Supplementary material 1
A systematic review and network meta-analysis of injectable antibiotic treatment options for naturally occurring swine respiratory disease

Annette M. O'Connor, DVSc; Sarah C. Totton, PhD; Douglas Shane, DVM, PhD

AMO: Ames, Iowa.

SCT: Guelph, Ontario, Canada.

DS: Bayer Animal Health, Shawnee Mission, Kansas.

Corresponding author: Dr Douglas Shane, Shawnee Mission, KS 66216; Email: douglas.shane@bayer.com.

Supplementary material to: O'Connor AM, Totton SC, Shane D. A systematic review and network meta-analysis of injectable antibiotic treatment options for naturally occurring swine respiratory disease. *J Swine Health Prod.* 2019;27(3):133–149.

Original article is available online at http://www.aasv.org/shap.html.

Time-stamped final protocol

1 Protocol title

A systematic review and network meta-analysis of injectable antibiotic treatments for swine respiratory disease.
Prepared by Annette O'Connor
Date finalized: September 30, 2017

1.1 Registration

We will develop a time-stamped protocol prior to beginning the review and this will be submitted with any manuscript for review as evidence that a protocol was developed.

1.2 Author Contact

Annette O'Connor BVSc, MVSc, DVSc, FANZCVSc Ames, Iowa, USA
Sarah Totton, DVM, PhD, Guelph, Ontario, Canada

1.3 Author Contributions

AOC- Responsible for development of the protocol, literature search, relevant study identification, data extraction, meta-analysis, interpretation, and draft preparation
ST- Responsible for relevant study identification, data extraction, interpretation, and draft preparation

1.4 Support

Bayer US

1.5 Role of sponsors

The sponsor (and sponsor designate) has a role in developing the protocol to ensure that the review studies the correct swine populations, interventions, outcomes and study designs of interest. If needed the sponsor designate will provide feedback about potential relevant study where the 2 main reviewers are in conflict about eligibility. The sponsor designate is not involved in data extraction, conduct of the analysis, interpretation of the results or the discussion. As the sponsor has a role in developing the protocol, the sponsor designate will be an author on any publication and conflicts of interested noted.

2 Introduction

2.1 Rationale

Respiratory disease represents a major health issue in swine production. Although prevention of respiratory disease is the preferred approach to control, when cases of swine respiratory disease (SRD) do occur antibiotic treatment is required to ensure the best welfare of the animal. Many products are registered for the use of treatment of SRD; however, studies often compare products to older products (which are unrealistic comparisons) or to placebo groups. Therefore, the comparative efficacy of these antibiotic treatments for SRD are rarely known, despite this being critical information for producers and veterinarians. Knowledge of comparative efficacy is critical because it establishes a baseline for antibiotic selection. Once the comparative efficacy is known, it enables consideration of cost and convenience in antibiotic choice. Ideally, comparative efficacy would be assessed in large multi-arm randomized controlled clinical trials; however, such trials are rarely conducted or available. An alternative approach to assessing comparative efficacy is a network meta-analysis (also known as a mixed treatment comparison meta-analysis). This approach has been widely used in human health, and evidence from bovine respiratory disease suggests that estimates of comparative efficacy obtained from network meta-analysis are very reasonable approximations of those observed in controlled trials.

2.2 Objective

The objective of this project is to conduct a network meta-analysis of injectable antibiotic treatments for SRD. The project will provide estimates of comparative efficacy and ranking of efficacy for 1st treatment response at 5-14 days post-treatment.

3 Methods

3.1 Eligibility Criteria

Population

Studies relevant to the review will describe weaned swine (nursery, grower, finisher) with naturally occurring undifferentiated or differentiated SRD in modern production systems.

Interventions and comparisons

Studies relevant to the review will describe per-label use of the injectable antibiotic treatments listed in Table 1. Studies of antibiotics in conjunction with adjunct therapies are not relevant.

Table 1: List of injectable antibiotic treatments for SRD relevant to the review

Active	Trade Name	Dose
Enrofloxacin	Baytril 100, Kinetomax, Baytril Max, Baytril OneJect	7.5 mg/kg once, 2.5 – 5 mg/kg SID q 3-5 days for enrofloxacin
Marbofloxacin	Marbox / Marbocyl (100 mg/ml) / Forcyl Swine (160 mg/mL)	2 mg/kg SID q 3 days / 8 mg/kg once
Danofloxacin	-	1.25 mg/kg SID q 3 days
Ceftiofur crystalline free acid	Excede, Excede for Swine (100 mg/ml)	5.0 mg CE/kg
Ceftiofur hydrochloride	Excenel / Excenel RTU EZ	3 mg/kg - 5 mg/kg SID q 3 days
Ceftiofur sodium	Naxcel / Cevaxel	3 mg/kg - 5 mg/kg SID q 3 days
Tulathromycin	Draxxin (100 mg/ml) / Draxxin (25 mg/ml)	2.5 mg/kg once
Gamithromycin	Zactran	6 mg/kg once
Tildipirosin	Zuprevo (40 mg/mL)	4 mg/kg once
Lincomycin hydrochloride	Lincomix 100 (100 mg/mL) / Lincomix 300 (300 mg/mL)	5 mg/lb (2.27 mg/kg) once
Oxytetracycline	Liquamycin LA-200 (200 mg/ml) / Agrimycin 200 / Engemycin (100 mg/mL)	9 mg/lb (4.1 mg/kg) once / 5 mg/kg to 10 mg/kg once
Florfenicol	Nuflor Swine injectable / Florkem	15 mg/kg twice, 48 hours apart
Penicillin	Agri-cillin / Depocillin 300 mg/mL	3,000 units per lb SID q 4 days / 15 I.U./kg SID q 4 days
Tylosin Injectable	Tylan 200 (200 mg/ml)	4 mg/lb (1.8 mg/kg)
Amoxicillin	Vetramoxin LA	15 mg/kg twice, 48 hours apart
Ampicillin	Polyflex	6 mg/kg once
Gentamicin sulfate	Gentamycin 50 / Gentamycin 100 / Genta-100	2 mg/kg to 5 mg/kg BID q 3 days

Outcomes

The outcome of interest is first-treatment cure risk (or the inverse of treatment failure) at 5-14 days. The definition of cure (or failure) will be based on the authors' definition. When authors define the failure risk, we will convert this to cure risk. When the outcome is measured at multiple days in the 5-14 day, we will use the outcome closest to the 7-day metric used by FDA for registration purposes.

Study design

Studies of interest will contain a concurrent control group (active comparator or placebo). Random allocation to treatment group will not be used as an exclusion criterion due to evidence that this may be rare in trials of SRD; however, this will be included as a source of bias and assessed as a source of heterogeneity.

3.2 Information Sources.

The information sources used will be CABI, MEDLINE® and the **FDA Freedom of Information summaries of New Animal Drug Applications (NADA**) from 1970 onwards. The European Medicines Authority (EMA) data will not be searched because neither the European Public Assessment Report (EPAR) nor the **Product Information** provide data similar to that FDA FOI summaries. We will also search the AASV Conference Proceedings and IPVS and ISU Swine Disease's Conferences for all available years.

3.3 Search Strategy

3.3.1 Electronic databases:
The search strategy will be based on the population, the intervention, and the outcome. The approach to developing the search strategy is provided in Appendix 1. The final proposed search strategy for CABI, which will be modified for MEDLINE®, is included in Table 2.

3.3.2 Swine information Library
The Swine Information Library will be searched for the conference proceedings; however, it is not possible to exclude JSAP which was already been searched by the CABI search. Therefore, the search strategies are not well developed (i.e., line-by-line results not available). Therefore, to determine how many relevant manuscripts are likely to be found, we used the two most common terms found in the relevant CABI studies "compared with" and "trials". In addition, we used the terms "treatment" and "effica*". The results of these single-word searches of titles in AASV are listed in Table 4. Although this seems like a large number of relevant studies, many of these are short and unlikely to provide enough information to assess relevance.

3.3.3 FDA NADA information:
We will search FDA site using the NADA numbers listed in Table 3.

3.4 Hand searching of reference list of relevant studies
We will hand search the bibliography of relevant studies.

3.5 Estimation of number of papers:
It is estimated the review will have 40 to 70 studies for the meta-analysis. Three hundred and fifty references from the 1204 were screened for relevance, based on the title and abstract (i.e. a very liberal criteria), and 33 potentially relevant studies were identified. This suggests that approximately 120 full texts might be retrieved from the electronic sources of which perhaps 40-50 might be truly relevant. We can expect around 15-20 FDA FOI but some will be duplicates of published articles. Perhaps 10 unique studies with sufficient information for extraction will be retrieved from the conference proceedings. Therefore, our estimate is that approximately 40-70 articles might be available to inform the review.

3.6 Data Management
Citations searches will be stored in RIS or csv file formats; de-duplication will be conducted based on author, title and year. All eligibility assessment forms, trial characteristics, outcome extraction, and risk-of-bias forms will be pre-tested.

3.7 Selection Process
Two independent reviewers will evaluate the records obtained from the search for relevance to the review questions, based on the eligibility criteria. A record will only need one reviewer to indicate it is relevant to be forwarded to the full-text relevance screening; however, both reviewers will need to agree that the study is not relevant to exclude it from further consideration. Selection of eligible studies will be conducted using systematic review software.

3.8 Data Collection Process

All data extraction will be conducted using pre-tested forms using systematic review software with two reviewers.

Data items-clinical heterogeneity

Sources will be:

- Country of conduct
- Year of conduct
- Class of animal (piglet, grower, finisher etc.)
- Age of enrolled pigs (if provided)- units =kg, range, median or mean by group
- Weight of enrolled pigs (if provided) - units = weeks, range, median or mean by group
- Presence of mycoplasma in the herd (yes/no)
- Prevalence of mycoplasma in pigs in herd (as reported by authors % or r/n)
- The length of time for assessment of outcome (between 5-14 days closest to 7 days)
- The authors' definition of eligibility criteria for animals - extract the text
- The authors' definition of “cure” or “failure” - - extract the text
- Sponsor and drug arm owned by sponsor based on funding or co-authorship

Data items-outcome

These studies are treatment trials; therefore, for each treatment group we will extract:

- The number of animals with SRD enrolled for each treatment arm. When studies only report the effect size, we will extract the effect size and measure of precision
- For multi-site studies, we will extract site level information when available. If investigators combine multiple sites in a single analysis and only report such information we will use the adjusted effect measure (risk ratio or odds ratio) if available. If not available, we will extract the unadjusted data but this will be considered a high risk of bias due to the potential for unit of analysis error (see ROB below)
- Antibiotic used (dose, route et will not be extracted as only label indicates are relevant)
- The number of “cured” animals

3.9 Risk of Bias assessment

The risk of bias form will be based on Cochrane ROB 2.0 tool for randomized trials, modified to ensure relevance to the topic area.

Bias due to randomization process: The Cochrane original schema will be modified, such that manuscripts that do not report the allocation approach, but do report a random allocation method AND baseline data for all treatment groups separately with no meaningful differences, will be assigned a low level of risk of bias

Bias due to deviations from intended interventions: The potential for this bias is very low in commercial settings, so we will assume no deviations even in the absence of reporting. We envision all scenarios will result in a low risk of bias and will not evaluate this item.

Bias due to missing outcome data: This refers to loss to follow-up and we currently do not propose to modify the Cochrane Risk of Bias 2.0 tool. However, we do not expect that many studies with have loss to follow-up issues.

Bias in measurement of the outcome: This will refer to knowledge of the intervention for outcome assessment, and we propose no modifications. If outcome assessors are aware of the interventions but we consider that the outcome is unlikely to be biased even with knowledge of the allocation (for example if temperature is one of the criterion used to assess treatment failure) this can still be listed as a low risk of bias

Bias in selection of the reported results: For this review, only studies that report the results at 5-14 days post-treatment will be included, and other studies that are potentially relevant but report a different outcome will not be included. This domain is therefore not relevant. We will track of how many studies were excluded because the outcome was measured on a different time periods, this will be reported at full text exclusion.

Other issues: Risk of error due to unit of error analysis. An additional issue we will assess is unit of bias error. This error arises due to non-independence of observations within pens or within farms. A frequently observed error in livestock production is when data from multiple site studies with correlated units are combined but the investigators provide no information about correct adjustment for farm or pen effect. If studies provide site level data, these will be extracted separately, and unit of analysis error will not be relevant. Studies that combine multiple sites but do not provide evidence of adjustment for pseudo-replicates will be listed as having high risk of bias. However, of the data are obtained from FDA FOI, as it is very likely that such data were correctly analyzed, and companion studies that appear to be used for regulatory purposes (For example, sometimes there is an FDA FOI and a peer-reviewed manuscript of the same study, and they are combined to provide the most complete picture of the study.).

3.10 Data synthesis

The proposed approach to analysis is a Bayesian Network Analysis with comparative efficacy estimation and ranking of antibiotics. We propose to include all antibiotics for which data can be extracted. We do not propose to develop country specific network meta-analyses based on registered products. We will assess sponsorship bias, randomization, mycoplasma in the herd (reported versus not reported) and blinding as sources of heterogeneity in a meta-regression as described previously. One discussion had with the sponsor was if it was possible to assess if the presence of mycoplasma as an effect modifier. The ability to assess this question will be dependent upon the number of antibiotics included, trial size, and the total number of studies that have sufficient data to be included in the review. It is possible we will not assess this aspect of the review.

3.11 Meta bias

We will assess the potential for small studies effects using funnel plots and other approaches. We will also assess the geometry of the network. We will provide results of the comparative efficacy analysis, with appropriate discussion of the confidence of estimates. We will not conduct a GRADE process to provide recommendations about which product to use as such recommendations require an extended process of consultation.

4 Outputs and timelines

Includes:

- Conference calls to discuss each 2 weeks or as needed.
- Tasks listed in Time table
- Preparation of conference abstract for IPVS
- Preparation of publication and submission for 1st journal and response to reviews for 1st journal.
- Citations list for full text assessed papers and reason for exclusion.
- All extracted data in CSV file

Timelines

Task	Time required	Expected start	Expected end
Step 1: complete and finalize protocol	2 weeks	Mid September	End Sept
Step 2: Conduct search, de-duplicate and upload to software	2 weeks	Early Oct	Mid Oct
Step 3: relevance screening – title and abstracts	1 week	Mid Oct	End Oct
Step 3: relevance screening - full text	1 week	Mid Oct	End Oct
Step 4: data extraction	1 month	Early Nov	End Nov
Step 5: risk-of-bias assessment	1 month, concurrent with Step 4	Early Nov	End Nov
Step 6: summary and meta-analysis	1 month	Early Dec	End Dec
Step 7: Final draft	1 month	Early Dec	End Feb
Step 8: Publication and response to review	1 month		

Table 2: CABI Web of Science search results on 20th Sept 2017 Indexes=CAB Abstracts Timespan=1970-2017

#	Hits	term
#8	991	#3 AND #4 AND #7
#7	47,998	#5 OR #6 Indexes=CAB Abstracts Timespan=1970-2017
# 6	34,968	TS =(pneumonia OR pleuritis OR pleuropneumonia OR "respiratory disease" OR SRD)
# 5	16,540	TS =("Mycoplasma hyopneumoniae" OR “M. hyo” OR "Actinobacillus pleuropneumoniae" OR APP OR "Bordetella bronchiseptica" OR "Pasteurella multocida" OR "Streptococcus suis" OR "Haemophilus parasuis" OR Glasser’s Disease OR "Actinobacillus suis")
# 4	508,827	TS=(swine OR pig* OR piglet* OR gilt* OR boar* OR sow* OR weaner* OR hog* OR porcine OR pork* OR “Sus scrofa” OR “Sus domesticus”)
# 3	42,221	#2 OR #1
# 2	2,213	TS =(Baytril OR Kinetomax OR Marbox OR Marbocyl OR Forcyl OR Excede OR Excenel OR Naxcel OR Cevaxel OR Draxxin OR Zactran OR Zuprevo OR Lincomix OR Liquamycin OR Agrimycin OR Engemycin OR Nuflor OR Florkem OR Agri-cillin OR Depocillin OR Tylan OR Vetramoxin OR Polyflex OR Gentamycin OR Genta-100)
# 1	41,558	TS = (Enrofloxacin OR Marbofloxacin OR Danofloxacin OR Ceftiofur OR Tulathromycin OR Gamithromycin OR Tildipirosin OR Lincomycin OR Oxytetracycline OR Florfenicol OR Penicillin OR Tylosin OR Amoxicillin OR Ampicillin OR Gentamicin)

Table 3: FDA NADA numbers based on trade names.

Trade Name	NADA #
Baytril 100	NADA 141-068
Marbox / Marbocyl (100 mg/ml) / Forcyl Swine (160 mg/mL)	NONE
Excede, Excede for Swine (100 mg/ml)	NADA 140-338, NADA 140-890, NADA 141-209 NADA 141-235
Excenel / Excenel RTU EZ	NADA 141-288, NADA 140-890
Naxcel / Cevaxel	NADA 140-338
Draxxin (100 mg/ml) / Draxxin (25 mg/ml)	NADA 141-244
Zactran	~~NADA 141-328 (ONLY CATTLE NOT SWINE?)~~
Zuprevo (40 mg/mL) / Zuprevo (	NADA 141-334
Lincomix 100 (100 mg/mL) / Lincomix 300 (300 mg/mL)	~~NADA 97-505 , NADA 111-636, NADA 97-505, NADA 111-636 all in feed approvals~~
Liquamycin LA-200 (200 mg/ml) / Agrimycin 200 / Engemycin (100 mg/mL)	NADA 113-232, ANADA 200-154, ANADA 200-066, ANADA 200-128
Nuflor Swine injectable	NADA 141-206, ~~NADA 141-264 (in feed)~~
Agri-cillin / Depocillin 300 mg/mL	COULD NOT FIND NADA
Tylan 200 (200 mg/ml)	COULD NOT FIND NADA # for injectable
Vetramoxin LA	COULD NOT FIND NADA
Polyflex	COULD NOT FIND NADA
Gentamycin 50 / Gentamycin 100 / Genta-100	COULD NOT FIND NADA

Table 4: Single-term searches used in AASV title list from Swine Information Library.

Term and novel relevant hits	Potentially relevant
Treatment (#41)	Comparative Efficacies of Florfenicol and Ceftiofur in the Treatment of Naturally Occurring Swine Respiratory Disease [213.PDF] James A. Jackson, Max T. Rodibaugh, Jeffrey W. Harker, Steven A. Bales, Terry L. Katz and Patrick W. Lockwood, Schering-Plough Animal Health Efficacy of Florfenicol Administered in Drinking Water in the Treatment of Naturally Occurring Swine Respiratory Disease [215.PDF] James A. Jackson, Gary W. Davis, Kelly F. Lechtenberg, Terry L. Katz and Patrick W. Lockwood, Schering-Plough Animal Health Clinical Safety and Efficacy Study of Enrofloxacin Administered as a Single Injection for the Treatment and Control of Naturally Occurring Bacterial Respiratory Disease in Pigs [103.PDF] Kent J. Schwartz, Kathleen M. Ewert Efficacy of a single intramuscular dose of ceftiofur hydrochloride (Excenel(TM) RTU) at 5mg ceftiofur equivalents/kg body weight for the treatment of naturally occurring bacterial swine respiratory disease [203.PDF] David M. Meeuwse, BS; Fabian M. Kausche, MS, DVM; W. Lawrence Bryson, PhD; et al. Evaluation of the efficacy and safety of Nuflor injectable solution (15 mg/kg twice 48 hours apart) in the treatment of swine respiratory disease (SRD) [043.pdf] Robert Zolynas, DVM, MBA; Jean Cao, MS; Robert Simmons, DVM Efficacy of tulathromycin injectable solution (Draxxin®) for the treatment of naturally-occurring swine respiratory disease in North America and Europe [223.pdf] Robert G. Nutsch, DVM, MS, MBA; Fred J. Hart, MSc, PhD; Kathleen A. Rooney, DVM; et al Efficacy of tulathromycin injectable solution (Draxxin®) for the treatment of naturally-occurring swine respiratory disease in North America and Europe [223.pdf] Robert G. Nutsch, DVM, MS, MBA; Fred J. Hart, MSc, PhD; Kathleen A. Rooney, DVM; et al Efficacy of tulathromycin for the treatment of at risk nursery pigs [071.pdf] Matt Allerson; John Deen, DVM, MVSc, PhD; Stephanie Rutten, DVM Clinical effectiveness of Baytril 100® (enrofloxacin) administered as a single injection of 7.5 mg/kg body weight for the treatment and control of naturally occurring bacterial respiratory disease in pigs [387.pdf] Andy Holtcamp, DVM Comparison of efficacy of tulathromycin (DRAXXIN(R)) and tildipirosin (ZUPREVO(R)) in the treatment of Mycoplasma hyopneumoniae infection in pigs [415.pdf] J. W. Eubank; M. K. Senn; R. G. Nutsch; et al. Effect of antibiotic treatment on the development of Haemophilus parasuis disease and seroconversion [073_Macedo.pdf] Nubia Macedo, DVM, MS; Andy Holtcamp, DVM; Maxim Cheeran, DVM, MS, PhD; et al. Safety of DRAXXIN(R) 25 injectable solution (tulathromycin 25 mg/mL) in swine for treatment and control of SRD [403_Nutsch.pdf] Robert G. Nutsch, DVM; Merlyn J. Lucas, DVM; Wendy Collard, PhD; et al.
Random (0)	No unique relevant studies
Trial (21)	A field trial investigating the effectiveness of tulathromycin injection for the control of porcine pleuropneumonia due to Actinobacillus pleuropneumoniae on a grower-finisher farm in an outbreak situation [333.pdf] Kristen Reynolds, MSc, BSc; Zvonimir Poljak, DVM, MSc, PhD; Robert M. Friendship, DVM, MSc, DipABVP; et al.
Compare (#3)	No unique relevant studies
Efficacy (#106)	Pulmotil Efficacy Against Porcine Respiratory Disease Complex in a Commercial Swine Herd Practicing AI/AO Pig flow. [175.PDF] Jeffrey W. Harker and Lee E. Watkins, Elanco Animal Health, Greenfield, IN

Table 5:Example references from level 1 screening from search. The full text of these would be assessed (if available in English)

1) , G., emange, E., Perrin, P.A., Cvejic, D., Haas, M., Rowan, T., Hellmann, K., 2017. Randomised controlled field study to evaluate the efficacy and clinical safety of a single 8 mg/kg injectable dose of marbofloxacin compared with one or two doses of 7.5 mg/kg injectable enrofloxacin for the treatment of Actinobacillus pleuropneumoniae infections in growingfattening pigs in Europe. Porcine Health Management 3, (10 May 2017).
2) , T., ier, J.J., 1973. Porcine enzootic pneumonia: treatment and prophylaxis by drugs Pneumonie enzootique du proc: traitement et prophylaxie medicale. Recueil de Medecine Veterinaire 149, 1393-1402. May not be in English
3) Burch, D.G.S., 1984. The evaluation of tiamulin by injection for the treatment of enzootic pneumonia and mycoplasmal arthritis of pigs. Proceedings of the 8th International Pig Veterinary Society Congress., 117.
4) Cole, J.R., Jr., Sangster, L.T., Cooper, J.A., 1978. Haemophilus parahaemolyticus associated with pleuropneumonia in Georgia swine. Veterinary Medicine & Small Animal Clinician 73, 1444-1446.
5) Couper, A., Cromie, L., Neeve, S., Pommier, P., Keita, A., Pagot, E., 2006. Treatment of pneumonia in pigs with long-acting injectable tylosin. Veterinary Record 159, 805-807.
6) Gestin, G., Ascher, F., Loaec, E., 1995. Long acting antibiotic formulations in the treatment of acute respiratory diseases in the pigs: comparative study Formulations antibiotiques "longue action" dans le traitement des maladies respiratories aigues du porc: etude comparative. Bulletin des G.T.V., 59-65. May not be in English
7) Giles, C.J., 1991. Danofloxacin - a new antimicrobial for the therapy of infectious respiratory diseases in cattle and swine. Proceedings of the Royal Veterinary College/Pfizer Ltd symposium: on respiratory diseases in cattle and pigs: at the Royal Veterinary College, Hawkshead Campus 2nd July 1991., 87-96.
8) Giles, C.J., Vestergaard-Nielsen, K., Agger, N., 1990. The efficacy of danofloxacin in the therapy of acute bacterial pneumonia in a Danish swine herd. Proceedings, International Pig Veterinary Society, 11th Congress, July 1-5, 1990, Lausanne, Switzerland., 102.
9) Hardie, H., 1973. Spectinomycin in veterinary practice. Veterinary Record 92, 123.
10) Herrerias, J.F.Z., Ortega, M.E.T., Diaz, J.M.D., 1995. Comparative efficacy of two quinolones (norfloxacin-nicotinate and enrofloxacin) and trimethoprim with sulfamethoxazole in treatment of respiratory infection with Actinobacillus pleuropneumoniae in pigs Efecto de dos quinolonas (nicotinato de norfloxacina y enrofloxacina) y del trimethoprim en combinacion con sulfametoxazole en el tratamiento de enfermedades respiratorias (Actinobacillus pleuropneumoniae). Veterinaria Mexico 26, 95-101. May not be in English
11) Hoflack, G., Maes, D., Mateusen, B., Verdonck, M., Kruif, A.d., 2001. Efficacy of tilmicosin phosphate (Pulmotil premix) in feed for the treatment of a clinical outbreak of Actinobacillus pleuropneumoniae infection in growing-finishing pigs. Journal of Veterinary Medicine. Series B 48, 655-664.
12) Kamminga, M., Vernooy, J.C.M., Schukken, Y.H., Pijpers, A., Verheijden, J.H.M., 1994. The clinical recovery of fattening pigs from respiratory disease after treatment with two injectable oxytetracycline formulations. Veterinary Quarterly 16, 196-199.
13) Lang, I., Rose, M., Thomas, E., Zschiesche, E., 2002. A field study of cefquinome for the treatment of pigs with respiratory disease. Revue de Medecine Veterinaire 153, 575-580.
14) Luchsinger, J., Chester, S., Dame, K., 1990. Effect of ceftiofur sodium sterile powder for treatment of naturally occurring swine respiratory disease. Proceedings, International Pig Veterinary Society, 11th Congress, July 1-5, 1990, Lausanne, Switzerland., 103.
15) Markowska-Daniel, I., Pejsak, Z., 1999. Efficacy of a combination of amoxicillin and clavulanic acid in the treatment of pneumonia of pigs Wirksamkeit einer Kombination von Amoxicillin und Clavulansaure in der Therapie von Lungenentzundungen bei Schweinen. Deutsche Tierarztliche Wochenschrift 106, 518-522. May not be in English
16) Meeuwse, D.M., Kausche, F.M., Hallberg, J.W., Bryson, W.L., Dame, K.J., 2002. Effectiveness of a single intramuscular dose of ceftiofur hydrochloride for the treatment of naturally occurring bacterial swine respiratory disease. Journal of Swine Health and Production 10, 113-117.
17) Nanjiani, I.A., McKelvie, J., Benchaoui, H.A., Godinho, K.S., Sherington, J., , S., , S.J., Weatherley, A.J., Rowan, T.G., 2005. Evaluation of the therapeutic activity of tulathromycin against swine respiratory disease on farms in Europe. Veterinary Therapeutics 6, 203-213.
18) Neri, R.A., Hilley, H.E., Leman, A.D., 1980. A comparative study of lincomycin and tylosin in preventive mycoplasmal pneumonia in neonatal and growing pigs. Philippine Journal of Veterinary Medicine 19, 92-97.

19) Nie, J., Zhang, X., Huang, X., Du, Z., 2003. Efficacy of tyclosone injection against Mycoplasma pneumoniae in swine. Chinese Journal of Veterinary Medicine 39, 22-23.
20) Nutsch, R.G., Hart, F.J., Rooney, K.A., Weigel, D.J., Kilgore, W.R., Skogerboe, T.L., 2005. Efficacy of tulathromycin injectable solution for the treatment of naturally occurring swine respiratory disease. Veterinary Therapeutics 6, 214-224.
21) Palomo, A., Jimenez, M., Menjon, R., 2013. Study of efficacy and security of ZUPREVO 40 mg/ml (Tildipirosin) applied to treatment of pig respiratory complex. Proceedings of the Joint Meeting of the 5th European Symposium of Porcine Health Management and the 50th Anniversary Meeting of the Pig Veterinary Society of Great Britain, Edinburgh, UK, 22nd - 24th May 2013, 184.
22) Pepovich, R., Nikolov, B., Genova, K., Hristov, K., Tafradjiiska-Hadjiolova, R., Nikolova, E., Stoimenov, G., 2016. The comparative therapeutic efficacy of antimicrobials in pigs infected with Mycoplasma hyopneumoniae. Scientific Works. Series C. Veterinary Medicine 62, 76-81.
23) Sala, V., Faveri, E.d., Gusmara, C., Costa, A., 2015. Comparative evaluation of two quinolones in the treatment of bacterial acute respiratory disease of pig during growing-fattening phase Valutazione comparativa in campo di due chinoloni a diversa concentrazione nel trattamento delle batteriosi respiratorie acute del ciclo magronaggio-ingrasso del suino. Large Animal Review 21, 129-134. May not be in English
24) Scheidt, A., Froe, D., Cline, T., Mayrose, V., Einstein, M., 1990. The use of long-acting oxytetracycline (LA 200) in two swine herds for control of enzootic pneumonia. Proceedings, International Pig Veterinary Society, 11th Congress, July 1-5, 1990, Lausanne, Switzerland., 87.
25) Schmid, G., 1955. Prophylaxis and treatment of contagious broncho-pneumonia in pigs Uber Prophylaxe und Therapie der ansteckenden Bronchopneumonie der Schweine. Schweizer Archiv fur Tierheilkunde 97, 401-412. May not be in English
26) Scuka, L., Oven, I.G., Valencak, Z., 2009. Porcine respiratory disease complex (PRDC) - a meta-analysis and systematic review of the efficacy of enrofloxacin. Slovenian Veterinary Research 46, 29-41.
27) Singh, K.P., 1974. Pasteurellosis in pigs. U.P. Veterinary Journal 2, 1-5.
28) Sumano, L.H., Hevia, P.C.d., Ruiz, S.A.L., Vazquez, S.A., Zamora, M.A., 1998. Clinical efficacy and pharmacokinetics of low doses of ceftriaxone in healthy pigs and pigs with respiratory disease. Pig Journal 42, 33-42.
29) Terreni, M., Colzani, A., Cevidalli, A.E., 2002. Efficacy of injectable florfenicol and enrofloxacin in the treatment of PRDC Efficacia clinica del florfenicolo, paragonato all'enrofloxacina, nel trattamento parenterale delle infezioni respiratorie del suino. May not be in English
30) Thomas, E., , G., emange, E., Pommier, P., Wessel-Robert, S., Davot, J.L., 2000. Field evaluation of efficacy and tolerance of a 2% marbofloxacin injectable solution for the treatment of respiratory disease in fattening pigs. Veterinary Quarterly 22, 131-135.
31) Tokach, L.M., 1993. Streptococcus suis meningitis in finishing pigs of a repopulated herd. Swine Health and Production 1, 29-30.
32) Villarino, N., Brown, S.A., Martin-Jimenez, T., 2013. The role of the macrolide tulathromycin in veterinary medicine. Veterinary Journal 198, 352-357.
33) Volkov, I.B., Kovalev, V.F., 1991. Solvovetin - an original injectable form of oxytetracycline. Vestnik Sel'skokhozyaistvennoi Nauki (Moskva), 126-132. May not be in English

Appendix 1 Description of the search development strategy

The initial approach to developing the search is described here.

Population terms: We also explored the use of TS versus DE=(pigs) and in no situation were records found in the DE =(pigs) search that was not captured by the TS search; therefore, we preferred the final larger TS search.

14 TS=(swine OR pig* OR piglet* OR gilt* OR boar* OR sow* OR weaner* OR hog* OR porcine OR pork* OR "Sus scrofa" OR "Sus domesticus") Indexes=CAB Abstracts Timespan=All years = 643,510
13 = DE=(pigs) = Indexes=CAB Abstracts Timespan=All years 239,133
#13 NOT #14 = 0

Intervention: Interventions were described by generic drug names and branded names provided by the sponsor. The word stem antibioti* was not included based on the assumption that very few authors would write a title or abstract for a relevant study and not mention either the generic or brand name of the product. Further, the addition of the term "antibioti*" increased the number of hits from 55000 to 145850. After screening the first 200 reference of the 90450 that were captured by the "antibioti*", none were found to be relevant.

We original used a list of generic drug names for the intervention

TS = (amoxicillin OR ampicillin OR erythromycin OR ceftiofur OR cloxacillin OR danofloxacin OR enrofloxacin OR florfenicol OR gentamycin OR lincomycin OR oxytetracycline OR penicillin OR spectinomycin OR sulfamethoxazole OR tilmicosin OR trimethoprim OR tulathromycin OR tylosin OR gamithromycin OR danofloxacin OR tildipirosin)

However the modified search based on a list provided by the company representative was as follows:
TS = (Enrofloxacin OR Marbofloxacin OR Danofloxacin OR Ceftiofur OR Tulathromycin OR Gamithromycin OR Tildipirosin OR Lincomycin OR Oxytetracycline OR Florfenicol OR Penicillin OR Tylosin OR Amoxicillin OR Ampicillin OR Gentamicin)

This later search resulted 146 fewer studies in the total combined search and nearly all related to tilmicosin which is an oral preparation and therefore the later search was preferred.

Disease outcome term: The terms that would capture porcine reproductive and respiratory disease virus were included, as this term added approximately 2000 records to that search and even fewer to the combined search.

In CABI, organism descriptions (DE) were not used, as records captured by the DE field tag were also captured by the TS tag.

> DE=(Mycoplasma hyopneumoniae OR Actinobacillus pleuropneumoniae OR Bordetella bronchiseptica OR Pasteurella multocida OR Streptococcus suis OR Haemophilus parasuis OR Actinobacillus suis OR Salmonella choleraesuis OR porcine reproductive "and" respiratory syndrome OR Porcine reproductive "and" respiratory syndrome virus) Indexes=CAB Abstracts Timespan=All years= #20,298
>
> TS =("Mycoplasma hyopneumoniae" OR “M. hyo” OR "Actinobacillus pleuropneumoniae" OR APP OR "Bordetella bronchiseptica" OR "Pasteurella multocida" OR "Streptococcus suis" OR "Haemophilus parasuis" OR "Actinobacillus suis" OR "Salmonella choleraesuis" OR PRRS OR "porcine reproductive and respiratory syndrome") Indexes=CAB Abstracts Timespan=All years =#24,299

Based on further discussion it was proposed to remove several terms and to add an older name for Haemophilus parasuis (Glassers disease)
TS =("Mycoplasma ~~hyopneumoniae~~" OR “M. hyo” OR "Actinobacillus pleuropneumoniae" OR APP OR "Bordetella bronchiseptica" OR "Pasteurella multocida" OR "Streptococcus suis" OR "Haemophilus parasuis" OR Glasser’s Disease OR "Actinobacillus suis" ~~OR "Salmonella choleraesuis" OR PRRS OR "porcine reproductive and respiratory syndrome")~~ Indexes=CAB Abstracts Timespan=All years =#33927

An evaluation of the 16000+ additional references identified by the modified search suggested that the vast majority where mycoplasma species from difference species and none in the 1st 100 related to SRD.

Finally, we assessed only removing the last three terms,
TS =("Mycoplasma hyopneumoniae" OR “M. hyo” OR "Actinobacillus pleuropneumoniae" OR APP OR "Bordetella bronchiseptica" OR "Pasteurella multocida" OR "Streptococcus suis" OR "Haemophilus parasuis" OR Glasser’s Disease OR "Actinobacillus suis" ~~OR "Salmonella choleraesuis" OR PRRS OR "porcine reproductive and respiratory syndrome")~~ Indexes=CAB Abstracts Timespan=All years =#17817

An evaluation of the ~6000+ additional references identified by the modified search suggested that the vast majority where PRRS studies species and none in the 1st 100 related to SRD.