statistically significant differences among treatments in total number of bacteria isolated or in copper resistance

Methodological quality

The methodological quality of these studies is captured in Table 3. Three references were judged to have a good methodological quality (26, 128, 203) for the review question. The other references were considered to have an intermediate or poor methodological quality:

- Ref 24: poor methodological quality because the number of total tested samples per group varied between groups and through the follow-up, leading to biased results. Also it was not clear if two isolates were derived from the same sample or from two different samples. The internal validity of this reference when determining the prevalence of *tcxB* gene in the isolates of the different groups is low;
- Ref 202: it was considered of poor methodological quality because of a lack of detailed information, lack of statistical analysis, lack of adequate experimental design. This experimental set-up could not be repeated.
- Ref 219: intermediate methodological quality because there were no results at baseline and no information on the number of bacteria isolated per sample.
- Ref 284, 285 and 295: intermediate methodological quality because of uncertainty concerning the independence of the samples (three piglets out of five per pen were sampled per sampling day, so the same piglet could have been sampled at different weeks). No details are provided about the determination of the sample size, nevertheless it is assumed to be adequate since there are 40 piglets/treatment.
- Ref 785: intermediate methodological quality because of the low sample size. All other methodologies were correct.
- Ref 937: poor methodological quality owing to vagueness about the sampling process. It is unclear how many samples were taken, which pigs were sampled and how many isolates obtained per sample. The number of total tested samples per group varied between groups and through the follow-up, leading to biased results.

Some overall comments concerning methodological quality for all references were raised:

- Study power: none of the studies provide information about the desired study power and the according sample size.
- Blinding of the outcome assessors: none of the studies mention anything about this subject. This is why all received a neutral face for this question in Table 3.
- Withdrawing/missing data: these data are either not reported or in case they are, then it is often not discussed how they have been handled in the statistical analysis. Nevertheless, if these data are not reported, it could often be seen in the tabulated data whether data were missing or not.
- Appropriateness of the statistical methods: some scientific papers describe (completely or incompletely) the statistical method but they do not present the results. Some methods are simplistic as they only summarise the observed data. Biological relevance of the results is not discussed in any of the papers. When p-values are provided, there is seldom mention of the method or model applied.
- Only one study (128) performed a confirmatory analysis of the copper content in the feed, but even in such case there is no total certainty as the measured values were not reported. None of the other studies has confirmatory data about the copper concentrations in the feed, so the results should be interpreted with caution.

Table 3: Assessment of the methodological quality of the field studies

ID	Amachawadi <i>et al.</i> (2010) 24	Amachawadi <i>et al.</i> (2011) 26	Hasman <i>et al.</i> (2006) 128	Pupavac <i>et al.</i> (1996) 202	Ragland <i>et al.</i> (2006) 203	Shelton <i>et al.</i> (2009) 219	Agga <i>et al.</i> (2014) 284	Agga <i>et al.</i> (2015) 285	Amachawadi <i>et al.</i> (2015) 295	Holt <i>et al.</i> (2008a) 785	Holt <i>et al.</i> (2008b) 937
Is the study adequately powered to meet the objectives ?	😊	😊	😊	😞	😊	😊	😊	😊	😊	😞	😊
Were experimental units randomly assigned to the treatment groups?	😊	😊	😊	😞	😊	😊	😊	😊	😊	😊	😊
Prior to the intervention, were the outcomes tested (measurement at base line)?	😊	😊	😊	😞	😊	😊	😊	😊	😊	😊	😊
Were the interventions clearly described to enable reproducibility?	😊	😊	😊	😊	😊	😊	😊	😊	😊	😊	😊
Where groups treated evenly, apart from the intervention?	😞	😊	😊	😊	😊	😊	😊	😊	😊	😊	😊
Was an appropriate control group used?	😊	😊	😊	😊	😊	😊	😊	😊	😊	😊	😊
Was the outcome assessor appropriately blinded to the intervention status of the treatment units?	😊	😊	😊	😊	😊	😊	😊	😊	😊	😊	😊
Were laboratory tests used to determine the outcome described and adequate?	😊	😊	😊	😊	😊	😊	😊	😊	😊	😊	😊
Was the time from the administration of the intervention until the end of the study sufficient to meet the objectives of the trial?	😊	😊	😊	😊	😊	😊	😊	😊	😊	😊	😊
Were withdrawn/missing data reported and taken into consideration in the analysis?	😊	😊	😊	😞	😊	😞	😊	😊	😊	😊	😊
Was the proportion of lost to follow-up adequate?	😞	😊	😊	😞	😊	😊	😊	😊	😊	😊	😊
Appropriateness of the statistical analysis for the design?	😊	😊	😊	😞	😊	😊	😊	😊	😊	😊	😊
Were the estimates and measures of variability used to address the research question presented?	😊	😊	😊	😞	😊	😊	😊	😊	😊	😊	😊

Environmentally controlled studies

To this group belonged experimental studies as well, but they were not performed applying an intervention to pigs and following up. Most of these studies ascertained the mechanism of resistance (which genes are involved, how are they regulated, what are the characteristics of the operon...). These studies do not answer immediately the review question, although they provide useful information. It was decided to consider them as supporting studies and to not submit them to the methodological quality assessment, due to the difference in experimental set ups and methodologies applied compared to the field and cross-sectional studies.

The following ten references could be assigned to the group of environmentally controlled, experimental studies: 92 (Elguindi *et al.*, 2011), 102 (Freitas *et al.*, 2011), 120 (Hasman, 2005), 121

(Hasmann & Aarestrup, 2002), 124 (Hasman & Aarestrup, 2005), 180 (Morgan *et al.*, 1987), 233 (Tetaz & Luke, 1983), 456 (Lüthje *et al.*, 2014), 503 (Qin *et al.*, 2014) and 589 (Zhang *et al.*, 2015).

Characteristics of the field studies

ID. 92. Year 2011

ABSTRACT

The exact mechanism of killing bacteria which come in contact with copper is not fully understood. This study showed that the kinetics of contact killing of copper surfaces depended greatly on the amount of moisture present, copper content of alloys, type of medium used, and type of bacteria. Antibiotic- and copper ion-resistant strains of *Escherichia coli* and *Enterococcus faecium*, isolated from pig farms following the use of copper sulphate as feed supplement, were examined. Rapid killing occurred when samples were spread in a thin, moist layer on copper alloys with 85% or greater copper content. *E. coli* strains were rapidly killed under dry conditions, while *E. faecium* strains were less affected. Copper ion-resistant *E. Coli* and *E. Faecium* cells suspended in 0.8% NaCl showed prolonged survival rates on electroporated copper surfaces with benzotriazole coating and thermal oxide coating compared to surfaces without anti-corrosion treatment.

ID. 102. Year 2011

ABSTRACT

Vancomycin-resistant enterococci (VRE) from pigs (n=29) and healthy persons (n=12) were recovered during surveillance studies in Portugal, Denmark, Spain, Switzerland, and the US and were compared to outbreak VRE clinical strains. The characterization of plasmids containing glycopeptide (= vancomycin) resistance and copper resistance was performed by PCR mapping, hybridization and conjugation experiments. Thirty clonally related *Enterococcus faecium* clonal complex 5 (CC5) were obtained from faeces of swine and humans. A variant of Tn1546 (encoding resistance for vancomycin) and *tcrB* (encoding copper resistance) were consistently located on 150 to 190 kb plasmids. One *Enterococcus faecalis* strain from pigs corresponded to a multidrug resistant clone widely disseminated in hospitals. These results indicated a current intra- and international spread of clones and plasmids among swine and humans.

CONCLUSION

All vancomycin-resistant *E. faecium* strains contained the *tcrB* gene located on the same plasmid, confirming the link between both resistance genes.

ID. 120. Year 2005

ABSTRACT

The plasmid-localized *tcrB* gene from *Enterococcus faecium* was identified to be part of an operon called the *tcrYAZB* operon. Putative promoter and repressor binding sites were identified upstream of the operon. The promoter was cloned in both the absence and the presence of the proximal repressor-encoding *tcrY* gene. Induction of the promoter was shown in liquid growth medium containing increasing concentrations of copper sulphate. Growth of a *tcr*-deletion mutant was compared with that of the wild type strain in sublethal concentrations of copper sulphate in a competition assay. This showed that copper sulphate concentrations of 3 mM and above are sufficient to select for copper resistance.

CONCLUSION

Concentrations of copper above 3mM are sufficient to select for copper resistance. Copper supplementation of 175 ppm in piglets is equal to 2.8 mM and could therefore lead to selection of copper resistant *E. faecium* strains.

ID. 121. Year 2002

ABSTRACT

A newly discovered gene, designated *tcxB*, which is located on a conjugative plasmid conferring acquired copper resistance in *Enterococcus faecium*, was identified in an isolate from a pig. The *tcxB* gene encodes a putative protein belonging to the CPx-type ATPase family with homology (46%) to the CopB protein from *Enterococcus hirae*. The *tcxB* gene was found in *E. faecium* isolated from pigs (75%), broilers (34%), calves (16%), and humans (10%) but not in isolates from sheep. Resistant isolates, containing the *tcxB* gene, grew on brain heart infusion agar plates containing up to 28 mM CuSO₄ compared to only 4 mM for the susceptible isolates. Copper resistance, and therefore the presence of the *tcxB* gene, was strongly correlated to macrolide (erythromycin) and glycopeptide (vancomycin) resistance in isolates from pigs, and the *tcxB* gene was shown to be located on the same conjugative plasmid as the genes responsible for resistance to these two antimicrobial agents. The frequent occurrence of this new copper resistance gene in isolates from pigs, where copper sulphate is being used in large amounts as feed additive, suggests that the use of copper has selected for resistance.

CONCLUSION

Copper resistance in *E. faecium* isolated from both animal and human reservoirs showed a good correlation between the use of copper sulphate in the feed and the number of copper-resistant bacteria isolated from each reservoir. Furthermore, copper resistance was genetically linked to macrolide and glycopeptide resistance.

ID. 124. Year 2005 (Isolates 1997-2003)

ABSTRACT

A significant relationship between copper resistance (*tcxB*), glycopeptide resistance (Tn1546), and macrolide resistance [*erm(B)*] in *Enterococcus faecium* isolated from pigs was found. The *tcxB* gene was located closely upstream of the Tn1546 element. However, the continued use of copper sulphate has not been able to maintain high levels of macrolide and glycopeptide resistance. From 1997 to 2003, the number of erythromycin resistant isolates, which are also copper resistant, decreased from 31 to 11 and the number of vancomycin resistant isolates, which are also copper resistant, decreased from 12 to 2. In this period copper resistance remained unchanged among isolates.

CONCLUSION

Co-selection caused by copper is not supported by the data presented here, as glycopeptide resistance has been decreasing since the ban of avoparcin (glycopeptide) since 1995 and tylosin (macrolide) since 1998, while copper resistance has not. Therefore, there seem to be other factors which contribute more to elimination of the glycopeptides-resistant *E. faecium* (GREF) isolates. As we still find GREF 8 years after the ban, the possibility that addition of especially the largest amount of copper to the feed contributes to delaying the elimination of GREF, given the close proximity of the two resistance determinants, cannot be completely excluded. However, significant selection of GREF in pig production seems to have occurred only when the strong selective pressure of glycopeptide or macrolide administration was present.

ID. 180. Year 1987

ABSTRACT

Plasmid-determined resistance to copper has been demonstrated previously (Tetaz and Luke, 1983). Some enterotoxigenic *E. coli* (ETEC) isolated from scouring pigs have now been shown to be resistant and the determinants of resistance shown to be transferable *in vitro*. When 79 *E. coli* isolates from

cases of suspected colibacillosis were examined by gene probe analysis and conventional procedures for copper resistance, 12 hybridized with the copper resistance probe. Given the association of copper resistance and virulence in some strains of ETEC, management implications of feeding copper-supplemented ratios to weaners need to be considered. Considering the risk of selecting resistant pathogens at the critical time of weaning, it may be appropriate to omit copper from weaners diets. Investigations are continuing to determine whether the inclusion of copper in pig diets lead to a build-up of resistant organisms in the piggery environment.

CONCLUSION

Considering the risk of selecting resistant pathogens at the critical time of weaning, it may be appropriate to omit copper from weaners diets.

ID. 233. Year 1983

ABSTRACT

The copper resistance of a strain of *Escherichia coli* isolated from the effluent of a piggery where pigs were fed a diet supplemented with copper sulphate was controlled by a conjugative 78-megadalton plasmid designated pRJ1004. Plasmid pRJ1004 exhibited surface exclusion and incompatibility with standard plasmids belonging to incompatibility groups I1 and K. Sensitive strains of *E. coli* K-12 were unable to form colonies on nutrient agar containing more than 4 mM copper, whereas transconjugants which harboured pRJ1004 were able to form colonies on medium containing up to 20 mM copper.

CONCLUSION

Authors found that the copper resistance of one porcine *E. coli* isolate is controlled by a conjugative plasmid, which was designated pRJ1004.

ID. 456. Year 2014

ABSTRACT

The draft genome sequences of two copper resistant *Escherichia coli* strains (77-3009-5 and 77-30253-3) were determined. These had been isolated from healthy copper-fed pigs in Denmark at or just prior to slaughter and contained additional putative operons conferring copper and other metal and metalloid resistances.

CONCLUSION

Strain 77-3009-5 had a mobile copper resistance island containing 20 genes including the *pco* determinant. Strain 77-30253-3 lacked the 20-gene copper resistance island, but contained genes for synthesis and handling of yersiniabactin that protects against copper toxicity.

ID. 503. Year 2014

ABSTRACT

The draft genome sequences of the *Salmonella typhimurium* strains S7, S15, and S23, isolated from copper-fed pigs in Denmark were determined. They were found to contain additional putative determinants conferring resistances to copper and other metals and metalloids.

CONCLUSION

All 3 strains contained several copper resistance genes like *CopA* and *CueO* and as well as a mobile 20-gene copper resistance determinant with *pco* and *sil* (silver resistance) determinants. Two additional genes were found between these 2 determinants: *pcoG* (probably encodes a metallopeptidase) and *pcoF* (probably encodes a copper binding protein). All strains also contained an

RND-type *CusCFBA* system (efflux system) and *CueP* (copper sequestration).

ID. 589. Year 2015

ABSTRACT

Six strains of *Enterococcus faecalis* (S1, S12, S17, S18, S19 and S32) were isolated from copper fed pigs in Denmark. The genome of strains S1, S12, S17, S18, S19 and S32 contained 41, 42, 27, 42, 32 and 44 genes encoding antibiotic and metal resistance, respectively. Differences between Cu resistant and sensitive *E. faecalis* strains, and possible co-transfer of Cu and antibiotic resistance determinants were detected through comparative genome analysis.

CONCLUSION

All 6 strains contain the four gene operon *copyZAB* (encoding a Cu resistance determinant), the *cutC* gene (encoding a cytoplasmatic Cu homeostasis protein) and a putative copper resistance gene *ctpA*. The *tcryAZB* operon and adjacent *cueO* were only identified in the Cu resistant strains S1, S18 and S32. On the mobile 20-gene Cu pathogenicity/fitness island, transposase and mobile element protein genes were identified next to *tcryAZB*, indicating mobility. The *tetM* antibiotic resistance gene was identified in all resistant strains, which is consistent with the MDR *Enterococcus* strains observed in the environment.

Overall results

The so-called environmentally controlled studies evidence the genetic relation between the copper-resistance gene (*tcrB*) on the one hand and macrolide (erythromycin, *ermB*) or glycopeptide (vancomycin, *Tn1546*) resistance genes on the other hand in *Enterococcus faecium*. Further, study 124 demonstrates a dramatic decrease in the isolates resistant to erythromycin and vancomycin from 1997 to 2003, while copper resistance has not decreased. Although the genetic linkage between these copper and antibiotic resistance genes is confirmed, co-selection through the use of copper could not be proven. The study 121 demonstrates that the *tcryAZB* mediated copper resistance is inducible and that the occurrence of the *tcrB* gene is higher in isolates from pigs, which are the species in which more copper supplementation is used, compared to sheep (very low supplementation) where the gene was not identified. Also, in studies 120 and 180 it was suggested that high supplementation of copper may select towards copper resistant isolates. Study 589 shows that in another *Enterococcus* sp., *E. faecalis*, the *tcryAZB* only occurred in the copper resistant strains and that it was always accompanied by the *tetM* gene for tetracycline resistance.

The *tcrB* gene does not occur in gram negative bacteria. Instead a mobile island of 20 genes containing the *pco* determinant (also encoding copper resistance) was identified in *E. coli* (study 456) and *Salmonella typhimurium* (study 503). Study 233 confirmed that the resistance in *E. coli* was caused by a conjugative plasmid. On the other hand it seems that copper resistance can also be caused by a variety of other than *pco* alone. Study 180 indicates that there is a risk at feeding copper to weaner pigs since some ETEC strains are copper resistant and feeding copper could select for these virulent strains.

3.3.2. Cross-sectional studies

The studies assigned to this group tested a collection of isolates for susceptibility to copper and/or antibiotics or screened these isolates for the presence of resistance genes. Twelve references belonged to this group: 13 (Aarestrup *et al.*, 2004), 15 (Aarestrup *et al.*, 2002), 75 (Chuanchien *et al.*, 2008), 88 (Dutta & Devriese, 1981), 95 (Fard *et al.*, 2011), 108 (Gedek, 1981), 149 (Koowatananukul *et al.*, 2010), 220 (Siebert, 1982), 257 (Williams *et al.*, 1993), 465 (Medardus *et al.*, 2014), 678 (Blake, 2002) and 765 (Huysman *et al.*, 1988).

Characteristics of the cross-sectional studies

The main characteristics of these studies are represented in Table 4.

Table 4: Characteristics of the cross-sectional studies

ID	Year	Country	Bacteria species (number isolates)	Isolated from (animal species)	Age of the animals	Level of Cu in feed	Parameters analysed	Statistics	Comments
13	2004	Denmark	Total of 569 isolates distributed as follows: <i>Escherichia coli</i> (202), <i>Salmonella</i> (156), <i>Enterococcus faecium</i> (78), <i>Enterococcus faecalis</i> (52), <i>Staphylococcus aureus</i> (43) and <i>Staphylococcus hyicus</i> (38)	Pig, broiler and cattle	not indicated	CuSO ₄ : Piglet 175 ppm and pig 35 ppm	Susceptibility to CuSO ₄ , benzalkonium, chloride, hydrogen peroxide, chlorhexidine and formaldehyde	Not performed	Useless because it only presents aggregated data of all species
15	2001 (Samples from 1998 to 2000)	Denmark, Spain and Sweden	Denmark total 190 samples (<i>Enterococcus faecalis</i> 102 and <i>E. faecium</i> 88); Spain total 124 (<i>E. faecium</i>); Sweden total 66 (<i>E. faecalis</i> 48, <i>E. faecium</i> 18)	Denmark pigs submitted to a diagnostic laboratory; Spain pigs submitted to a diagnostic laboratory and also healthy pigs, all isolates vancomycin resistant; Sweden colon of pigs from five different slaughterhouses (representing 66 different farms)	Denmark and Spain is unknown. Swedish pigs at the age of slaughter	Denmark CuSO ₄ at 175 ppm in weaners and 35 ppm in fatteners; Spain Cu(CH ₃ COO) ₂ , CuCO ₃ , Cu(OH) ₂ , CuCl ₂ , CuO, Cu(C ₅ H ₁₀ NO ₂) ₂ at the same concentration as Denmark; Sweden CuSO ₄ at 35 ppm regardless of age	Susceptibility to CuSO ₄ , avilamycin, bacitracin, chloramphenicol, erythromycin, gentamicin, kanamycin, penicillin, streptomycin, quinupristin-dalfopristin, tetracycline and vancomycin; Antibiotic resistance genes (chloramphenicol, gentamicin, kanamycin, macrolide-lincosamide-streptogramin B, quinupristin-dalfopristin and tetracycline)	Not performed	Selection bias of Danish and Spanish samples.
75	2007 (samples of 2003 to 2005)	Thailand	<i>Salmonella enterica</i> (132 isolates pertaining to 24 serotypes)	Healthy swine (feces, rectal), drinking water and feed	not indicated	not indicated	Susceptibility to CuSO ₄ , ampicillin, chloramphenicol, gentamicin, ciprofloxacin, tetracycline, trimethoprim, sulphamethoxazole, benzalkonium chloride, chlorhexidine and ZnCl ₂ . Presence of antibiotic resistance genes	Chi square or Fishers' exact test for significant difference between proportions. Wilcoxon rank sum test for differences between MIC values	From the 132 isolates attributed to swine, there is uncertainty in the proportion of isolates originated from feed or from drinking water. Selection bias.
88	1980 (samples from 1979)	Belgium	Lactobacilli (45 isolates): <i>L. acidophilus</i> (14 isolates), <i>L. salivarius</i> (2), <i>L. plantarum</i> (1), <i>L. sp.</i> (3), <i>L. fermentum</i> (16), <i>L. brevis</i> (9)	22 pigs brought for autopsy to the Veterinary Faculty Gent, isolated from caeca, representing 16 farms	not indicated	not indicated	susceptibility to CuSO ₄ , avoparcin, bacitracin, carbadox, flavomycin, lincomycin, nitrovin, oleandomycin, spiramycin, tylosin, virginiamycin	Not performed	Selection bias (post-mortem examination diagnostic service)

ID	Year	Country	Bacteria species (number isolates)	Isolated from (animal species)	Age of the animals	Level of Cu in feed	Parameters analysed	Statistics	Comments
95	2009	Australia	Enterococci (192 isolates): <i>E. faecalis</i> (75), <i>E. faecium</i> (68), <i>E. gallinarum</i> (13), <i>E. casseliflavus</i> (13), and <i>E. hirae/durans</i> (15)	Intestinal tract of slaughter pigs	Age of slaughter	not indicated	Susceptibility to CuSO ₄ (considered susceptible if MIC ≤ 2 mM and resistant > =28 mM); susceptibility to antibiotics (avoparcin, gentamicin, tetracycline, tiamulin, tylosin, vancomycin and virginiamycin) and ZnCl ₂ . Determination of antibiotic resistance genes and copper resistance gene <i>tcxB</i> .	Not performed	Practically no information on the reference population (Barton <i>et al.</i> , 2005 could not be retrieved)
108	1981 (samples from 1977-1980)	Germany	<i>E. coli</i> : Trial I (°77/78): 680 isolates Trial II (°79/80) : 1516 isolates Trial III (°79/80): 500 isolates	Faeces from 10 pigs (30-35 kg) per farm from 17 commercial farms Faeces from 194 piglets (7-25 kg) from non-commercial farms from 2 different regions in Germany Faeces from 120 fattening pigs (50-100 kg) from 4 non-commercial farms from 2 different regions in Germany (12 groups of 10 animals)	Not indicated	100, 125, 175 or 200 ppm No proper control group 20, 40 or 200 ppm No proper control group 20, 40, 150 or 200 ppm	Susceptibility to chloramphenicol Susceptibility to chloramphenicol, tetracycline, streptomycin, ampicillin, kanamycin Susceptibility to chloramphenicol	Not performed	Data may be biased by the presence of antimicrobial growth promoters in the basal diets, except for 1 farm Not clearly reported when the basal diets contained antimicrobial growth promoters (Olaquinox, Tylosin), possible bias Only the 6 groups without antimicrobial growth promoter are considered
149	2010	Thailand	<i>E. coli</i> (180 isolates)	Faeces pigs Farm environment (water, feed)	Not indicated	Not indicated	Susceptibility to copper sulphate, zinc chloride, ampicillin, chloramphenicol, gentamicin, ciprofloxacin, erythromycin, tetracycline, trimethoprim, streptomycin, sulphamethoxazole	Not performed	Isolates from the farm environment also incorporated in the analyses
220	1982	Germany	<i>E. coli</i> (100 isolates)	Faeces from 24 pigs	Not indicated	Mostly not indicated One trial with addition of copper methionine (PABUSANR 300 and 600 ppm, corresponding to 50 and 100 ppm copper)	Susceptibility to tetracycline, streptomycin, chloramphenicol, ampicillin, kanamycin, trisulfonamide, furazolidon	Not performed	

ID	Year	Country	Bacteria species (number isolates)	Isolated from (animal species)	Age of the animals	Level of Cu in feed	Parameters analysed	Statistics	Comments
257	Isolates from years 1979, 1988-1990. Paper received by Journal in 1993	Australia, UK	<i>Escherichia coli</i> 1979. 4 strains (Australia) 1988. 7 strains (UK-a) 1989. 5 strains (UK-a) 1990. 5 strains (UK-a), 3 strains (UK-b), 1 strain (UK-c) <i>Citrobacter freundii</i> : 1988. 3 strains (UK-a) 1989. 3 strains (UK-a) 1990. 1 strain (UK-d) <i>Salmonella sp.</i> : 1989. 1 strain (UK-a)	Faecal swabs from pigs	Not indicated	Not specified. Copper used as growth promoter	- Resistance to copper of several isolates, by growing 13 isolates (from 3 microorganisms) in an enriched-Cu medium (more growth= more resistance) - Identification of plasmids giving the Cu-resistance characteristics - Determination of transferability of Cu-resistance by conjugative plasmids	Not performed Only Standard deviations reported for the growth of various isolates in Cu-enriched medium.	
465	Isolates from years 2007-2009 Paper received by Journal in 2013	USA	<i>Salmonella sp.</i>	Pigs: Faeces: 4504 isolates Feed: 30 isolates Barn floors: 1628 isolates	Early finishing stage (6 to 9 weeks of age) and late finishing stage (26 to 28 weeks of age)	- Copper level ranged from 3.2 to 365.2 mg/kg feed with a median of 31.5 mg/kg. - Zinc level ranged from 77 to 2000 mg/kg feed with a median of 139.8 mg/kg.	- Susceptibility to copper sulphate, zinc chloride, ampicillin, amoxicillin-clavulanic acid, amikacin, ceftriaxone, cephalothin, chloramphenicol, ciprofloxacin, gentamicin, kanamycin, streptomycin, sulfisoxazole and tetracycline. - Detection of copper and zinc tolerance genes: <i>pcoA</i> , <i>czcD</i> - Serotyping of the isolates	Generalised linear model for testing heavy metal tolerance (copper and zinc in a separate model), with company, farm and barn as random effects. Only one isolate per sample was included in the statistical modelling.	As the study is from the US, possibly other feed nutritional practices are involved, even if the Cu and Zn median levels are in the range of those authorised in the EU.
678	2002	Scotland, United Kingdom	<i>E. coli</i>	Faeces from pigs: - 8 intensively reared on 4 local commercial units - 2 extensively reared on a local smallholding	Not indicated	Not indicated. Intensively reared pig presumably exposed to 175 mg/kg.	Susceptibility to copper sulphate, ampicillin, apramycin, cephalothin, chloramphenicol, ciproflaxin, gentamicin, imipenem, nalidixic acid, streptomycin, tetracycline, trimethoprim/sulphamethoxazole	Not performed	Study performed before prohibition of antibiotics as growth promoters. The description of the study is a bit unclear.
765	1988	Belgium	<i>E. coli</i> <i>Clostridium perfringens</i>	Fresh manure from piglets, fattening pigs, sows and cows	Not indicated	Ranging from 0 to 175 mg/kg	Susceptibility to copper, chloramphenicol, kanamycin, novobiocin, penicillin, streptomycin	Not performed	

Results of the cross-sectional studies

The results of these studies are summarized in Table 5.

The cross-sectional studies were heterogeneous in different aspects:

- The exposure depends on the feeding practices of the different countries (different levels of copper sulphate). For some countries as Thailand, Germany, UK or Australia there were no indications on the exposure of the animals to copper.
 - The species of microorganisms that were isolated were diverse.
 - The threshold concentrations of susceptibility/resistance for copper sulphate or the different antibiotics varied among studies. In addition, some studies did not even indicate these thresholds of susceptibility/resistance used for copper sulphate or for the antibiotics.
-
- Study 13 did not provide useful information because it presents aggregated data of different species.
 - In study 15, the occurrence of copper and antibiotic resistant isolates from Sweden was lower than in Denmark or Spain. This could be a result of the low supplementation levels of copper sulphate (35 ppm independently of the age) compared with Denmark or Spain. However, the selection of isolates from Denmark or Spain might have been biased. The resistance to copper sulphate seemed to be higher in *E. faecium* than in *E. faecalis*. It remained difficult to determine if there was any antibiotic resistance associated to the resistance to copper sulphate.
 - Study 75 presented data on *Salmonella* serotypes, which were all susceptible to >12.8 mM copper sulphate. However, the proportion of isolates originating from pig microbiota was not clear (samples from water and feed were also incorporated in the study).
 - Study 88 was on lactobacilli in Belgium. Most isolates had susceptibility of >3.2 mM copper sulphate. However, selection of the samples might be biased (pigs submitted to post-mortem examination at Gent University).
 - In Study 95, none of the 192 enterococci were resistant to copper sulphate (maximum MIC was 7 mM), but only if the sampling would be considered unbiased.
 - Study 108 presented data on *E. coli* isolated from pigs in Germany. A supplementation level of 200 ppm copper slightly favoured the selection of *E. coli* with multiple resistance to antibiotics, especially chloramphenicol, in comparison to lower copper levels. However the results may be biased by the simultaneous presence of growth promoters (e.g. carbadox, olaquinox, tylosin, Zn-bacitracin) in the diet.
 - Study 149 demonstrated that most *E. coli* in Thailand were susceptible to copper sulphate (MIC is 6.4 mM). However, selection of the isolates was not representative (also from farm environment).
 - Study 220 indicated no increase in antibiotic resistance of *E. coli* isolates from pigs in Germany after supplementation of 50 ppm copper methionine in the diet of the pigs.
 - Study 257 showed genotypic and phenotypic similarities concerning the copper resistance between isolates of Australia and UK. Furthermore, the mechanism of transferability of copper resistance was demonstrated.
 - Study 465 clearly demonstrated the presence of a strong association between decreased susceptibility to heavy metals and antimicrobial resistance among *Salmonella* serovars isolated from swine, swine feed and barn floors. Carriage of the *pcoA* gene or level of copper in swine feed was not significantly associated with copper tolerance of *Salmonella* isolates.

- Study 678 could not demonstrate a preferential selection of antibiotic resistant *E. coli* by dietary-level copper exposure. This suggests no direct danger of pig feed copper inclusion selecting for resistant bacteria.
- Study 765 detected high levels of copper resistant coliforms in the manure of pigs receiving copper in their feed, while no resistant isolates were detected in manure of pigs receiving no copper. The resistance against copper was accompanied by an increased resistance against several antibiotics. It should, however, be noted that a “high level of copper resistance” is only 0.1%, so in fact very low.

Table 5: Results of the cross-sectional studies

ID	Characteristics of the samples	Susceptibility to CuSO ₄
13	Aggregated data from pig, cattle and broiler	<i>Salmonella</i> (156 isolates of pig, cattle and broiler): MIC range 26 to 46 mM
		<i>E. coli</i> (202 isolates of pig, cattle and broiler): MIC range 12 to 24 mM
		<i>S. aureus</i> (43 isolates of cattle): MIC range 2 to 12 mM
		<i>S. hyicus</i> (38 pig isolates): MIC 8 to 12 mM
		<i>E. faecalis</i> (52 isolates of pig and broiler): MIC range 2 to 16 mM
		<i>E. faecium</i> (78 isolates of pig, cattle and broiler): MIC range 4 to 24 mM

ID	Country (sample characteristics)	Species (number of isolates)	Resistance to CuSO ₄ (threshold not indicated)	Antibiotic resistance (threshold in µg/mL)								
				Avila-mycin	Chloram-phenicol (≥32)	Erythro-mycin (≥8)	Gentamycin (≥1024)	Kanamycin (≥2048)	Penicillin (≥16)	Strepto-mycin (≥2048)	Tetra-cycline (≥16)	Vanco-mycine (≥32)
15	Denmark (Pig samples submitted to a diagnostic laboratory, weaners exposed to 175 ppm and fatteners to 35 ppm CuSO ₄)	<i>E. faecium</i> (88).	75%	4%	7%	81%	0%	18%	9%	27%	63%	17%
		<i>E. faecalis</i> (102)	17%	0%	4%	85%	1%	24%	0%	39%	68%	0%
	Spain (only vancomycin resistant pig isolates were tested, weaners exposed to 175 ppm and fatteners to 35 ppm CuSO ₄)	<i>E. faecium</i> (124)	56%	4%	19%	86%	5%	45%	21%	64%	94%	2%
		Sweden (Samples of slaughter pigs exposed to 35 ppm CuSO ₄)	<i>E. faecium</i> (18)	6%	0%	0%	17%	0%	2%	0%	15%	65%
	<i>E. faecalis</i> (48)		2%	0%	0%	6%	0%	0%	6%	0%	22%	6%

ID	Characteristics of the sample	Susceptibility to CuSO ₄	Resistance to antibiotics (the threshold of resistance is not indicated)							
			ampicillin	chloramphenicol	ciprofloxacin	gentamycin	tetracycline	trimethoprim	sensitive to these six antibiotics	resistant to ≥2 of these six antibiotics
75	132 <i>Salmonella</i> samples (feces, rectal swabs, drinking water and feed) of healthy swine	100 % had a MIC ≥ 12.8 mM	52.8%	32.6%	0.8%	15.2%	71.2%	31.1%	22.0%	56%

ID	Characteristics of the sample	Susceptibility to CuSO ₄	Resistance to antibiotics (resistance threshold not indicated)							
			Avoparcin	Bacitracin	Carbadox	Flavomycin	Lincomycin	Nitrovin	Macrolides	Virginiamycin
88	Lactobacilli 45 isolates from 22 pigs sent to the Veterinary School of Gent for post-mortem examination: <i>L. acidophilus</i> (14 isolates), <i>L. salivarius</i> (2), <i>L. plantarum</i> (1), <i>L. sp.</i> (3), <i>L. fermentum</i> (16), <i>L. brevis</i> (9)	98 % ≥ 3.2 mM	66%	0%	38%	20%	70%	2%	70%	35%

ID	Characteristics of the sample	Microorganism (number of isolates)	Susceptibility to CuSO ₄ (break points (≤2 or ≥28 mM))	Occurrence of <i>tcrB</i>	Resistance to ZnCl ₂ (≤4 or ≥12 mM)	Resistance to antibiotics (µg/mL)				
						Bacitracin (≤32 or ≥64)	Flavophospholipol (≤8 or ≥16)	Tiamulin (≤4 to ≥32)	Vancomycin (≤4 or ≥8)	Virginiamycin (<8 or ≥8)
95	Enterococci (192 isolates) from the intestinal tracts of slaughtered pigs	<i>E. faecalis</i> (75)	All them had a MIC range from 5 to 7 mM	57%	95%	35%	1%	97%	0%	68%
		<i>E. faecium</i> (68)		68%	4%	93%	96%	72%	0%	15%
		<i>E. gallinarum</i> (21)		67%	0%	100%	67%	95%	100%	0%
		<i>E. casseliflavus</i> (13)		92%	0%	92%	69%	31%	92%	8%
		<i>E. hirae/durans</i> (15)		7%	0%	93%	63%	53%	0%	47%

ID	Characteristics of the samples	Resistance to antibiotics trial I	Resistance to antibiotics in supplementation trial for 10 weeks in two farm regions; trial II (n=number of isolates)					Comments
		Chloramphenicol (n=680 isolates)	Farm region 1: Cu 20 ppm: n=120 (beginning), n=80 (end); Farm region 2: Cu 40 ppm: n=128 (beginning), n=193 (end); Cu 200 ppm: n=194 (beginning), n=120 (end); Cu 200 ppm: n=320 (beginning), n=361 (end)	Chloramphenicol	Tetracycline	Streptomycin	Ampicillin	
108	<i>E. coli</i> faecal samples from: - 170 piglets (only tested against Chloramphenicol; trial I) - from 194 piglets (tested against 5 antibiotics; trial II) - from 120 fattening pigs (only tested against Chloramphenicol; trial III)	- Cu (100 ppm): 0 to 23.1 % - Cu (125 ppm): 0 % - Cu (175 ppm): 0 % - Cu (200 ppm): 0 to 22.5 %	Farm 1 - Cu (20 ppm): from 24.2 % to 7.5 % - Cu (200 ppm): from 60.8 % to 38.5 %	- Cu (20 ppm): from 74.1 % to 37.5 % - Cu (200 ppm): from 74.1 % to 37.5 %	- Cu (20 ppm): from 77.5 % to 37.5 % - Cu (200 ppm): from 96.9 % to 82.6 %	- Cu (20 ppm): from 14.2 % to 2.5 % - Cu (200 ppm): from 50.0 % to 23.5 %	- Cu (20 ppm): from 19.2 % to 0 % - Cu (200 ppm): from 41.2 % to 7.4 %	- Besides copper supplementation, sometimes co-supplementation with antibiotics (tylosin, carbadox, olaquinox,...) which can influence the occurrence of resistance. - For the 10 week trial, no information is present on the supplementations before the trial - thresholds for resistance by values represented also in ref 220.
		Resistance to antibiotics trial III	Farm 2 - Cu (40 ppm): from 57.0 % to 9.8 % - Cu (200 ppm): from 77.2 % to 48.2 %	- Cu (40 ppm): from 57.0 % to 9.8 % - Cu (200 ppm): from 77.2 % to 48.2 %	- Cu (40 ppm): from 92.9 % to 79.2 % - Cu (200 ppm): from 83.8 % to 82.0 %	- Cu (40 ppm): from 24.2 % to 8.8 % - Cu (200 ppm): from 26.0 % to 9.4 %	- Cu (40 ppm): from 7.8 % to 0 % - Cu (200 ppm): from 4.1 % to 0.3 %	
		Chloramphenicol (n=500 isolates)						

ID	Characteristics of the samples	Susceptibility to CuSO ₄	Copper resistance mechanism	Susceptibility to ZnCl ₂	Resistance to antibiotics (n=180)								Comments	
					Ampicillin	Chloramphenicol	Ciprofloxacin	Erythromycin	Gentamycin	Streptomycin	Sulfamethoxazole	Tetracycline		Trimethoprim
149	180 <i>E. coli</i> isolates from faeces, water, feed ...	One large population between 6.4 mM to 12.8 mM 92% had MIC of 6.4 mM 7.8% had MIC of 12.8mM	Reduced susceptibility to CuSO ₄ possibly mediated active efflux systems driven by proton motive force	One large population between 3.2 mM to 6.4 mM 98.9% had MIC of 6.4 mM 1.1% had MIC of 3.2 mM	84.5%	73.4%	40.6%	100%	52.2%	74.5%	56.7%	93.9%	72.2%	No separation in prevalence between isolates from faeces and isolates from farm environment

ID	Characteristics of the samples	Resistance to antibiotics (n=50 isolates)						Comments	
		Tetracycline	Streptomycin	Chloramphenicol	Ampicillin	Kanamycin	Trisulfonamide		Furazolidon
220	Faeces from pigs with diet supplemented without or with copper methionine (PABUSAN), background copper is 20 ppm	No additional copper							Data obtained from <i>in vitro</i> studies and data from studies with diets containing both supplemental copper and a growth promoter (Olaquinox) were not further considered. From the other results it is not clear if the pigs received a supplementation of copper in their diet. Threshold values for resistance are represented for different antibiotics (in µg/ml); R=resistant, S=susceptible: Amikacin: R ≥ 32; S ≤ 8; Ampicillin: : R ≥ 16; S ≤ 8; Carbenicillin: : R ≥ 32; S ≤ 16; Cephalotin: : R ≥ 16; S ≤ 8; Chloramphenicol: : R ≥ 16; S ≤ 8; Gentamycin: : R ≥ 8; S ≤ 4; Kanamycin: : R ≥ 8; S ≤ 4; Nalidixin acid: : R ≥ 32; S ≤ 16; Polymyxin B: : R ≥ 4; S ≤ 2; Streptomycin: : R ≥ 32; S ≤ 8; Sulfonamide: : R ≥ 512; S ≤ 128; Tetracycline: : R ≥ 8; S ≤ 4.
		56%	54%	0%	0%	0%	24%	2%	
		50 ppm copper							
		60%	58%	0%	0%	0%	20%	2%	

ID	Resistance to Copper	Other results	Comments
257	- Australian isolates high resistance to Cu and resistance is inducible - UK isolates with variable resistance and induction	- Copper resistance was transferable by conjugation from the new Australian isolates to <i>E. coli</i> K-12 recipients. - Copper resistance plasmids were non-identical - There is a DNA homology between the <i>pco</i> determinant and DNA from the U.K. <i>E. coli</i> , <i>Salmonella</i> sp., and <i>Citrobacter freundii</i> isolates - Transconjugants from one <i>E. coli</i> and one <i>C. freundii</i> donor, with <i>E. coli</i> K-12 strain UB1637 as a recipient, showed copper resistance levels and inducibility of resistance which differed from that expressed from plasmid pRJ1004	Authors conclude that closely related resistance determinants in nonidentical plasmids are responsible for copper resistance in enteric bacteria isolated at separate geographic locations. Authors proposed that <i>pco</i> and related sequences have transferred between strains now found in geographically distinct locations and that these determinants may be a widespread cause of copper resistance among the enterobacteria.

ID	Characteristics of the samples	Susceptibility to CuSO ₄	Occurrence of <i>pcoA</i>	Susceptibility to ZnCl ₂	Occurrence of <i>czcD</i>	Resistance to antibiotics	Comments
465	- Samples from 9 pig farms with each 4 barns at 2 stages in 4 replicates. - Of the 6162 <i>Salmonella</i> isolates confirmed, only 283 tested originating from: * Floor swabs (n=179) * Faeces (n=94)	134/283 isolates copper tolerant (MIC ≥24Mm); Isolates from faecal origin are significantly more tolerant than those originating from floor or feed samples	99/283 isolates; Carriage of the gene not significantly associated with copper tolerance	171/283 isolates zinc tolerant (MIC ≥8Mm);	85/283 isolates; Carriage of the gene significantly associated with zinc tolerance	Antimicrobial resistance very common; - 4415/4504 isolates from faecal samples resistant to one or more of the antimicrobials tested; - 3428/4504 were multidrug resistant (≥3 drugs)	For more detailed results of antimicrobial resistance patterns and serotypes we refer to the original text and tables.

	* Feed (n=10)					
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ID	Characteristics of the samples	Susceptibility to CuSO ₄	Resistance to antibiotics (cfu/g)					Comments
			Total number isolates	Tetracycline	Ampicillin	Apramycin	Nalidixic acid	
678	<i>E. coli</i> faecal samples from 8 intensively and 2 extensively reared pigs	No isolates grew on media supplemented with 10 mM Cu, indicating no resistance at this concentration and a lower MIC	<p>- No significant difference between <i>E. coli</i> isolated on media with or without 0.7mM cupric sulphate in the number of antibiotics to which an isolate was resistant. Neither in the resistance to 4 specific antibiotics tested (ampicillin, apramycin, nalidixic acid and tetracycline).</p> <p>- No absolute resistance numbers are provided. An estimation from the corresponding graph allowed to extract following figures that should be taken with caution (about the same results from isolates on media with and without CuSO₄):</p>					Data not provided in absolute numbers, only in graphs.
			Intensive 316 000	100 000	20000	32	10	
			Extensive 1 000 000	10 000	3160	32	10	

ID	Characteristics of the samples	Susceptibility to CuSO ₄ (resistance: MIC ≥ 8mM)	Resistance to antibiotics (MIC ≥ 50 mg/kg)	Comments
765	<i>E. coli</i> isolated from samples of piggery manures obtained from various farms and regions in Belgium	Coliforms in manure of: - copper-fed pigs: 0.13% resistant - copper-restricted pigs: 0% resistant (MIC ranged from 5.6 to 14.3 mM with median, chosen as arbitrary reference value, 8 mM)	The resistance against copper is accompanied in almost all cases by an increased resistance against several antibiotics. (no precise data displayed)	Only few data displayed. Further research is warranted for the distribution of antibiotic resistant Clostridia and the transfer of the resistance genes.

Methodological quality

The methodological quality of these studies is captured in Table 6. The main issues encountered were:

- Ref 13: useless for this review because only aggregated data of pig, broiler and cattle isolates were represented. Therefore, the population was not representative for this review question. Further, the external validity may be influenced by a bias in the selection of isolates;
- Ref 15: isolates from Denmark (pigs were sent to a diagnostic lab) and Spain (only vancomycin resistant strains) could be biased. The external validity was compromised. Pigs fed with different copper concentrations in each country which might not be representative for the review question;
- Ref 75: the external validity may be compromised due to the selection of samples. Isolates (from faeces but also from water and feed) did not represent the population of this review question;
- Ref 88: the external validity may be compromised by the way the samples were collected (biased due to post-mortem examination). Also, there is no information on the exposure to copper. The internal validity of this paper was good;
- Ref 95: the internal validity was good but the selection of the population was not well described (Barton *et al.* (2005), which could not be retrieved) and we cannot exclude a selection bias;
- Ref 108: the number of tested isolates per group in the 10 week trial varied. Not much information on the exposure to copper;
- Ref 149: the isolates were not only from faeces but also from the farm environment;
- Ref 220: internal validity is good but there is limited information on the exposure of copper. The origin of the samples is a bit unclear;
- Ref 257: there is a low number of isolates tested, the selection of isolates may be biased and the exposure to copper remained unclear;
- Ref 465: the external validity may be compromised due to the selection of the farms (biased due to selection based on history of *Salmonella* occurrence). There is an inconsistency between the values displayed in the text and in table 2;
- Ref 678: unclear how many isolates per pig were tested and unbalanced number of pigs per treatment group (8 intensive versus 2 extensive). Laboratory tests could be improved. Overall a confusing text with only few data mentioned in the results and discussion;
- Ref 765: materials and methods poorly described which results in a lack of clarity on the amount of samples analysed, performed analyses and statistics.

It should be noted that a statistical analysis was only performed in two studies (75, 465). The neutral faces (Table 6) assigned to the two questions about the confidence interval and the appropriateness of the statistical design for all other studies indicate that there was no statistical analysis performed.

Table 6: Assessment of the methodological quality of the cross-sectional studies

ID	Aarestrup & Hasman (2004)	Aarestrup <i>et al.</i> (2002)	Chuanchuen <i>et al.</i> (2008)	Dutta & Devriese (1981)	Fard <i>et al.</i> (2011)	Gedek (1981)	Koowatananukul <i>et al.</i> (2010)	Siebert (1982)	Williams <i>et al.</i> (1993)	Medardus <i>et al.</i> (2014)	Blake (2002)	Huysman <i>et al.</i> (1988)
Is the study adequately powered to meet the objectives ?												
Were the isolates/pigs (subpopulation selected for the study) representative of the target population object of the systematic review question												
The same methods/procedures (sampling of pigs or processing the isolates) are applied to all the samples?												
Were laboratory tests used to determine the outcome adequate?												
Are there prevalence (or proportion) values given?												
Is the confidence interval given?												
Appropriateness of the statistical analysis for the design?												
Were withdrawn/missing data (if any, with respect to the sample size initially calculated) reported and taken into consideration in the analysis?												
Were the estimates and measures of variability used to address the research question presented?												

4. Conclusions

The total number of studies managed during the first SLR was very low (only 22 studies). The current update of this review could add eleven more. This resulted in 11 field studies, 10 environmentally controlled studies and 12 cross-sectional studies. Furthermore, the methodological quality of the studies for the purpose of the present review was in general inadequate. From the eleven field studies, only three showed a good methodological quality. If all field studies are considered, the relation between copper supplementation and copper resistance appears equivocal. However, when only the results of the three studies with good methodological quality are evaluated, it can be concluded that an increased supplementation of copper (125 ppm compared to 16.5 ppm and 208 ppm compared to 6.4 ppm) will result in an increased resistance to copper sulphate of the enterococci population of piglets. In general *E. faecium* strains are more likely to acquire copper resistance than *E. faecalis* strains. In addition, the presence of the *tcrB* gene seems to correlate well with copper resistance. The transferability of the *tcrB* gene to enterococci from the same or other species was demonstrated.

Resistance to erythromycin is most probably associated with this acquired copper resistance. The co-selection of copper and erythromycin became evident from the environmentally controlled studies as well. Both resistance genes are present in close proximity on the same plasmid, which makes co-transfer of both genes plausible. This close genetic proximity is also the case for vancomycin and copper resistance, although the field studies did not result in conclusive evidence that copper resistance is associated with vancomycin resistance.

These conclusions only concern gram positive bacteria. Reliable data regarding gram negative bacteria and especially *E. coli* are very scarce. According to our general impression, feeding elevated copper levels and the presence of the *pcoD/A* gene are presumably not related to higher copper resistance.

All the cross-sectional studies showed rather poor methodological quality. This was mainly due to the selection of isolates that was biased or not representative for this review question or because of the limited information on the copper levels to which animals were exposed. Therefore, it is very difficult to draw conclusions from these studies.

To conclude, the limited number of studies available from the SLR, and the limitations in terms of results and methodological quality do not unequivocally allow to demonstrate the absence of a correlation between copper supplementation above requirements and development of antibiotic resistance in pigs under commercial farm practices. In addition, there is undoubtedly a genotypic relationship between both. More field studies are needed to address the issue, especially for the gram negative bacteria. For the time being, and in view of the inconclusive results, the recommendation might be not to increase the levels of copper supplemented in feed above allowances. Furthermore, considering the increasing research and interest on the matter in the latest years, it is recommended to repeat the SLR in future considering new approaches, if necessary.

5. General Remarks

As stated above it appears that the research matter has recently raised the interest of scientists, since many of the relevant papers have been published in the latest years. It can be expected that additional studies will be published in the coming years.

While implementing this systematic literature review some suggestions or remarks were raised:

- The methodological quality of the papers was generally judged to be low for the present review. It might be opportune to update the protocol and subsequently revise the methodological quality assessment of the relevant studies. It is suggested to construct a specific form for the environmentally controlled studies, of which currently the methodological quality was not evaluated. In general, the revision of the questions in the methodological quality assessment is also suggested, to adapt the forms to the specificities of animal nutrition studies.

- It was decided to include exclusively pig studies (including piglets) in this review, because piglets belong to the category of animals in which highest copper levels are authorised and used in feed. However, with this limitation of species, some information might have been lost. It may be worthwhile to consider also other animal species in a potential continuation of this SLR. Other animal species in which the level of copper usage is lower, could e.g. provide information on the level of baseline resistance.
- As became apparent from the studies, the definition of copper resistance is controversial. There is a lack of agreement on the threshold value.

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Glossary

Cross-sectional study	Observational study which report on the prevalence of copper and/or antibiotic resistant gut microbiota originating from copper exposed pigs
Environmentally controlled study	Experimental study that did not apply a copper intervention to pigs. Studies that aimed to ascertain the mechanism of resistance
Field study	Experimental study conducted with pigs that receive copper and are followed up for several weeks to assess the appearance of resistant isolates to copper and/or antibiotics
<i>tcxB</i> gene	a plasmid-borne transferable copper resistance gene found in some gram positive bacteria
<i>pco</i> gene	a plasmid-borne copper resistance determinant consisting of seven genes (<i>pcoABCDRSE</i>) identified in some gram negative bacteria

Abbreviations

ADG	Average daily gain
BW	Body weight
EFSA	European Food Safety Authority
MIC	Minimum inhibitory concentration
SLR	Systematic literature review

Appendix A – Pilot study and Preliminary Study Selection

Testing of the Eligibility Criteria

Following 19 references were used to assess the eligibility criteria:

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First remarks after examination of the dataset:

- One duplicate reference was found, namely 5 is the same study as 13.
- From some references (2, 4, 6, 7, 10, 11, 12, 14, 16), full text could not be retrieved by the contractor of Ghent University. Assessment was based on title and abstract only.
- From some references (2, 4, 10, 14), no abstract could be retrieved by the contractor of Ghent University. These references were further excluded from the assessment.

First criteria: Available as of 1980 onwards: This criteria was captured by the search process, so all references complied to it.

Second criteria: They are primary research studies: Most references are primary research studies, except reference 14 (proceedings, could be primary research) and reference 11 (review).

Third criteria: Full-text documents in English, French, Italian, Spanish and German: All references for which full-text could be retrieved met the language criteria. For references where only title and/or abstract is available, this remained unclear.

Fourth criteria: The Population is gut microbiota in pigs and piglets: Reference 15 studies the microbiota in poultry, not pigs. Reference 8 concerns the characterisation of the *tcxB* gene in an *Enterococcus faecium* strain, but it is not clear from the abstract if this strain is isolated from pig. After examination of the full text, it became clear that it is a pig isolate.

Fifth criteria: The Intervention/Exposure is copper, administered through feed and/or water: Based on title and abstract only, it was very difficult to conclude if copper was administered to the feed or water in several references (1, 5, 9, 18, 19). After assessing the full text, it was clear copper was added to the feed of the pigs in references 1, 9 and 19. In reference 5, composition of the diet was referred to another study.

Sixth criteria: The Outcome of interest is any resistance or susceptibility to copper and/or antimicrobial agents of gut microbiota: References 3 and 18 did not concern resistance of gut microbiota after administration of copper. Reference 3 reports on the effect of copper on electrophysiological response to glucose and chloride secretagogues. Reference 18 reports on heavy metal and bacterial contamination between swine farms.

Adaptation of the Table for Data Extraction

After assessing the eligibility criteria, six references (because full text was available) were used to test data extraction. The references used were 1, 5, 8, 9, 17, 19. Based on these references, changes on data that needs to be extracted or can be removed from Table 6 (data extraction) in the protocol are made.

Reference 1

Methods: most data about methods is extracted through Table 6. The copper susceptibility test was performed on gradient agar plates. Detection of *tcrB* gene and other antimicrobial resistance genes was performed with PCR.

- **Population:** only *Enterococcus faecalis* and *Enterococcus faecium* strains were used. Data that is not extracted is the country from which the pig isolates originated. This is of importance since different regulations in different countries determine the concentration of copper and antibiotics allowed in the feed. This should be included in Table 6.
- **Intervention:** this is not clearly indicated in the study. Only mentioning of the concentrations of copper in the feed that is allowed in the specific countries.
- **Outcomes and results:** first, it was determined if isolates were susceptible to copper. Second, if they possess the *tcrB* gene. This was done to confirm if this gene is responsible for copper resistance. Both outcomes should be clearly separated in Table 6. Presence of other antimicrobial resistance genes was investigated, however, susceptibility to these antibiotics was not determined.

Reference 5

- **Methods:** in this study, only enterococci were isolated and were identified using biochemical tests and PCR. It is important to extract the method of isolation in order to identify if a specific genus was targeted or not. Further, the identification of the isolates is of importance and should be extracted. Antimicrobial resistance was tested by agar dilution method and the genes were detected by PCR.
- **Intervention:** this is not clearly indicated in the study.
- **Outcomes and results:** all results are extracted using Table 6.

Reference 8

- **Methods:** this study describes the *tcrB* gene, which was identified to be part of an operon called *tcrYAZB* operon.
- **Outcomes and results:** putative promoter- and repression binding sites were found, which may help in understanding the regulation of expression of this gene. Although this study does not directly investigate the relation between copper in the diet and resistance, it gives interesting information about the mechanism behind resistance. Data of these type of studies may be extracted in a second stage.

Reference 9

- **Methods:** the copper susceptibility test was performed on gradient agar plates and MIC was determined. Detection of *tcrB* gene was performed with PCR. Transferability of copper and other antibiotics to resistant pig isolates was assessed. This difference between transfer of copper and/or transfer of other antimicrobial resistance should be more extensively dealt with in Table 6. Also, data about susceptibility of the transconjugants needs to be extracted in order to compare this with the resistant strains.
- **Population:** only *E. faecium* strains were investigated. How strains were isolated is referred to other studies. Strains were identified to strain level with PFGE (pulsed field gel electrophoresis) to detect if resistant isolates are all the same strain and if resistance is limited to specific strains. This data should be extracted as well.
- **Intervention:** this is not clearly indicated in the study. Only mentioning of the concentrations of copper in the feed that is allowed.

- **Outcomes and results:** it was determined if isolates were susceptible to copper and if they have the *tcxB* gene. Both outcomes should be clearly separated in Table 6. Based on conjugation assay, it was clear that other antibiotic resistance genes co-transferred with the copper resistance gene. This suggested a correlation between the presence of copper resistance and resistance to other antibiotics. Also, MIC of transconjugants was determined. This data should be included in Table 6 as well. Further, the gene location on a plasmid, together with other antibiotic resistance genes on this plasmid was determined. It could be interesting to extract this type of data as well.

Reference 17

- **Methods:** fecal samples were collected and coliforms were isolated. Antibiotic resistance and MIC were determined by agar dilution method.
- **Population:** weanling pigs, 21 d of age, were used.
- **Intervention:** a 42 d trial was performed to compare effects of copper, but also zinc and in-feed antibiotic, on antibiotic resistance.
- **Outcomes and results:** it was investigated if supplementation of copper, zinc or in-feed antibiotics affected the number of coliforms isolated. Further, it was investigated if a copper-zinc interaction on antibiotic resistance was present. This extraction of data needs to be added to Table 6. If present, the type of microbiota isolated in relation to the supplementations of the diet is important to extract. Also, the relation between duration of supplementation and/or time of sampling and the type of microbiota isolated and its resistance is important to extract.

Reference 19

- **Methods:** pig isolates from Australia and UK were tested for resistance to copper by gradient agar plates. Transferability of copper and other antibiotics was tested by conjugation assay. Detection of copper resistance gene was performed by DNA-DNA hybridization and PCR.
- **Intervention:** this is not clearly indicated in the study.
- **Outcomes and results:** the copper resistance gene was located on a plasmid and was linked to a tetracycline resistance marker. It could be interesting to extract this type of data as well.

Preliminary Study Selection

The flow diagram of this preliminary study selection is represented in Figure 4.

From the 270 references, 43 duplicate references were found. Based on the title and abstract, the remaining 227 references were classified into three categories:

- a) Yes, suitable for SR;
- b) No, not suitable for SR;
- c) Doubtful.

To category 'a', eight references were assigned, which are included for SR. To category 'b', 198 references were assigned, which are excluded for SR. To category 'doubtful', 21 references were assigned to. For the references in the category of 'doubtful', full-text documents were retrieved and examined to assess if references were:

- i) suitable for SR;
- ii) not suitable for SR;
- iii) no full text could be retrieved.

To category 'i', 11 references were assigned, which are included for SR. To category 'ii', two references were assigned, which are excluded for SR. To category 'iii', eight references were assigned.

The main step where references were excluded was that they did not meet eligibility criteria 4 (population of gut microbiota in pigs). This was the case for 160 references. For example, these references reported on copper requirements or intoxication in plants. In 13 references, the language criteria (eligibility criteria 3) were not fulfilled. In some references, the intervention was not copper (eligibility criteria 5) or they did not report on the outcome of interest, i.e. resistance (eligibility criteria 6).

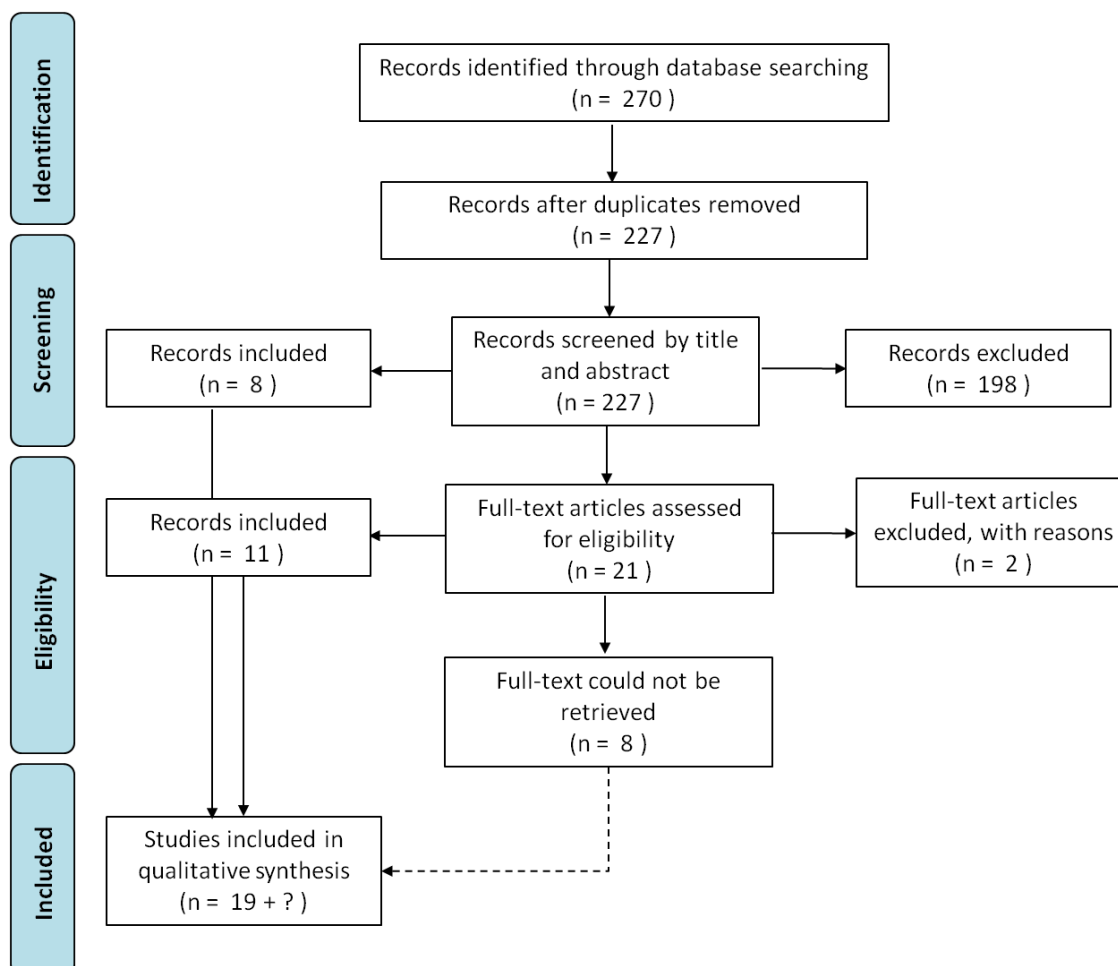


Figure 4: Flow diagram preliminary study selection

Lists of references from the preliminary study selection

• Category i: suitable for SLR

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• Category ii: not suitable for SLR

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- **Category iii: doubtful**

After a second checking and agreement between reviewers, these studies could be classified in these three subgroups

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Appendix B – Lists of included/excluded references using web-based software

Records Included

Field studies

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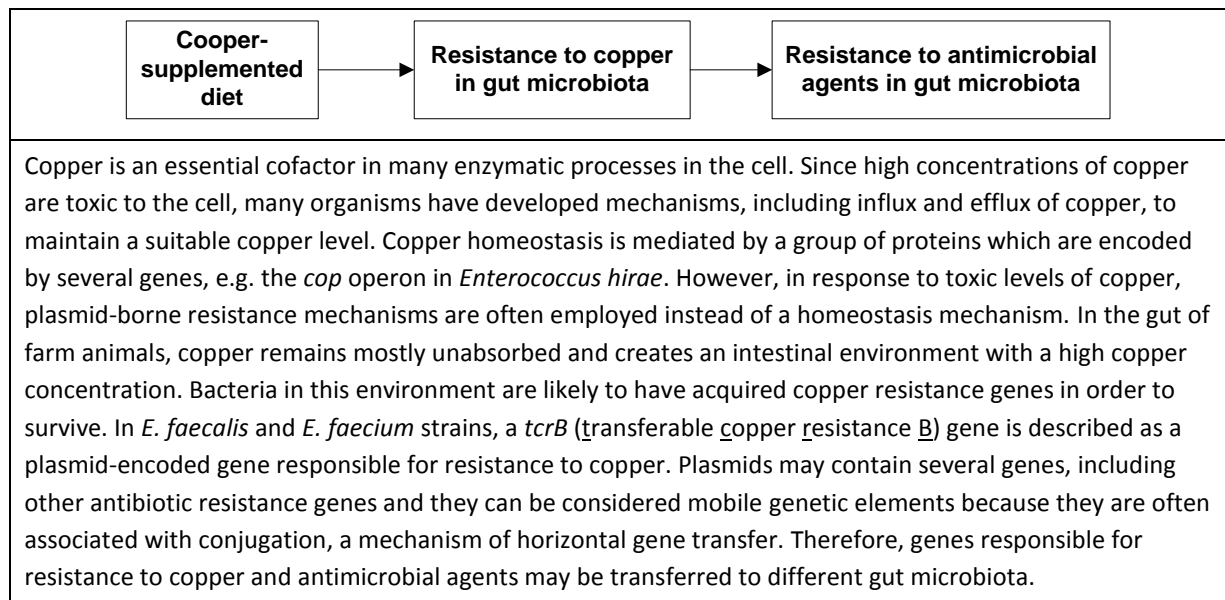
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Annex A – Updated protocol of the systematic review of Influence of Copper on antibiotic resistance of gut microbiota in pigs (including piglets)

Background

In the context of the mandate on maximum copper content in complete feed¹ the working group on “Revision of maximum content of copper in feed” of the FEEDAP Panel considered necessary to conduct a systematic review (SR) on the influence of copper on antibiotic resistance of gut microbiota on pigs (including piglets).

Figure 1: How copper might work



Drawing upon a previous SR performed in 2012 in the context of the mandate on the re-evaluation of copper as feed additive² the current document describes the protocol for conducting the systematic review on the influence of copper on antibiotic resistance of gut microbiota on pigs (including piglets).

The whole SR conducted in 2012 is available in EFSA in terms of literature collected, screening results, data extraction and methodological quality appraisal. The scope of the contract will be to update the previous SR considering the period since 2012 and additional grey literature. Articles already identified during the 2012 SR will not be processed anymore.

¹ <http://registerofquestions.efsa.europa.eu/roqFrontend/questionsListLoader?mandate=M-2015-0130>

² http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/2969.pdf

Review question

“Influence of copper on antibiotic resistance of gut microbiota on pigs and piglets”.

Objectives of the review

To assess the potential of copper (as feed additive/supplement) to increase antibiotic resistance of gut microbiota in pigs (including piglets).

Criteria for assessing study relevance (i.e. eligibility criteria for study selection)

The criteria that will be applied to select the studies that are to be included in or excluded from the review are described in Table 1. They were pilot tested in the previous 2012 SR.

Table 1: Eligibility criteria for studies

#	Studies will be included in the review if presenting the following characteristics ³
1.	Available as of 1980 onwards
2.	They are primary research studies ⁴
3.	<p>Study types:</p> <p>a) <i>Experimental studies</i> assessing the resistance/susceptibility to copper OR to antimicrobial agents OR both of gut microbiota in pigs/piglets that are given a copper-supplemented diet;</p> <p>b) <i>Experimental studies</i> ascertaining the mechanism of resistance.</p> <p>c) <i>Experimental studies</i> that assess aspects a) and b).</p> <p>d) <i>Descriptive cross-sectional studies</i> on the prevalence of copper and/or antibiotic resistant gut microbiota in pigs (and piglets) exposed to copper diet will be included as they can provide complementary information.</p>
4.	Full-text documents in English, French, Italian, Spanish and German for papers extracted from electronic databases. All EU languages for not published papers requested to EU countries (see point 1 of “Methods foreseen for performing the systematic review”).
5.	The Population is pigs (e.g. >12 weeks) and piglets (e.g. 0-12 weeks)
6.	<p>The Intervention (and, for cross-sectional studies, Exposure) is:</p> <p>a. Copper</p> <p>b. Way of administration: feed (additive/supplement) and/or water</p> <p>Studies including the intervention/exposure of interest (copper as feed additive) combined with another intervention/exposure (e.g. other feed additives) will be included.</p>
7.	<p>The Outcome of interest is:</p> <p>a. Any resistance or susceptibility (including “none”) to copper of gut microbiota and/or</p> <p>b. Any resistance or susceptibility (including “none”) to antimicrobial agents of gut microbiota</p> <p>c. (For descriptive cross sectional studies) prevalence of copper and/or antibiotic resistant gut microbiota</p>

³ As for the information sources (e.g. bibliographic databases) foreseen to be searched, see section 1 of “Method foreseen for performing the systematic review”.

⁴ A primary research study is the original study in which data are produced. The term is sometimes used to distinguish such studies from secondary research studies (e.g. reviews) that re-examine previously collected data (EFSA, 2010b).

Method foreseen for performing the systematic review

1. Searching for research studies

The search process will aim at retrieving primary research studies relevant to the review question as described above.

Search strategy: the search strategy is displayed in Table 2.

Information sources:

- Published scientific literature will be searched using the following four bibliographic databases: Web of Science (WoK), CCC (WoK), CABI (WoK) and FSTA (WoK).
- Grey literature will be searched using the following databases: Système Universitaire de Documentation (SUDOC), Trove, International information system for the Agricultural Sciences and Technology (AGRIS), Global ETD search, OpenGREY.
- In addition relevant non-published studies (e.g. national reports) will be requested to the relevant European countries (including European Union (EU) Member States (MS) and EEA/EFTA countries) through a survey that will be managed by the EFSA FEED unit.

Due to the limited time and resources information sources other than the above mentioned will not be searched.

The search will be performed by EFSA staff that will then merge the search results using appropriate reference management software (i.e. EndNote®) and remove duplicate records.

The possible studies retrieved from grey literature or received from the EU MS will be inserted into the reference management software by EFSA staff (FEED unit). The papers received from the European relevant countries will be identified already in their title so that different language eligibility criteria can be applied for papers extracted from electronic databases and for not published papers received from European countries (see above point 4, Table 1).

The new information retrieved will then be uploaded by EFSA staff (AMU unit) into the systematic review system (DistillerSR, Evidence Partners, Ottawa, Canada) where the results of the previous SR are already available.

An additional check for duplicate records will be performed by EFSA staff (AMU unit) in order to upload only studies that were not considered in the previous SR.

Table 2: bibliographic databases and search strategy to be applied

Name	Timespan of the database	Search strategy to be applied*
Web of Science™ Core Collection (Editions=SCI-EXPANDED, SSCI. Interface= Web of Science)	1975-present	(1)
Current Contents Connect® (Editions= all. Interface= Web of Science)	1998-present	(1)
CABI : CAB Abstracts® (Interface= Web of Science)	1910-present	(1)
FSTA® - the food science resource (Interface= Web of Science)	1969-present	(1)
Medline® - (Interface= Web of Science)	1946-present	(2)
Système Universitaire de Documentation (SUDOC) http://www.sudoc.abes.fr	18xx-present	(3)
Trove http://trove.nla.gov.au	Not specified	(4)
International information system for the Agricultural Sciences and Technology (AGRIS) http://agris.fao.org/	1975-present	(5)
Global ETD search http://search.ndltd.org/	1900-present	(6)
OpenGREY http://www.opengrey.eu/	1990-present	(7)
N°	*Search strategy details	
(1)	Topic=(Boar\$ OR gilt\$ OR hog\$ OR pig\$ OR piglet\$ OR porcine OR sow\$ OR swine OR sus) AND Topic=(intestinal OR gut* OR entero* OR (supplement* OR additive\$ OR diet* OR food OR feed OR treatment OR medicine) OR flora OR bacteria) AND Topic=(Copper* OR cupric OR cuprous) AND Topic=(Susceptibility OR toleran* OR resistan* OR tcrB OR transferable OR "selection pressure") Timespan=1980-2015. Lemmatization=On	
(2)	Topic - Add MeSH=(Boar\$ OR gilt\$ OR hog\$ OR pig\$ OR piglet\$ OR porcine OR sow\$ OR swine OR sus) AND Topic - Add MeSH =(intestinal OR gut* OR entero* OR (supplement* OR additive\$ OR diet* OR food OR feed OR treatment OR medicine) OR flora OR bacteria) AND Topic - Add MeSH =(Copper* OR cupric OR cuprous) AND Topic - Add MeSH =(Susceptibility OR toleran* OR resistan* OR tcrB OR transferable OR "selection pressure") Timespan=1980-2015. Lemmatization=On	
(3)	copper ET pig* OU swin* ET antib* resist*	
(4)	(copper AND (pig* OR swin*)) AND ("antibiotic resistance" ~ 1)	
(5)	copper AND pig* OR swin* AND antib* resist*	
(6)	copper AND (pig* OR swin*) AND (antib* resist*)	
(7)	copper AND pig* OR swin* AND antib* resist*	

2. Selecting the studies

The study selection process and all the other steps of the SR process will be performed using the systematic review system (DistillerSR, Evidence Partners, Ottawa, Canada) where the results of the previous SR are already available and the forms for study selection, data extraction and appraisal of methodological quality are already defined.

The contractors will be given access to the system by EFSA.

The stepwise selection process and related responsibilities are described in Table 3 here below.

Table 3: study selection process

#	WHAT	WHO
1.	Examine titles and abstracts to remove obviously irrelevant citations (reviewers must be over-inclusive at this stage). Disagreements will be solved by discussion between the two reviewers. In case of doubts the paper will proceed to data extraction. Moreover, in case the reply from both reviewers will be neutral ("Cannot tell" in the Distiller form) a decision shall be taken by discussion between them and the answers shall be changed in line with the decision.	In parallel by 2 mutually independent reviewers per reference (one Contractor and one EFSA staff).
2.	Retrieve full-text documents of the potentially relevant citations. If within 15 days from the beginning of the search the full text is not found the paper will be marked as not available.	EFSA staff.

Additional information on how the study selection process will be undertaken:

1. Reviewers will be domain experts and experts with broader expertise in feed safety.
2. The records will not be blinded for e.g. authors names, journal etc. The study selection will be performed in parallel by 2 mutually independent reviewers per paper (one Contractor and one EFSA staff).

3. Collecting the data from the included studies

The methodology that will be applied for the data extraction process is summarised as follows:

- 3.1 The data that will be extracted from the included studies are illustrated in Table 4. They were pilot tested in the previous systematic review and the data extraction form is already available in DistillerSR.

- 3.2 The data extraction will be performed in parallel by 2 mutually independent reviewers per paper (one Contractor and one EFSA staff).
- 3.3 Disagreements will be solved by discussion between the two reviewers. In case of doubts the paper will be put to the attention of the FEED working group in charge of the assessment that will decide on the data to be extracted.
- 3.4 Full-text documents written in a language not readable by the reviewers will be put to the attention of EFSA and will be translated in English by EFSA.
- 3.5 Studies published more than once in multiple reports will be identified and included only once in the final review.

Table 4: Data to extract from the included studies

Category	Data to extract	Definition/Unit of measurement /Comment
Methods	1. Study type	<p>The study is</p> <p>(a) Experimental Study, including</p> <p>(i) association between copper supplemented in diet and copper resistance/tolerance in gut-flora;</p> <p>(ii) association between copper supplemented in diet and gutflora antimicrobial resistance/tolerance; or</p> <p>(iii) both aspects;</p> <p>(b) Descriptive cross-sectional study (i.e. on prevalence of copper and/or antimicrobial resistance)</p>
	2. Study settings	<p>The settings may be:</p> <p>(i) Field experimental study: in vivo studies with an intervention and follow-up.</p> <p>(ii) Environmentally controlled studies: laboratory studies (animals not directly involved) aimed to determine either the mechanism of action, the genes involved, etc.</p> <p>(iii) Other</p> <p>[Not Applicable for descriptive cross-sectional studies]</p>
	3. Randomisation of treatments?	<p>Yes/No/Unclear</p> <p>[Not Applicable for descriptive cross-sectional studies]</p>
	4. Experimental unit	<p>Pen (pigs per pen)/pig/Other</p>

Category	Data to extract	Definition/Unit of measurement /Comment
		[Not Applicable for descriptive cross-sectional studies]
	5. Number of treatments	Number is known/Unclear [Not Applicable for descriptive cross-sectional studies]
	6. Replications	Yes/No/Unclear [Not Applicable for descriptive cross-sectional studies]
	7. Blocking	Yes/No/Unclear [Not Applicable for descriptive cross-sectional studies]
	8. Sampling schedule	How many sampling weeks/How many samples per week/how many samples per day [Not Applicable for descriptive cross-sectional studies]
	9. Method for detecting copper susceptibility/resistance	Agar dilution method/Other/Not performed
	10. Presence of <i>tcrB</i> gene in DNA?	Yes/No/Not specified
	11. Presence of other genes besides <i>tcrB</i> responsible for copper resistance	Yes[Specify the name of the gene (open field)]/No/Not specified
	12. Method for detecting antibiotic susceptibility/resistance	Agar dilution method/Other/Not performed Determination of the antibiotic concentration (in mM) at which growth of microorganisms is inhibited. Usually performed <i>in vitro</i> with agar dilution method
	13. Method for assessing the transferability of the copper resistance gene	Open field Are copper susceptible strains after a conjugation assay resistant to copper? Determination <i>in vitro</i> with agar dilution method or confirming the presence of a resistance gene with PCR

Category	Data to extract	Definition/Unit of measurement /Comment
		If information is available, to assess if the gene is located on plasmid or not
	14. Method for assessing the transferability of the other antibiotic resistance genes besides copper resistant	Open field To check if other resistance genes are co-transferred or not with copper resistance gene? Determination <i>in vitro</i> with agar dilution method or conforming the presence of a resistance gene with PCR
	15. Date of study	DD/MM/YYYY Sample collection period. In case it is not indicated, the date of first submission of the study to the scientific journal.
Population	1. Age group (i.e. pigs or piglets) Isolates	Pigs:>12 weeks; piglets: 0-12 weeks; not available/Isolate/Other Isolates: Applicable to descriptive cross-sectional studies
	2. Country	Denmark/Spain/Sweden/Other
	3. Type of microbiota/bacteria isolated	Enterococci/E.coli/Salmonella/Staphylococci/Other Which microbiota was isolated from the samples? Was it selective towards only one/some specific genus e.g. enterococci, <i>E. coli</i> ? What method was used? Gram+; Gram-; and specific bacterium
	4. Identification of microbiota	Species level/Strain level/Other/Not performed E.g. 16S PCR, PFGE (pulsed field gel electrophoresis),...
	5. Antibiotics for which susceptibility/resistance is tested for	Avilamycin/bacitracin/chloramphenicol/erythromycin/gentamicin/kanamycin, penicillin/ quinupristin-dalfopristin/ streptomycin/tetracycline/vancomycin,/virginiamycin/other

Category	Data to extract	Definition/Unit of measurement /Comment
Intervention / Exposure	1. Intervention 1 (Copper)	Compound (Name and/or formula) E.g. Copper sulfate (use the name of the compound and formula)) Dose (In ppm or mg/Kg) Other Name with Letters “a” to “n” the groups of treatments [Not Applicable for descriptive cross-sectional studies]
	2. Intervention 2 (Copper and Zinc)	Compound (Name and/or formula) E.g. Copper sulfate (use the name of the compound and formula)) Dose (In ppm or mg/Kg) Other Name with Letters “a” to “n” the groups of treatments [Not Applicable for descriptive cross-sectional studies]
	3. Intervention 3 (Copper and Antibiotics)	Compound (Name and/or formula) E.g. Copper sulfate (use the name of the compound and formula)) Dose (In ppm or mg/Kg) Other Name with Letters “a” to “n” the groups of treatments

Category	Data to extract	Definition/Unit of measurement /Comment
		[Not Applicable for descriptive cross-sectional studies]
	4. Intervention 4 (Control - Describe)	Compound (Name and/or formula) E.g. Copper sulfate (use the name of the compound and formula)) Dose (In ppm or mg/Kg) Other There is a minimum dose of Copper (animal requirements) [Not Applicable for descriptive cross-sectional studies]
	5. Duration of the treatment	In weeks [Not Applicable for descriptive cross-sectional studies]
	6. Exposure	Compound Dose used, if available Other [Not Applicable for experimental studies]
Outcomes	1. Occurrence of copper susceptible/resistant bacteria	Number of cases and denominator (sampled pigs)/which species or strains/% isolates or inadequately reported/other
	2. Occurrence of copper resistant bacteria at different sampling times	Number of cases and denominator (sampled pigs)/which species or strains/% isolates or inadequately reported/other

Category	Data to extract	Definition/Unit of measurement /Comment
	3. Occurrence of copper resistant bacteria in different treatment groups	Open field Specific selection towards certain species/strains. Influence of other additives (Zinc, antibiotics in feed) on species/strains isolated?
	4. Copper resistance/susceptibility: MIC	Open field Mean Minimum inhibitory concentration (MIC) of copper (expressed in mM; CI) for copper resistant and susceptible isolates; significance of the difference (p value)
	5. Occurrence of <i>tcrB</i> gene in copper resistant strains	Open field (specify yes or not)
	6. Occurrence of bacteria resistant to antibiotics	Open field Number of cases and denominator (sampled pigs), which genes e.g. <i>erm(B)</i> , <i>tet(M)</i> , <i>van(A)</i> , <i>van(B)</i> , or inadequately reported
	7. Antibiotic resistance/susceptibility:MIC	Open field Mean Minimum inhibitory concentration (MIC) of antibiotic
	8. Occurrence of antibiotic genes in <i>tcrB</i> -positive and <i>tcrB</i> -negative isolates	Open field Link between copper resistance and other antibiotic resistance
	9. Transferability of the <i>tcrB</i> gene	Open field To which species. Co-transfer of other resistance genes.

Category	Data to extract	Definition/Unit of measurement /Comment
	10. Copper and antibiotic: resistance/susceptibility in conjugants:MIC	Open field Mean Minimum inhibitory concentration (MIC)
	11. Mechanism of copper resistance?	Open field
Miscellaneous	1. Funding source	Open field
	2. Key conclusions of the study authors	Open field
	3. Miscellaneous comments from the study authors	Open field
	4. References to other relevant studies	Open field
	5. Correspondence required	Open field
	6. Miscellaneous comments by the review authors	Open field

4. Assessing the methodological quality of the included studies

The aim of this step is to appraise the internal validity (i.e. risk of bias) of the studies included in the review.

However, due to a high variability of the studies identified as relevant already in the previous SR, it was decided to describe study quality considering the overall methodological quality of the studies (i.e. considering e.g. also study power, or adequateness of the statistical analysis). The appraisal of methodological quality form is already available in DistillerSR.

The methodology that will be applied for assessing the methodological quality is summarised as follows:

1. Full-text documents that pass the eligibility criteria will be assessed using the checklists illustrated in Table 5 and Table 6, for experimental studies and cross-sectional studies, respectively.
2. The methodological quality assessment will be performed in parallel by 2 mutually independent reviewers per paper (one Contractor and one EFSA staff).
3. Disagreements will be solved by discussion between the reviewers. In case of doubts the paper will be put to the attention of the FEED working group in charge of the assessment that will decide on the appraisal.

Experimental studies with an environmentally controlled setting are highly variable and provide information aimed at determining e.g. the mechanism of action, the genes involved etc. of a possible antibiotic resistance. They do not provide information able to establish a correlation between the use of copper (as feed additive/supplement) and antibiotic resistance of gut microbiota in pigs (including piglets). It was hence decided to consider these studies as supporting information in case such a correlation is identified and to not submit them to methodological quality assessment.

Table 5: Checklist for assessment of the methodological quality of Experimental Studies

	Quality item	Coding	Explanation
Objectives and Study Population	Is the study adequately powered to meet the objectives ?	Yes	Yes: Use of sample-size formulas, based on desired power or precision and estimate of expected variability to detect differences.
		Partial	Partial: Informal guesses of a sample size or not enough information to reproduce sample size.
		No	No: No details in the text.
		Other	
Intervention (treatment allocation, blinding)	Were experimental units randomly assigned to the treatment groups?	Yes	Yes: computer or random numbers table, a-priori assignment of tagged numbers, alternation or systematic allocation,...
		Partial	Partial: 'randomized' or randomly allocated without explanation, a day assignment.
		No	No
	Prior to the intervention, were the outcomes tested (measurement at base line)?	Yes	Yes
		No	No
		Other	
	Were the interventions clearly described to enable	Yes	Yes

	reproducibility?	No Other	No
	Were groups treated evenly, apart from the intervention?	Yes No Other	Yes No
	Was an appropriate control group used?	Yes No Other	Yes No
	Was the outcome assessor appropriately blinded to the intervention status of the treatment units?	Yes No Other	Yes No
Outcomes	Were laboratory tests used to determine the outcome described and adequate?	Yes No Other	Yes No
	Was the time from the administration of the intervention until the end of the study sufficient to meet the objectives of the trial?	Yes No	Yes: Study allows enough time to observe the outcome of interest after the intervention is performed (a minimum of 5 weeks was considered enough). No

		Other	
Withdrawals and loss to follow-up	Were withdrawn/missing data reported and taken into consideration in the analysis?	Yes Partial No Other	Yes: Numbers stated or deducible from tables and reasons provided for each group or no losses. Partial: numbers but not reasons (or vice versa). No
	Was the proportion of lost to follow-up adequate?	Yes No Other	Yes: Percentages of lost of subjects <15%. No: >15% or not described.
Statistical analysis	Appropriateness of the statistical analysis for the design?	Yes No Other	
	Were the estimates and measures of variability used to address the research question presented?	Yes No Other	Yes: parameter estimates + measure of variability or P value provided or sufficient data provided for post-hoc corrected statistics. No

Note: Randomisation will be essential for a study to be considered of good methodological quality.

Table 6: Checklist for assessment of the methodological quality of cross-sectional studies

	Quality item	Coding	Explanation
Objectives, study population and Sampling	Is the study adequately powered to meet the objectives?	Yes Partial No Other	Yes: Use of sample-size formulas, based on desired power or precision and estimate of expected variability to detect differences. Partial: Informal guesses of a sample size or not enough information to reproduce sample size. No: No details in the text.
	Were the isolates/pigs (subpopulation selected for the study) representative of the target population object of the systematic review question?	Yes No Other	Yes No
Exposure	The same methods/procedures (sampling of pigs or processing the isolates) are applied to all the samples?	Yes Unclear No Other	Yes: specifically mentioned in the text Unclear: no information provided on it No: specifically mentioned in the text
Methods	Were laboratory tests used to determine the outcome adequate?	Yes Not described No	Yes Not described No

		Other	
	Are the prevalence (or proportion) values given?	Yes No Other	Yes No
	Is the confidence interval given?	Yes No Other	Yes No
Statistical analysis	Appropriateness of the statistical analysis for the design?	Yes No Other	Yes No
	Were withdrawn/missing data (if any, with respect to the sample size initially calculated) reported and taken into consideration in the analysis?	Yes Unclear No Other	Yes: withdrawn/missing data reported Unclear: sample size was not calculated at the beginning No: withdrawn/missing data not reported
	Were the estimates and measures of variability used to address the research question presented?	Yes No Other	Yes: parameter estimates + measure of variability or P value or sufficient data provided for post-hoc corrected statistics. No

Note: Representativeness of the study subpopulation for the target population object of the systematic review question will be considered essential for a study to be considered of good methodological quality.

5. Synthesising the data from the included studies

The study results for the whole updates SR will be synthesised separately according to the study type, i.e. experimental and cross sectional by the contractor as the cross-sectional studies do not answer the review question and simply provide complementary information on the prevalence of antibiotic or copper resistance in microbiota of copper-fed pigs.

For this systematic review, a meta-analysis of the results of the experimental studies will not be feasible since the study designs and outcome definitions among studies will be too heterogeneous to be combined into one pooled estimate. Therefore, a narrative synthesis of the evidence is more adequate than a meta-analysis. The results will be structured in tables or through graphical methods (forest plot) or textual description.

The following are proposed outcomes for analysis: existence of a dose related effect, main bacteria genus, species presenting acquired resistance to copper/antibiotics, number of resistances to antibiotics in a given isolate.

The contractor will be provided with the report summarising the results of the previous systematic review.

6. Timeline for performing the review

<i>Selecting the studies</i>	<i>10 December 2015</i>
<i>Data extraction</i>	<i>31 December 2015</i>
<i>Assessing methodological quality</i>	<i>15 January 2016</i>
<i>Synthesis of data</i>	<i>30 January 2016</i>
<i>Draft final report</i>	<i>15 February 2016</i>
<i>Final report</i>	<i>25 February 2016</i>

7. History of the amendments

The protocol was agreed on 30 September 2015.

On 10 February 2016 considering that experimental studies with an environmentally controlled setting:

- are highly variable and provide information aimed at determining e.g. the mechanism of action, the genes involved etc. of a possible antibiotic resistance;

- do not provide information able to establish a correlation between the use of copper (as feed additive/supplement) and antibiotic resistance of gut microbiota in pigs (including piglets)

it was decided to consider these studies as supporting information in case such a correlation is identified and to not submit them to methodological quality assessment.