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The supplementary materials are included at the end of this PDF.

COMMENTARY

# 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

## Summary

Based on an *a priori* protocol, a review of injectable antibiotic regimens to treat swine respiratory disease (SRD) in weaned swine was conducted to assess the first-treatment failure at 5 to 14 days post-treatment. Information sources included Cambridge Agricultural and Biological Index, MEDLINE, Food and Drug Administration New Animal Drug Approval summaries, Swine Information Library abstracts, and bibliographies of relevant studies and reviews. Two reviewers screened the records, extracted data, and assessed bias risk. From 1266 records screened, 25 relevant records described 41 relevant studies. Thirty-four relevant studies were included in a meta-analysis. The top 3 model-estimated SRD treatments based on mean rank were enrofloxacin (7.5 mg/kg once or 2.5-5 mg/kg once daily for 3-5 days; n = 5; rank = 2; 95% CI, 1-4), gamithromycin (6 mg/kg once, n = 2; rank = 5; 95% CI, 1-14), and marbofloxacin (8 mg/kg once, n = 1; rank = 6; 95% CI, 1-16). When treating SRD, this information should be combined with antibiotic treatment selection criteria including sensitivity testing results, the farm's pathogen susceptibility monitoring data, local antibiotic prescribing policies, product label recommendations for use and warnings, cost, convenience, importance of the antibiotic to human health, and prudent antibiotic use guidelines.

**Keywords:** swine, antibiotics, meta-analysis, respiratory disease, systematic review

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**Resumen - Una revisión sistemática y meta-análisis en la red de las opciones de tratamiento con antibióticos inyectables para enfermedades respiratorias porcinas que ocurren naturalmente**

En base de un protocolo *a priori*, se realizó una revisión de los regímenes de antibióticos inyectables para tratar la enfermedad respiratoria porcina (SRD, por sus siglas en inglés) en cerdos destetados para evaluar el fracaso del primer tratamiento entre los 5 y los 14 días posteriores al tratamiento. Las fuentes de información incluyeron el Índice Agrícola y Biológico de Cambridge, MEDLINE, resúmenes de la Aprobación de Nuevos Medicamentos para Animales de la Administración de Alimentos y Medicamentos, resúmenes de la Biblioteca de Información Porcina y bibliografías de estudios y revisiones relevantes. Dos revisores seleccionaron los registros, extrajeron los datos y evaluaron el riesgo de parcialidad. De los 1266 registros seleccionados, 25 registros relevantes describieron 41 estudios relevantes. Se incluyeron 34 estudios relevantes en un meta-análisis. Los 3 principales modelos de tratamiento para SRD basados en la categoría promedio fueron enrofloxacina (7.5 mg/kg una vez o 2.5-5 mg/kg una vez al día durante 3-5 días; n = 5; categoría = 2; IC 95%, 1-4), gamitromicina (6 mg/kg una vez, n = 2; categoría = 5; IC 95%, 1-14) y marbofloxacina (8 mg/kg una vez, n = 1; categoría = 6; IC 95%, 1-16). Cuando se trata la SRD, esta información debe combinarse con los criterios de selección del tratamiento con antibióticos, incluidos los resultados de las pruebas de sensibilidad, los datos de monitoreo de susceptibilidad a patógenos de la granja, las políticas locales de prescripción de antibióticos, las recomendaciones de uso y las advertencias en la etiqueta del producto, el costo, conveniencia, la importancia del antibiótico con relación a la salud humana, y pautas prudentes sobre uso de antibióticos.

**Résumé – Revue systématique et méta-analyse en réseau des options de traitement par antibiotiques injectables pour les maladies respiratoires naturellement présentes chez le porc**

Sur la base d'un protocole *a priori*, une analyse des schémas thérapeutiques d'antibiothérapie par injection pour traiter les maladies respiratoires porcines (MRP) chez les porcs sevrés a été réalisée pour évaluer l'échec du premier traitement 5 à 14 jours après le traitement. Les sources d'information comprenaient le Cambridge Agricultural and Biological Index, MEDLINE, les résumés du Food and Drug Administration sur les approbations des nouveaux médicaments pour les animaux, les résumés de la Swine Information Library, et les bibliographies des études et revues pertinentes. Deux examinateurs ont étudié les dossiers, extrait les données et évalué le

AMOC: 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.

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Supplementary materials 2: Tables and Figures (SM2) is available online at http://www.aasv.org/shap/issues/v27n3.

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risque de biais. Sur 1266 dossiers examinés, 25 dossiers pertinents décrivaient 41 études pertinentes. Trente-quatre études pertinentes ont été incluses dans une méta-analyse. Les trois principaux traitements des MRP estimés selon le modèle sur la base du rang moyen étaient l'enrofloxacine (7.5 mg/kg une fois ou 2.5 à 5 mg/kg une fois par jour pendant 3-5 jours; n = 5; rang = 2; IC à 95%, 1-4), la gamithromycine (6 mg/kg une fois, n = 2; rang = 5; IC 95%, 1-14) et la marbofloxacine (8 mg/kg une fois, n = 1; rang = 6; IC 95%, 1-16). Lors du traitement des MRP, ces informations doivent être associées à des critères de sélection de traitement aux antibiotiques, notamment les résultats des tests de sensibilité, les données de surveillance de la sensibilité des agents pathogènes de la ferme, les règles locales de prescription d'antibiotiques, les recommandations d'utilisation et avertissements des étiquettes, le coût, la commodité, l'importance de l'antibiotique pour la santé humaine et les directives d'utilisation prudente des antibiotiques.

Respiratory disease represents a major health issue in swine production. Although prevention of respiratory disease is the preferred management approach, antibiotic treatment is required to ensure the best possible outcome regarding animal health and well-being when cases of swine respiratory disease (SRD) do occur. Many products are registered around the world for the treatment of SRD. Ideally, veterinarians would read the available literature about the efficacy of SRD treatments and combine the information. However, there are numerous barriers to such synthesis. First, veterinarians often lack both the access to and time for review of the literature. Further, many studies conducted and published for registration purposes often compare response to treatment in untreated animals. Such comparisons are often of little interest to producers or veterinarians who might be interested in comparisons between two or more active products. It is also extremely difficult, without statistical methods, to appropriately combine and compare studies from different trials and sample sizes. Because of these factors, the comparative efficacy of many 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.

Although comparative efficacy is important it is clearly not the only metric of importance in antibiotic selection. Veterinarians should also consider this alongside other relevant factors for antibiotic treatment selection, which may include sensitivity testing results for target animals, pathogen susceptibility monitoring data for the farm, local antibiotic prescribing policies, the recommendations for use and warnings on the product labels and leaflets, cost, convenience, importance of the antibiotic to human health, and guidelines for prudent antibiotic use.

Ideally, comparative efficacy would be assessed in large multi-arm randomized controlled clinical trials; however, such trials are rarely conducted or publicly available. An alternative approach to assessing comparative efficacy in large trials 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.[1,2]

The objective of this study was to evaluate the comparative efficacy of injectable antibiotic treatments for SRD and assess the risk-of-bias potential associated with the body of work. The project sought to provide estimates of comparative efficacy and ranking of efficacy based on the first treatment failure between 5 and 14 days post-treatment for antibiotics used to treat swine. The review question was framed using a format that explicitly defined the population, the intervention, the comparator, and the outcome of interest (sometimes known as the PICO format): In weaned swine with naturally occurring undifferentiated or differentiated SRD in modern production systems (population), what is the comparative efficacy of injectable antibiotic treatments (interventions, comparator) for the first treatment failure occurring between 5 and 14 days post-treatment (outcome)?

## Materials and methods

### Protocol and registration

The review protocol was developed before the start of the review. Development of a protocol prior to conduct of the review is standard practice for systematic reviews, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement provides the following rationale:

> A protocol is important because it pre-specifies the objectives and methods of the systematic review. For instance, a protocol specifies outcomes of primary interest, how reviewers will extract information about those outcomes, and methods that reviewers might use to quantitatively summarize the outcome data (see Item 13). Having a protocol can help restrict the likelihood of biased post hoc decisions in review methods, such as selective outcome reporting.

As a pharmaceutical company funded this review, concerns about selective inclusion of literature or selective reporting of outcomes and the influence of the company on the report might be relevant to readers, therefore a protocol is particularly important. The final protocol was approved and time-stamped on September 30, 2017. There is no mechanism to register protocols for systematic reviews in livestock at present, therefore, the time-stamped protocol was made and is included in the supplementary materials (SM1: Protocol). This report is prepared based on the PRISMA extension for network meta-analyses published in 2015.[3]

### Eligibility criteria

The eligibility criteria described herein do not differ from those proposed in the protocol.

**Population.** The population of interest was weaned swine, which might variably be described as nursery pigs, grower pigs, finishers, or based on weight and age. The swine also had to be diagnosed with naturally occurring, undifferentiated or differentiated SRD in modern swine production systems. Studies based only on sows, gilts, or boars were not considered relevant. No restrictions were placed on the country of conduct.

**Interventions.** Individual animal interventions of interest included injectable antibiotics listed in Table 1. The list of known SRD treatment regimens was provided by the sponsor designate (Dr Shane), who consulted work colleagues about treatment regimens of interest. These regimens were the registered label dose of the antibiotic in either Europe or the United States, and thus multiple antibiotic treatments and regimens would be considered extra-label use in the United States. Treatment regimens of parenteral products for SRD control, SRD control interventions added to food or water, antibiotics combined with non-steroidal anti-inflammatory drugs, and off-label use regimens were not considered relevant to the conclusions of the review. When the label included multiple dose regimens, these were combined into a single treatment. For example, if a three-arm trial had one placebo

group, a second group that assessed a single intramuscular dose of 3.0 mg/kg of ceftiofur sodium, and a third group that assessed a single intramuscular dose of 5.0 mg/kg of ceftiofur sodium, the second and third groups would be combined and compared to the placebo because these two doses are listed as equivalent on the product label and, therefore, these data were considered to represent one treatment. The rationale for this approach was that if labeled as such, the regimens were assumed to be therapeutically non-inferior. All non-active controls including placebo, saline, non-drug sterile diluent, or no treatment were combined into one group defined as non-active controls. A single comparator of interest was not identified, as the purpose of the review was to compare the efficacy across all the available interventions.

**Outcome.** The outcome of interest was first-treatment failure risk measured in the 5 to 14 days post-treatment. When the day of treatment was defined as day 0, then outcomes measured on days 4 and 13 were within the relevant follow-up period. When the day of treatment was defined as day 1, then outcomes measured on days 5 and 14 were within the relevant follow-up period. When the outcome was measured on multiple days in the 5 to 14 day period, the results closest to 7 days post-treatment were used. The rationale was that this period is commonly used by the US Food and Drug Administration (FDA) for registra-

**Table 1:** Injectable antibiotic regimens reported in studies and the final regimes used in a mixed-treatment comparisons meta-analysis

| Antibiotic regimen | Short name | Prespecified regimen | Abbreviation |
|---|---|---|---|
| Amoxicillin: 15 mg/kg 2 doses 48 hours apart | Amoxicillin | Yes | AMX |
| Amoxicillin and clavulanic acid: 7.0 and 1.75 mg/kg, respectively, once daily for 3 days | Amoxicillin/clavulanic acid (7.0/1.75 mg/kg 3 days) | No | AMXOL |
| Ampicillin: 6 mg/kg once | Ampicillin | Yes | . |
| Ceftiofur (HCl or NA not reported); 3 mg/kg once daily for 3 days | Ceftiofur (HCl or NA) | No | CEFOL1 |
| Ceftiofur crystalline free acid: 5.0 mg CE/kg once | Ceftiofur CFA | Yes (FDA) | CCFA |
| Ceftiofur hydrochloride: 3-5 mg/kg once daily for 3 days | Ceftiofur HCL (MD) | Yes (FDA) | . |
| Ceftiofur hydrochloride: 5 mg/kg once | Ceftiofur HCl (5 mg/kg once) | No | CEFOL3 |
| Ceftiofur sodium: 1-2 mg/kg once daily for 3 days | Ceftiofur NA (1-2 mg/kg 3 days) | No | CEFOL4 |
| Ceftiofur sodium: 3-5 mg/kg once daily for 3 days | Ceftiofur NA (MD) | Yes (FDA) | CEF |
| Danofloxacin: 1.25 mg/kg or 2.5 mg/kg once | Danofloxacin (1.25 or 2.5 mg/kg once) | No | DANOF |
| Danofloxacin: 1.25 mg/kg once daily for 3 days | Danofloxacin | Yes | . |
| Enrofloxacin: 2.5 mg/kg once daily for 3 days | Enrofloxacin (2.5 mg/kg 3 days) | No | ENFOL1 |
| Enrofloxacin: 7.5 mg/kg once or 2.5-5 mg/kg once daily for 3-5 days | Enrofloxacin | Yes | ENF |
| Enrofloxacin: 7.5 mg/kg once or once daily for 2 days | Enrofloxacin (7.5 mg/kg once or twice) | No | ENFOL2 |
| Florfenicol: 15 mg/kg twice 48 hours apart | Florfenicol | Yes | FLO |
| Gamithromycin: 6 mg/kg once | Gamithromycin | Yes | GAM |
| Gentamicin sulfate: 2-5 mg/kg twice daily for 3 days | Gentamicin | Yes | . |
| Lincomycin hydrochloride: 5 mg/lb (2.27 mg/kg) once | Lincomycin hydrochloride | Yes | . |
| Marbofloxacin: 8 mg/kg once or 2 mg/kg once daily for 3 days | Marbofloxacin | Yes | MAR |
| No treatment: saline, non-drug, sterile diluent, placebo | Non-active control | Yes (FDA) | NAC |
| Oxytetracycline: 9 mg/lb (4.1 mg/kg) once or 5-10 mg/kg once | Oxytetracycline | Yes (FDA) | OXY |
| Penicillin: 3000 units/lb once daily for 4 days or 15 IU/kg once daily for 4 days | Penicillin | Yes (FDA) | . |
| Tiamulin: 15 mg/kg once daily for 3 days | Tiamulin | No | TIAOL |
| Tildipirosin: 4 mg/kg once | Tildipirosin | Yes | TIL |
| Tulathromycin: 2.5 mg/kg once | Tulathromycin | Yes (FDA) | TUL |
| Tylosin Injectable: 4 mg/lb (1.8 mg/kg) once | Tylosin | Yes (FDA) | . |

HCl = hydrochloride; NA = sodium; CE = ceftiofur equivalents; CFA = crystalline free acid; FDA = on-label US Food and Drug Administration approved doses; MD = Multidose.

tion purposes. The definition of treatment failure, or the inverse of treatment success, was described by the investigators of the original research report. For the meta-analysis, when the success risk was defined, this was converted to failure risk.

**Study design.** Studies relevant to the review had to contain a concurrent control group (active comparator or placebo) and at least one of the registered antibiotic regimens listed in the protocol (Table 1). Experimental challenge trials, cluster-randomized trials, and observational studies were not considered relevant. Experimental challenge studies were not considered relevant, as the external validity of the disease model to practice can be unclear. Cluster-randomized trials were not considered because the treatments are administered to an individual pig at diagnosis with SRD and cluster-randomized studies are a design associated more commonly with prophylactic or metaphylactic antibiotic uses. Observational studies were excluded because the potential for bias due to indication is very high for such studies. Random allocation to treatment group was not used as an exclusion criterion due to evidence that this may be rare in SRD trials.

**Report characteristics.** Eligible studies had to be written in English and publicly available, although not necessarily open access, in conference proceedings or peer-reviewed journals.

## Information sources

The information sources used were Cambridge Agricultural and Biological Index (CABI), MEDLINE, the Swine Information Library (SIL), and FDA Freedom of Information (FOI) New Animal Drug Approval (NADA) summaries for registered regimens, and the bibliographies of relevant studies and potentially relevant reviews identified during screening. The European Medicines Authority data was not searched because neither the European Public Assessment Report nor the product information provides data similar to the FDA FOI NADA summaries. The Iowa State University Web of Science interface was used to search CABI and MEDLINE for literature from 1970-2017. The rationale for this limit was that few studies of antibiotics of greatest interest would be published before 1970 and the authors' experience suggests that such studies are often very poorly reported and of little value for meta-analyses. One impact of this approach is that pre-1970 literature may include placebo versus penicillin studies and these studies have no opportunity to be considered for the review. However, the decision was made that the benefit of finding such studies for inclusion was not considered sufficient relative to the cost needed to screen, retrieve, and extract data from them. The SIL enables access to the American Association of Swine Veterinarians Annual Meeting Proceedings (1999-2017), the International Pig Veterinary Society Congress proceedings (2000-2016), the Iowa State University Swine Diseases Conference proceedings (1996-2016), and the Allen D. Leman Swine Conference proceedings (2007-2016). These dates were dictated by the availability of electronic versions. The FDA FOI NADA summaries were available online (**https://animaldrugsatfda.fda.gov/adafda/views/#/foiDrugSummaries**).

## Search

The citation searches began on October 5, 2017 and were completed on November 30, 2017 after all relevant studies had been identified and their bibliographies assessed. The CABI search results are reported in the supplementary materials (SM2: Table S1). Details about the conduct of the search such as how the SIL was searched as it doesn't have indexation, handling of duplicates, and linked references are available in the supplementary materials (SM2: Tables and Figures).

## Study selection

The screening was conducted using systematic review management software (Distiller SR; Evidence Partners, Ontario, Canada). Forms for study selection and data extraction were pre-tested during the protocol drafting phase to ensure consistent interpretation of relevant studies and data by the two independent reviewers. The two reviewers (Drs O'Connor and Totton), both experienced systematic reviewers and veterinary epidemiologists, independently assessed the abstracts and titles for relevance based on the eligibility criteria. The entire article was acquired if one reviewer indicated the record might meet the inclusion criteria. The full text was then assessed for relevance by both reviewers. Four sequential questions based on the PICO elements of eligibility criteria were used to evaluate relevant studies. If a study failed a question, no further evaluation was conducted. All relevant studies were included in the systematic review. However, studies were only eligible for the meta-analysis if the numerical outcome data could be extracted and at least one treatment arm was connected to the rest of the evidence network.

Duplication refers to multiple citations of the same publication. Duplicates were removed initially in the reference management software, then again in the systematic review management software. Linked publications, ie, the same studies reported in part or in full in different sources, were sometimes identified during the relevance screening but more commonly during data extraction.[4] For linked publications, the more complete record was used as the citation. Reference lists from relevant reports and reviews were hand searched for additional relevant manuscripts. If these studies were published in years outside the original search range, they were still included. When disagreements arose about the relevance of the study between the two reviewers, these were resolved by discussion. It was not found necessary to consult the sponsor designate during the eligibility assessment.

## Data collection process

The systematic review management software was used to extract data into pre-tested forms by two reviewers (Drs O'Connor and Totton) working independently. The unit of concern for dataset extraction was the study level if available. As investigators can vary in reporting the outcome, the order of preference for extracting the outcome dataset was as follows: an adjusted estimate of the summary effect size, an unadjusted estimate of the effect size, and the group-level frequency data. The rationale for this preference was that swine populations are clustered in pens, rooms, and barns and often across multiple sites, therefore adjusted estimates that correctly account for non-independence of observations provide the least biased estimate of the variance. Interestingly all studies reported group-level data rather than summary-level data. Investigators were not contacted when data were missing. If studies were linked, all the available information was used but the version that was the most complete was cited, which was usually the one with site-specific results.

**Data items.** Data items extracted related to the conduct of the study, the definition of SRD, the trial interventions, and the outcome. The detailed list of items extracted from each paper is provided in the protocol (SM1: Protocol).

**Geometry of the network.** Network geometry was assessed using an approach

previously proposed.[5] The probability of an inter-species encounter (PIE) index was calculated using custom-written R script and the C-score test was performed via R package EcoSimR (version 0.1.0, ).[6] The PIE index is a continuous variable that decreases in value as unevenness increases. Values < 0.75 can be considered to reflect the limited diversity of interventions. Co-occurrence was also assessed using the C-score, which describes, based on a checkerboard analysis, if pairwise comparisons of specific treatments are preferred or avoided.[5]

**Risk of bias within individual studies.** The risk-of-bias form was based on the Cochrane Risk of Bias (ROB) 2.0 tool for randomized trials. However, this form was modified as follows to ensure relevance to the topic area.[7]

To assess bias due to the randomization process (ROB1), the ROB 2.0 tool provides the following signaling questions (SQ) to guide the reviewer:

> SQ 1.1 - Was the allocation sequence random?
>
> SQ 1.2 - Was the allocation sequence concealed until participants were recruited and assigned to interventions?
>
> SQ 1.3 - Were there baseline imbalances that suggest a problem with the randomization process?

In addition to the Cochrane guidance for SQ 1.1, *yes* was indicated if the study was conducted for regulatory purposes, ie, an FDA study or if the study was conducted using Good Clinical Practice Guidelines.

Also, the response to SQ 1.2 about allocation concealment was ignored. In ROB 2.0, any study that did not report allocation concealment was automatically at high risk of bias. The response to SQ 1.2 was not considered in the overall assessment of bias due to randomization. The schema used was as follows: If the response to SQ 1.1 was *yes* or *probably yes* and the response to SQ 1.3 was *no* or *probably no*, the study was considered low risk of bias for that domain. If the response to SQ 1.1 and SQ 1.3 was *no information*, the study was considered high risk of bias for that domain. If the response to SQ 1.1 was *no* or *probably no*, the answer to SQ 1.3 was not influential and the study was considered high risk of bias. If the response to SQ 1.1 was *yes* or *probably yes* and the response to SQ 1.3 was *no information*, the study was considered to be of some concern of bias for that domain. If the response to SQ 1.1 was *no information* and the response to SQ 1.3 was *no* or *probably no*, the study was considered to be of some concern of bias for that domain.

The rationale for this modification was that it was considered unlikely in swine production settings that caregivers would have differential preferences for groups of animals to receive a particular intervention. This modification was planned in the protocol.

Bias due to deviations from intended interventions (ROB2) refers to deviations due to care-giving or failure to complete an allocated treatment. The potential for this bias is very low in commercial settings using short-duration antibiotic treatments, so few or no deviations were assumed even in the absence of reporting on blinding of outcome assessors. No changes to the Cochrane ROB 2.0 SQs or ROB algorithm were made.

Bias due to missing outcome data (ROB3) refers to loss to follow-up, and neither the SQs nor the risk algorithm proposed by Cochrane ROB 2.0 tool were modified.

Bias in the measurement of the outcome (ROB4) refers to bias introduced due to knowledge of the intervention by outcome assessors. Even if outcome assessors were aware of the intervention or if this was unclear, the risk of bias was considered low if the definition of treatment success included an objective measure such as temperature and that a threshold for considering an animal to be pyrexic was reported.

Bias in selection of the reported results (ROB5) was also assessed. For this review, only studies that reported the results at 5 to 14 days post-treatment were included, and other studies that were potentially relevant but reported a different outcome were not included. Bias was considered possible when multiple poorly defined or undefined metrics of the outcome were used.

The risk-of-bias information was not included in the meta-analysis nor used as exclusion criteria. Instead the risk of bias was included mainly to convey to end users that substantial information about the conduct of the studies is missing, and the impact of this information on the certainty of the conclusions that can be reached.

**Summary measures.** The primary approach to summarizing the data was the comparative efficacy rankings. The rationale for using these as the primary outcome is that they are a relative measure of efficacy. Given the potential for publication bias in the topic area, it is theoretically possible that all companies owning products relevant to the review are publishing the most promising studies. Therefore, the actual magnitude of effect size observed in the studies might be biased upwards. For example, companies owning products relevant to the review might have conducted several placebo-vs-active trials but presented only the one with the largest effect size. If this occurs, the effect sizes might be distorted. However, if all companies owning products relevant to the review engage in this practice, the relative comparisons should still be reasonable. Interestingly, it was previously speculated that this bias might occur; however, previous research in bovine respiratory disease did not find empirical evidence of this bias.[1,2] For each simulation based on the probability of treatment failure, each treatment received a ranking. Lower rankings indicated a lower probability of treatment failure. All treatment regimens included in the meta-analysis received a ranking including off-label regimens, therefore, the range of rankings was 1 to 19 for each simulation. The reported data are the mean rankings and related 95% CI. Despite some reservations, the risk ratio (RR) and related 95% CI for all possible comparisons was also reported. This outcome was chosen because ease of interpretation is greater for the RR than for the odds ratio. The extracted data were organized such that an event (treatment failure) was an adverse outcome. Drugs with greater efficacy had lower event percentages. This approach was used because some studies reported success percentages (ie, failure to retreat), while others reported failure percentages (ie, retreatments). The data items, randomization to treatment arm (reported/not reported), outcome assessor blinding (reported/not reported), and pharmaceutical company sponsorship of treatment were also extracted and used for the assessment of methodological heterogeneity. When the RR is < 1, this implies that the drug in the numerator has a lower treatment failure risk than the drug in the denominator and is, therefore, more effective at treating SRD. When the RR is > 1, this implies that the drug in the numerator has a higher treatment failure risk than the drug in the denominator and is less effective at treating SRD. The baseline risk used to convert the odds ratios to the RR was obtained by using the distribution of the placebo group. Using these data,

the prior distribution of the log odds ratio ( $\mathcal{N}$ [mean (SD)]) was reported as $\mathcal{N}$ (−0.9633 [0.7344]).

**Planned method of statistical analysis**

The proposed method has been previously described in detail.[8] Briefly:

$$r_{jk} \sim Bin(p_{jk}, n_{jk}),\ \theta_{jk} = logit(p_{jk})$$

and

$$\theta_{jk} = \begin{cases} \mu_{jb}, & if\ k = b; b = A,B,C, \ldots \\ \mu_{jb} + \delta_{jbk}, & if\ k > b; b = A,B,C, \ldots \end{cases}$$

where $p_{jk}$ is the probability of the event in trial $j$ under treatment $k$ and $\delta_{jbk}$ is the trial-specific log odds ratio of treatment $k$ relative to the corresponding baseline treatment $b$ in trial $j$. The trial-specific treatment effects are distributed as:

$$\delta_{jbk} \sim \mathcal{N}(d_{bk}, \sigma^2_{bk}),$$

with priors

$$d_{bk} \sim \mathcal{N}(0\ [10000]),$$

and under the homogeneous variance assumption that $\sigma^2_{bk} = \sigma^2$, where $\sigma \sim U(0, 5)$.

**Handling of multi-arm trials.** The covariance between $\delta_{jAB}$ and $\delta_{jAC}$ was assumed to be $\sigma^2/2$ for multi-arm trials.[9,10]

**Selection of prior distributions in Bayesian analysis.** The prior distributions were originally based on the previously reported approach.[10,11] In prior similar models, $\sigma \sim U(0, 2)$ and $\sigma \sim U(0, 5)$ were assessed, and $\sigma \sim U(0, 5)$ was preferred. That assessment was repeated and the same prior used in a previous model was retained.[1,2]

**Implementation and output.** All posterior samples were generated using Markov Chain Monte Carlo (MCMC) simulation implemented using Just Another Gibbs Sampler (JAGS) software (version 3.4.0). All statistical analyses were performed using R software (version 3.2.1).[12] The model was fitted using JAGS, an MCMC sampler, by calling JAGS from R through the rjags package.[13] Three chains were simulated, and the convergence was assessed using Gelman-Rubin diagnostics. Five thousand "burn-in" iterations were discarded and inferences were based on an additional 10,000 iterations. The model output included all possible pairwise comparisons using log odds ratios for inconsistency assessment, RRs for comparative efficacy reporting, and the treatment failure rankings for comparative efficacy reporting.

**Assessment of model fit.** The fit of the model was assessed based on the log odds ratio by examining the residual deviance between the predicted values from the network meta-analysis model and the observed value for each study.[8] The deviance to the number of data points were compared and a ratio of one was vaguely equated for these two numbers as a good fit. When this ratio seemed subjectively large, the output was searched for signs of potential issues, including unrealistic outcomes such as rankings with no variation or very large credible intervals. If these were noted, treatment groups were combined or studies that appeared to be associated with the poor fit were removed and the reduced model was re-evaluated. Trace plots for the treatment effects were monitored to identify major issues with convergence.

**Assessment of inconsistency.** The back-calculation method was used to assess the consistency assumption.[8] The inconsistency evaluation did not rely only on the *P* values. The estimates from the direct and indirect models were also compared and the standard deviation of each estimate was considered. Comparisons for which the direct and indirect estimates had different signs were further evaluated and discussed.

**Risk-of-bias assessment.** The potential systematic biases resulting from the methodological variables, blinding, randomization, and sponsorship were described using indicator variables. The effect size and related 95% CI were reported. The impact of small-study effects was not assessed, as the potential to detect asymmetry was limited by the number of valid pairs available and any funnel plots would be too sparse to be meaningfully interpreted.

### Additional analyses

No additional analyses were conducted.

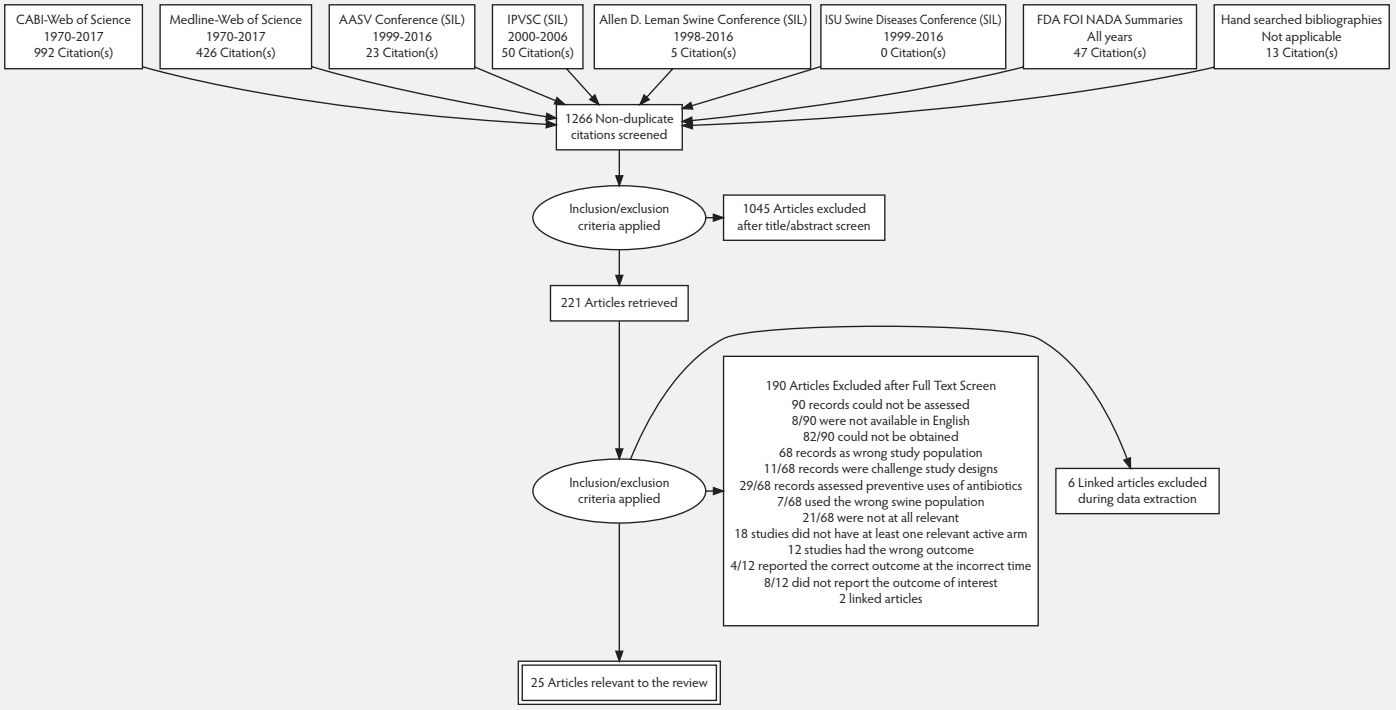
## Results and discussion

### Study selection

The flow chart for records retrieved for the review is reported in Figure 1. There were 1266 records screened, and 25 relevant records describing 41 relevant studies were identified. Thirty-four of the 41 relevant studies could be included in the meta-analysis. Of 1266 records screened, 221 were retrieved for full-text evaluation. One hundred ninety of the 221 full texts were excluded (see SM2: Table S2). This included two sets of linked publications, so exclusion reasons are available for 188 records. Thirty-one records were determined to contain studies relevant to the review. These are listed as 25 relevant articles in Figure 1 due to 6 linked publications.[14-38] Those 25 records contained 41 unique studies considered relevant to the review. Four unique studies from 3 records were excluded from the meta-analysis because, although meeting all the relevance criteria, they did not report the outcome data.[16,29,31] One unique study compared danofloxacin (1.25 mg/kg once daily for 3 days) to benzyl penicillin with dihydrostreptomycin. This was the sole study that evaluated these treatments, and therefore there was no link to the remaining evidence network. Consequently, this study was also excluded from the meta-analysis.[36]

During the model assessment, two unique studies in the same manuscript were removed from the network meta-analysis because the results were inconsistent with the network.[35] These 2 studies reported results for treatment failure where arm 1 was a non-active control (Farm A: 29 of 29; Farm B: 30 of 30), arm 2 was ceftiofur hydrochloride (3 mg/kg once daily for 3 days; Farm A: 8 of 30; Farm B: 2 of 30), and arm 3 was ceftiofur hydrochloride (5 mg/kg once daily for 3 days; Farm A: 7 of 30; Farm B: 0 of 30). As these doses were both on the same label, this represented two arms of multi-dose ceftiofur hydrochloride. This extremely high level of efficacy was unusual for ceftiofur regimens in the dataset. When these data were included in the model, the model was unstable. For example, multi-dose ceftiofur hydrochloride was ranked the highest with zero rank variation, yet the next nearest ceftiofur regimen was nine regimens lower. To explore the issue, the impact of creating a single category of multi-dose ceftiofur (3-5 mg/kg once daily for 3 days), which ignored the sodium or hydrochloride, was evaluated. However, this approach did not solve the issue. For example, several RR estimates were greater than 1000 indicating a major issue with model fit. Finally, the impact of excluding the 2 studies was assessed, which resolved the issue and the resulting model is reported here. Exclusion of this manuscript does not represent a deviation from the protocol, as consistency assessment is a required aspect of the meta-analysis.[8] Therefore, a total of 7 of the 41 relevant studies were excluded and the resulting 34 studies were used in the final reported meta-analysis.

**Figure 1:** The PRISMA flowchart describing the flow of literature through the review. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CABI = Cambridge Agricultural and Biological Index; AASV = American Association of Swine Veterinarians; SIL = Swine Information Library; IPVSC = International Pig Veterinary Society Congress; ISU = Iowa State University; FDA FOI NADA = Food and Drug Administration's Freedom of Information New Animal Drug Application.




## Presentation of network structure

The final evidence network used in the meta-analysis represented 34 studies and 73 arms. Some arms used treatment regimens that were off-label. These off-label arms were included in the network meta-analysis because they contributed data for estimation of regimens that were of interest. These non-protocol regimens are listed in Table 1. Information about the number of arms and the reporting of blinding and randomization is presented in Table 2.

## Summary of network geometry

The geometry of the network was sparse, with most regimens being assessed only once. The network would be considered quite diverse as measured by the PIE index (0.79). A PIE index > 0.75 often indicates the network was quite diverse.[5] This result is consistent with the visual examination of the network which includes a large number of treatments (Figure 2). However, this analysis can only consider the treatments included in the analysis, the diversity of which is bolstered by treatments not relevant to the review. Further, no studies were found for 5 of the 17 antibiotic regimens identified as relevant to the review in the protocol (Table 1). Therefore, the real diversity was considered to be lower than the PIE suggested, as it includes non-relevant regimens. However, the regimens for which data were available were likely of greatest interest to producers and those regimens for which no reports were found are likely of less interest. The C-score was 10.11 and the C-score test had a large $P$ value ($P = .55$). These metrics seek to evaluate how random encounters occur in ecological populations and, when used in a network meta-analysis, they assess if there are particular pairwise comparisons that occur more or less often than expected by random encounter. Although the results of hypothesis testing suggest little evidence of non-random pairs, visual examination of the network does suggest pairwise comparisons used in the network are not random, with a strong preference for comparisons with placebo-controlled trial arms.

## Study characteristics and study results

The descriptive information for the studies included in the meta-analysis is provided in Table 2. As the population definition was quite narrow, that information is not presented due to space limitations. The definitions of SRD (SM2: Table S3) and treatment success (SM2: Table S4) are presented in the supplementary materials. Studies varied in how success or failure was defined. Interestingly most studies tended to report metrics of success, and this differs from a review of bovine respiratory disease where most studies tended to define the outcome based on failure, ie, first-treatment failure risk.

## Individual risk of bias

For each study eligible for the review, the risk-of-bias judgment for each bias domain is presented in Table 3. The impact of modification on the risk of bias due to allocation can be seen. As no studies reported using allocation concealment, the original schema would have resulted in all studies being classified as high risk of bias for this domain. As the Cochrane ROB tool assigns the highest risk of bias across the domains to the report, then all reports would have been given an overall high risk of bias. Based on the change, some studies, generally those conducted for regulatory purposes and those reporting using Good Clinical Practices, are at low risk of bias. However, because the Cochrane ROB tool was modified, an overall ROB was not explicitly provided.

**Table 2:** Characteristics of relevant studies included in the meta-analyses

| Reference number | Year | Country | Arm 1 Regimen | Arm 1 Events* | Arm 1 Total | Arm 2 Regimen | Arm 2 Events* | Arm 2 Total | Arm 3 Regimen | Arm 3 Events* | Arm 3 Total | Random | Blinded |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 14 | 1996 | United States | Enrofloxacin (7.5 mg/kg once) | 33 | 49 | Non-active control | 49 | 49 | NA | NA | NA | No | Yes |
| 14 | 1996 | United States | Enrofloxacin (7.5 mg/kg once) | 4 | 39 | Non-active control | 33 | 36 | NA | NA | NA | No | Yes |
| 15 | 2010 | United States | Enrofloxacin (7.5 mg/kg once) | 29 | 75 | Non-active control | 55 | 75 | NA | NA | NA | Yes | Yes |
| 15 | 2010 | United States | Enrofloxacin (7.5 mg/kg once) | 6 | 75 | Non-active control | 50 | 75 | NA | NA | NA | Yes | Yes |
| 17 | NR | United States | Ceftiofur CFA | 175 | 233 | Non-active control | 195 | 237 | NA | NA | NA | Yes | Yes |
| 18 | NR | France, Germany | Florfenicol | 14 | 109 | Oxytetracycline (20 mg/kg once) | 31 | 110 | NA | NA | NA | No | No |
| 19 | NR | Denmark, France, Germany | Amoxicillin | 4 | 77 | Ceftiofur CFA | 3 | 77 | NA | NA | NA | Yes | Yes |
| 20 | NR | Italy | Enrofloxacin (2.5 mg/kg for 3 days) | 30 | 67 | Enrofloxacin (5 mg/kg for 3 days) | 10 | 48 | NA | NA | NA | No | Yes |
| 21 | 2007 | Spain | Florfenicol | 8 | 31 | Amoxicillin | 12 | 29 | NA | NA | NA | No | Yes |
| 22 | NR | Slovenia | Amoxicillin and clavulanic acid (7.0 and 1.75 mg/kg, respectively, on days 0, 1, and 2) | 21 | 34 | Tulathromycin | 22 | 35 | NA | NA | NA | Yes | Yes |
| 22 | NR | Germany | Amoxicillin and clavulanic acid (7.0 and 1.75 mg/kg, respectively, on days 0, 1, and 2) | 5 | 26 | Tulathromycin | 2 | 19 | NA | NA | NA | Yes | Yes |
| 23 | NR | Spain | Florfenicol | 1 | 25 | Ceftiofur (unclear if HCl or Sodium) | 4 | 25 | NA | NA | NA | Yes | Yes |
| 24 | NR | Germany | Amoxicillin | 23 | 102 | Enrofloxacin (7.5 mg/kg once or twice) | 14 | 96 | NA | NA | NA | Yes | Yes |

**Table 2 cont'd**: Characteristics of relevant studies included in the meta-analyses

| Reference number | Year | Country | Arm 1 Regimen | Arm 1 Events* | Arm 1 Total | Arm 2 Regimen | Arm 2 Events* | Arm 2 Total | Arm 3 Regimen | Arm 3 Events* | Arm 3 Total | Random | Blinded |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 24 | NR | Denmark, Germany | Enrofloxacin (7.5 mg/kg once or twice) | 2 | 85 | Florfenicol | 6 | 84 | NA | NA | NA | Yes | Yes |
| 25 | NR | Germany | Tildipirosin | 17 | 254 | Tulathromycin | 20 | 254 | NA | NA | NA | Yes | Yes |
| 26 | NR | Germany | Tildipirosin | 6 | 96 | Tulathromycin | 6 | 96 | NA | NA | NA | Yes | Yes |
| 27 | NR | Japan | Gamithromycin | 7 | 42 | Danofloxacin (1.25 mg/kg or 2.5 mg/kg) | 6 | 21 | NA | NA | NA | No | Yes |
| 27 | NR | Germany | Gamithromycin | 5 | 15 | Tildipirosin | 11 | 152 | NA | NA | NA | No | Yes |
| 30 | NR | France, United States | Ceftiofur HCl (5 mg/kg once) | 140 | 152 | Non-active control | 139 | 152 | NA | NA | NA | No | Yes |
| 32 | NR | United States | Tulathromycin | 10 | 48 | Non-active control | 14 | 48 | NA | NA | NA | Yes | Yes |
| 32 | NR | United States | Tulathromycin | 14 | 44 | Non-active control | 23 | 44 | Ceftiofur Sodium (3 mg/kg for 3 days) | 9 | 44 | Yes | Yes |
| 32 | NR | United States | Tulathromycin | 17 | 48 | Non-active control | 35 | 49 | Ceftiofur Sodium (3 mg/kg for 3 days) | 29 | 47 | Yes | Yes |
| 32 | NR | United States | Tulathromycin | 9 | 48 | Non-active control | 29 | 48 | Ceftiofur Sodium (3 mg/kg for 3 days) | 11 | 48 | Yes | Yes |
| 32 | NR | United States | Tulathromycin | 9 | 48 | Non-active control | 25 | 48 | Ceftiofur Sodium (3 mg/kg for 3 days) | 20 | 48 | Yes | Yes |
| 32 | NR | Canada | Tulathromycin | 18 | 30 | Non-active control | 17 | 30 | NA | NA | NA | Yes | Yes |
| 32 | NR | France | Tulathromycin | 4 | 40 | Florfenicol | 1 | 20 | NA | NA | NA | Yes | Yes |

**Table 2 cont'd:** Characteristics of relevant studies included in the meta-analyses

| Reference number | Year | Country | Arm 1 Regimen | Arm 1 Events* | Arm 1 Total | Arm 2 Regimen | Arm 2 Events* | Arm 2 Total | Arm 3 Regimen | Arm 3 Events* | Arm 3 Total | Random | Blinded |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 32 | NR | Germany | Tulathromycin | 8 | 78 | Tiamulin | 7 | 39 | NA | NA | NA | Yes | Yes |
| 32 | NR | The Netherlands | Tulathromycin | 13 | 44 | Tiamulin | 13 | 22 | NA | NA | NA | Yes | Yes |
| 32 | NR | United Kingdom | Tulathromycin | 17 | 41 | Tiamulin | 13 | 20 | NA | NA | NA | Yes | Yes |
| 32 | NR | United Kingdom | Tulathromycin | 1 | 37 | Tiamulin | 3 | 16 | NA | NA | NA | Yes | Yes |
| 33 | NR | Canada | Florfenicol | 19 | 71 | Non-active control | 25 | 42 | NA | NA | NA | Yes | Yes |
| 34 | 2009 | United States | Tildipirosin | 155 | 434 | Non-active control | 261 | 434 | Tulathromycin | 155 | 535 | No | Yes |
| 37 | 1992 | Korea | Ceftiofur Sodium (3 mg/kg for 3 days) | 6 | 30 | Ceftiofur Sodium (2 mg/kg for 3 days) | 35 | 60 | NA | NA | NA | No | No |
| 38 | 2013-2014 | Germany, Hungary | Marbofloxacin (8 mg/kg once) | 22 | 121 | Enrofloxacin (7.5 mg/kg once or twice) | 22 | 118 | NA | NA | NA | Yes | Yes |

*The event is first-treatment failure .
NA = not applicable; NR = not reported; CFA = crystalline free acid; HCl = hydrochloride.

## Individual study results

The individual results for studies included in the final meta-analysis are reported in Table 2.

## Synthesis of results

The final meta-analysis included results from 34 of the 41 relevant studies. For the final model, the deviance was 80, while the number of data points was 73, suggesting reasonable fit of the model as the deviance should be close to the number of data points. Convergence of the Bayesian model was within normal limits based on visual inspection of trace plots. The results of the model are presented several ways. The estimates of mean rank are provided in Figure 3. This plot only includes label-dose regimens, ie, those identified in the protocol *a priori*. The rankings for all regimens used in the meta-analysis, including off-label regimens, are provided in Table 4. Off-label regimens were excluded from Figure 3 to avoid the perception of promoting the use of off-label regimens. However, for transparency of the results, the ranks for all regimens in the meta-analysis are presented in the tables, knowing that most people will rely upon the figures for the results. Lower rankings are associated with fewer treatment failures. Not surprisingly, there is considerable overlap of confidence intervals of the rankings. This reflects the small number of studies informing some ranking estimates and the variation in observed results reported in the primary research. For example, marbofloxacin had a high level of efficacy. However, without more publicly available studies, the result remains a single, potentially random observation, and therefore the point estimate is tempered by the measures of uncertainty. Table 4 also shows that the other ceftiofur regimens were clustered together with mid-level rankings at best, which supports the decision to remove the inconsistent study.[35] The distribution of probability of treatment response for the label-dose protocols are presented in the supplementary materials (SM2: Table S5 and Figure S1). The top 4 model-estimated SRD treatments based on the mean rank were the enrofloxacin (7.5 mg/kg once or 2.5-5 mg/kg once daily for 3-5 days; n = 5; rank = 2; 95% CI, 1-4), gamithromycin (6 mg/kg once; n = 2; rank = 5; 95% CI, 1-14), marbofloxacin (8 mg/kg once; n = 1; rank = 6; 95% CI, 1-16) and florfenicol (15 mg/kg twice 48 hours apart; n = 6; rank = 7; 95% CI, 3-13).

**Figure 2:** The network of treatment arms used in the mixed-treatment comparison meta-analysis. The size of the dot is a relative indicator of the number of arms and the width of the lines is a relative indicator of the number of indirect comparisons. The number of study arms reporting the injectable antibiotic regimen is presented in parentheses. Antibiotic regimen abbreviation definitions are listed in Table 1.

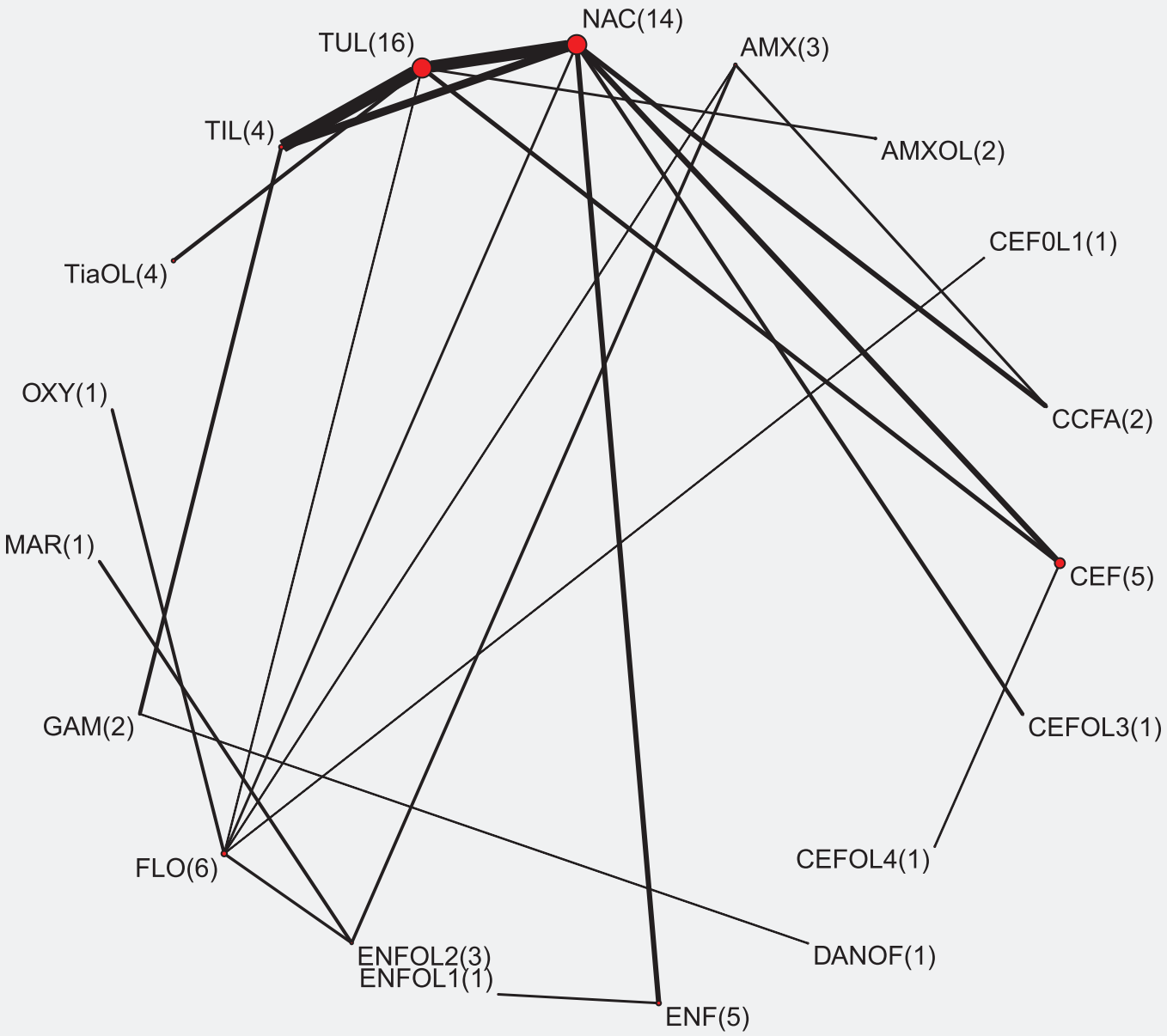



Table 5 provides the comparative RRs for only the label-dose regimens, ie, those identified in the protocol *a priori*. The data are organized such that the event is the risk of treatment failure for the treatment in the row divided by the risk of treatment failure in the column. For example, in the first row of the table, all the RR estimates are greater than one, meaning that the risk of treatment failure was higher in the non-active control groups when compared to all other antibiotics. The upper right-hand quadrant reports the estimated RR and the lower quadrant reports the 95% CI. The risk of treatment failure was 16-fold higher for untreated animals compared to enrofloxacin (RR = 16; 95% CI, 4-48). Only 3 antibiotics did not have a credible interval that excluded one when compared to non-active control: oxytetracycline, amoxicillin, and marbofloxacin. Given the point estimate and mean rank for marbofloxacin, this finding is likely a function of identification of only one publicly available study reporting the efficacy of marbofloxacin.

## Exploration of inconsistency

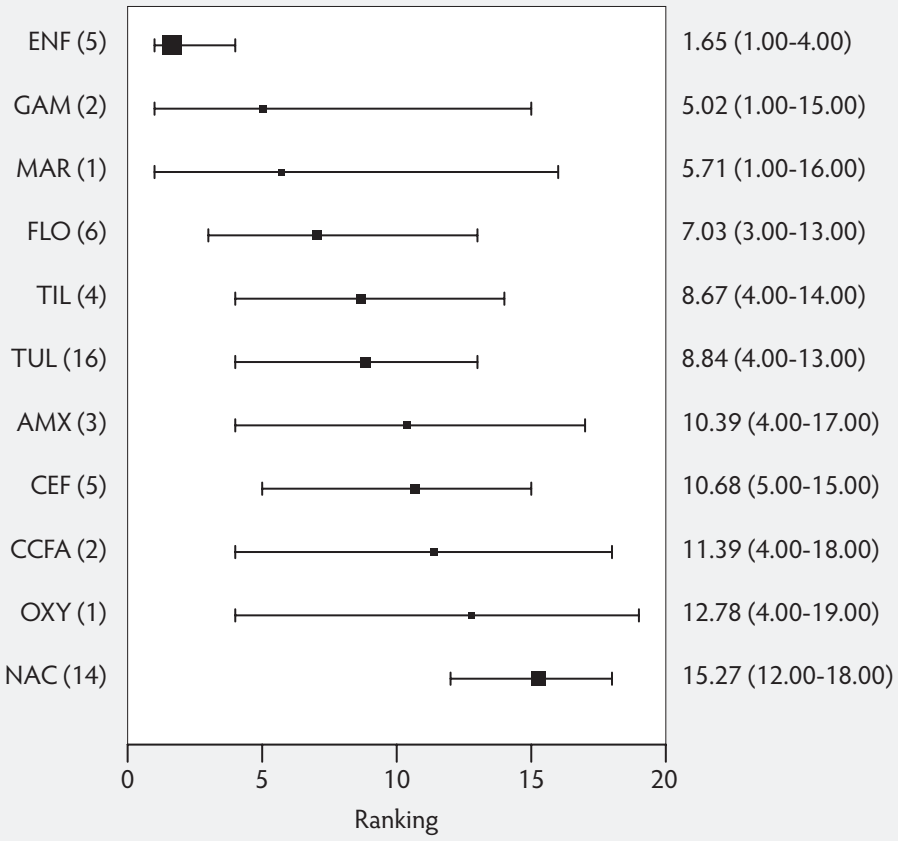
The consistency between the direct and indirect sources of evidence of the final model using 34 trials and 73 arms is reported in Table 6. In this model, no evidence of inconsistency was found between the direct and indirect estimates. However, this should not be interpreted as proof that inconsistency does not exist. The small number of studies available means that the precision of direct estimates is low (ie, wide credible intervals) making it difficult to detect differences in direct and indirect estimates.

**Table 3:** Risk of Bias for all 25 relevant studies identified in the systematic review[7]

| Reference number | SQ 1.1* | SQ 1.2† | SQ 1.3‡ | Original ROB1§ | Modified ROB1¶ | ROB2** | ROB3†† | ROB4‡‡ | ROB5§§ |
|---|---|---|---|---|---|---|---|---|---|
| 14 | Probably yes | Probably no | Probably no | High | Low | Low | Low | Low | Low |
| 15 | Probably yes | Probably no | Probably no | High | Low | Low | Low | Low | Low |
| 16 | Probably yes | Probably no | Probably no | High | Low | Low | Concerns | Low | Low |
| 17 | Probably yes | Probably no | Probably no | High | Low | Low | Low | Low | Low |
| 18 | No information | Probably no | No information | High | High | Low | Concerns | Low | Concerns |
| 19 | Probably yes | Probably no | No information | High | Concerns | Low | Low | Low | Low |
| 20 | No information | Probably no | No information | High | High | Low | Low | High | High |
| 21 | No information | Probably no | No information | High | High | Low | Concerns | Low | Concerns |
| 22 | No information | Probably no | No information | High | High | Low | High | Low | Concerns |
| 23 | No information | Probably no | Probably no | High | Concerns | Low | Concerns | Low | Concerns |
| 24 | Probably yes | Probably no | No information | High | Concerns | Low | Low | Low | Low |
| 25 | Probably yes | Probably no | Probably no | High | Low | Low | Concerns | Low | Low |
| 26 | No information | Probably o | No | High | Concerns | Low | Concerns | Low | Concerns |
| 27 | No information | Probably no | No information | High | High | Low | Concerns | Low | Concerns |
| 28 | No information | Probably no | No information | High | High | Low | Low | Concerns | Concerns |
| 29 | No information | Probably no | No information | High | High | Low | Concerns | Low | Concerns |
| 30 | No information | Probably no | No information | High | High | Low | Low | Low | Concerns |
| 31 | No information | Probably no | No information | High | High | Low | Concerns | Low | Concerns |
| 32 | No information | Probably no | No information | High | High | Low | Low | Low | Concerns |
| 33 | Probably no | Probably no | No information | High | High | Concerns | Concerns | Low | Concerns |
| 34 | No information | Probably no | No information | High | High | Low | Concerns | Low | Concerns |
| 35 | No information | Probably no | No information | High | High | Low | Low | Low | Concerns |
| 36 | No information | Probably no | No | High | Concerns | Low | Concerns | Low | Concerns |
| 37 | No information | Probably no | No information | High | High | Low | High | Concerns | Concerns |
| 38 | Probably yes | Probably yes | No | Low | Low | Low | Low | Low | Low |

* Was the allocation sequence random?
† Was the allocation sequence concealed until participants were recruited and assigned to interventions?
‡ Were there baseline imbalances that suggest a problem with the randomization process?
§ Risk of bias due to randomization process.
¶ In ROB 2.0, any study that did not report allocation concealment was automatically at high risk of bias, however this item was not considered in the overall assessment of bias due to randomization.
** Risk of bias due to deviations from intended interventions.
†† Risk of bias due to missing outcome data.
‡‡ Risk of bias in the measurement of the outcome.
§§ Risk of bias in selection of the reported results.
SQ = signaling question; ROB = risk of bias.

**Figure 3:** The ranking plot of relevant treatments. A ranking of 1 has the lowest treatment failure risk and 19 has the highest treatment failure risk. Ranking means (2.5 % lower limit of CI, 97.5% upper limit of CI) are reported for registered antibiotic regimens only. The number of study arms are presented in parentheses for each injectable antibiotic regimen reported. Antibiotic regimen abbreviation definitions are listed in Table 1.




## Assessing sources of systematic bias

The beta for the sponsorship indicator variable was -0.08 (95% CI, -1.39 to 1.32), while $\beta_{randomization}$ = -4.27 (95% CI, -18.59 to 10), and $\beta_{blinding}$ = -1.13 (95% CI, -4.47 to 1.14). These results do not suggest systematic bias in either direction thus they were not included in the final network meta-analysis model.

## Risk of bias across studies

Risk of bias across studies, such as looking for evidence of small-studies effect, was not assessed because the number of individual studies available for assessment within each treatment and pairwise comparison was low.

## Limitations

The major limitation of this review is the paucity of data available for inclusion in the review. Although SRD is an important disease, it is surprising that only 41 publicly available studies could be identified for inclusion in the review and data from only 34 studies could be included in the meta-analysis. If company websites had been included as a source of evidence, more studies might have been identified. Such sites were not included because they are not a time-stamped source and, therefore, not a reproducible source of data. After a review is published, relevant studies can be added to or removed from company websites without traceable documentation. This is not possible with conference proceedings and journals indexed in the SIL or CABI. Another aspect of the scientific literature in this body of work that should be addressed is the poor reporting associated with conference proceedings. As reported previously, many studies in swine production are not published in peer-reviewed journals.[39] Therefore, the studies in conference proceedings are a vital resource for practitioners and research synthesis. Further, conference proceedings are not subjected to peer review and authors are not required to indicate if the findings presented are the final results, which has the potential to increase favorable findings.

Another possible concern is the potential omission of antibiotic regimens of interest. A *post hoc* evaluation by the sponsor designate of possible SRD antibiotics did identify several registered antibiotic regimens in Europe that were not included in the protocol. For completeness, we re-assessed if studies excluded at level 2, because they were considered to have not used a relevant regimen, used these European-registered regimens. One study featured a treatment arm with oxytetracycline given at a dose of 20 mg/kg.[40] If the pigs were still sick 48 h after the first injection, they were given a second injection at the same dose. Injecting twice at this dose is not a registered use in the United States. The results for this arm were presented without distinguishing which pigs received 1 vs 2 injections and, therefore, this study would not have been eligible for the review. A second study included one treatment arm with amoxicillin at 7 mg/kg for 3 or 5 days (treatment was only given for 5 days if pigs were still sick at that point).[41] The outcome reported was cure risk by day 5. The other treatment arm received marbofloxacin at 2mg/kg once daily for 3 to 5 days rather than 3 days, which was the regimen of interest in the protocol. The combined registered (2mg/kg once daily for 3 days) and unregistered (2mg/kg once daily for 5 days) marbofloxacin dose regimen was the rationale for exclusion. The amoxicillin regimen was not identified *a priori* as a regimen of interest, although it is registered in Europe. If either regimen had been of interest, the results of the study could not have been included in the meta-analysis because neither treatment arm linked to the rest of the evidence network, ie, both arms were unique treatment regimens. As these are post-hoc regimens introduced for discussion and transparency, these studies are not included in the PRISMA diagram (Figure 1).

Another possible concern is the impact of the funding source on the meta-analysis. The highest-ranked product found by the review is owned by the sponsoring company. However, the data informing the review are publicly available data and are verifiable even though the company likely has additional data that could further narrow the 95% CI. Therefore, the authors propose that others using the same criteria would reach the same conclusion. To further address this concern several steps were taken: 1) a time-stamped *a priori*

**Table 4:** Mean ranking for treatment efficacy for antibiotic regimens for SRD based on mixed-treatment comparison meta-analysis.

| | | 95% Credible Interval and median rank | | |
|---|---|---|---|---|
| **Treatment arm** | **Ranking,* mean (SD)** | **2.50%** | **50%** | **97.5%** |
| Enrofloxacin | 1.65 (1.01) | 1 | 1 | 4 |
| Gamithromycin | 4.82 (3.53) | 1 | 4 | 14 |
| Enrofloxacin (7.5 mg/kg once or twice) | 5.34 (3.15) | 1 | 5 | 13 |
| Enrofloxacin (2.5 mg/kg 3 days) | 5.45 (3.73) | 1 | 4 | 15 |
| Marbofloxacin | 5.76 (4.27) | 1 | 4 | 16 |
| Florfenicol | 7.06 (2.76) | 3 | 7 | 13 |
| Danofloxacin (1.25 or 2.5 mg/kg once) | 8.42 (5.45) | 1 | 7 | 19 |
| Tildipirosin | 8.68 (2.92) | 4 | 9 | 14 |
| Tulathromycin | 8.83 (2.32) | 4 | 9 | 13 |
| Amoxicillin | 10.44 (3.69) | 4 | 11 | 17 |
| Amoxicillin/clavulanic acid (7.0/1.75 mg/kg 3 days) | 10.45 (4.09) | 3 | 11 | 18 |
| Ceftiofur (MD) | 10.69 (2.77) | 5 | 11 | 15 |
| Ceftiofur CFA | 11.41 (3.53) | 4 | 12 | 17 |
| Oxytetracycline | 12.80 (4.26) | 4 | 14 | 19 |
| Ceftiofur HCl (5 mg/kg once) | 14.84 (3.55) | 5 | 16 | 19 |
| Ceftiofur (HCl or NA) | 15.07 (4.75) | 3 | 17 | 19 |
| Non-active control | 15.27 (1.59) | 12 | 15 | 18 |
| Tiamulin | 15.44 (2.43) | 10 | 16 | 19 |
| Ceftiofur NA (1-2 mg/kg 3 days) | 17.57 (2.31) | 11 | 18 | 19 |

* A ranking of 1 has the lowest treatment failure risk and 19 has the highest treatment failure risk. Rankings are reported for all regimens included in the meta-analysis.

MD = Multidose; CFA = crystalline free acid; HCl = hydrochloride; NA = sodium.

protocol was created and followed with no deviations from the protocol, 2) the role of the sponsor designate was transparently reported and documented, and 3) once the protocol was time-stamped the sponsor designate was not responsible for the steps of the review from the search to the first draft of the full manuscript. Once the first draft was written, no further analyses were conducted, and the sponsor designate was only able to contribute to the interpretation and discussion.

It is important to recognize that a systematic review is neither a formal guideline for clinical use nor a recommendation for use. Inference is limited to the review question, which was comparative efficacy, whereas guidelines for clinical use should consider multiple factors. Comparative efficacy is only one dimension that should be considered when selecting an antibiotic. Other dimensions should include the spectrum (broad or narrow) of antibiotic, the sensitivity and specificity of the diagnosis of SRD, the organism likely to be involved based on the veterinarian's knowledge of the farm where the animals are raised, and guidelines from leading agencies about antibiotic stewardship in swine production.

## Implications

- The results of network meta-analysis can provide information about the comparative efficacy of antibiotics when primary studies of active-to-active trials are missing. This gives producers and veterinarians information that might overwise not be available.
- The network used was reasonably small due to an absence of publicly indexed data; however, the estimates suggest that the top 4 model-estimated SRD treatments based on the mean rank were enrofloxacin (7.5 mg/kg once or 2.5-5 mg/kg once daily for 3-5 days; n = 5; rank = 2; 95% CI, 1-4), gamithromycin (6 mg/kg once, n = 2; rank = 5; 95% CI, 1-14), marbofloxacin (8 mg/kg once, n = 1; rank = 6; 95% CI, 1-16), and florfenicol (15 mg/kg twice 48 hours apart, n = 6; rank = 7; 95% CI, 3-13).
- Producers would have greater confidence in the comparable efficacy of products available if more, better-reported trial results were available in publicly indexed locations.
- With respect to antibiotic choices, comparative efficacy is only one metric that should be considered when selecting an antibiotic. Other metrics should include the antibiotic spectrum (broad or narrow), the organism likely to be involved based on the veterinarian's knowledge of the system the animals are raised in, and guidelines from leading agencies about appropriate antibiotic stewardship in

**Table 5:** Risk ratio of all possible comparisons within the evidence network. The upper right-hand quadrant represents the estimated risk ratio and the lower quadrant represents the 95% CI. Risk ratios are reported for registered antibiotic regimens only.

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **NAC** | 2.46 | 1.92 | 1.88 | 16.46 | 3.53 | 8.86 | 9.42 | 1.95 | 2.54 | 2.30 |
| (0.65-8.01) | **AMX** | 1.04 | 1.16 | 10.15 | 1.76 | 5.32 | 3.89 | 0.99 | 1.55 | 1.40 |
| (0.69-5.32) | (0.22-3) | **CCFA** | 1.28 | 11.07 | 2.24 | 5.92 | 5.37 | 1.24 | 1.71 | 1.55 |
| (1-3.65) | (0.21-3.45) | (0.31-3.4) | **CEF** | 9.45 | 2.03 | 4.94 | 5.40 | 1.13 | 1.44 | 1.30 |
| (4.17-43.18) | (1.54-37.44) | (2.1-36.28) | (2.59-26.95) | **ENF** | 0.27 | 0.67 | 0.67 | 0.15 | 0.20 | 0.18 |
| (1.09-9.96) | (0.52-4.45) | (0.49-6.94) | (0.52-5.92) | (0.05-0.82) | **FLO** | 3.26 | 2.55 | 0.57 | 0.96 | 0.87 |
| (1.02-40.76) | (0.34-27.1) | (0.46-28.95) | (0.54-22.05) | (0.05-3.1) | (0.25-15.78) | **GAM** | 3.67 | 0.56 | 0.59 | 0.60 |
| (0.77-46.01) | (0.49-15.93) | (0.41-26.91) | (0.37-26.55) | (0.04-3.29) | (0.28-11.47) | (0.06-13.97) | **MAR** | 0.56 | 0.87 | 0.79 |
| (0.39-7.36) | (0.15-3.44) | (0.16-4.7) | (0.17-4.3) | (0.02-0.58) | (0.14-1.56) | (0.02-2.53) | (0.03-2.35) | **OXY** | 2.35 | 2.11 |
| (1.07-5.75) | (0.26-4.97) | (0.36-4.99) | (0.52-3.38) | (0.04-0.53) | (0.2-2.74) | (0.08-1.87) | (0.05-3.64) | (0.29-8.57) | **TIL** | 1.02 |
| (1.24-4) | (0.28-4.06) | (0.4-3.92) | (0.65-2.33) | (0.05-0.44) | (0.22-2.13) | (0.06-2.06) | (0.05-3.17) | (0.3-6.98) | (0.46-1.92) | **TUL** |

Antibiotic regimen abbreviation definitions are listed in Table 1.

swine production.

# Acknowledgments

## Authorship roles

Dr O'Connor developed the review protocol, coordinated the project team, conducted relevance screening, extracted data, conducted the data analysis, interpreted the results, and wrote the first manuscript draft. Dr Totton assisted with development of the protocol, conducted relevance screening, extracted data, provided guidance for the interpretation of results, commented on manuscript drafts, and approved the final manuscript version. Dr Shane conceived of the project question and the eligibility criteria, assisted with identifying relevant information sources, assisted with designing the terms used in the search strategy, approved the review protocol, and contributed to the interpretation of the results and conclusions. Dr Shane did not participate in relevance screening of retrieved records, extraction of data, or conduct of the data analysis.

## Publication declaration

The authors declare that this is a full and accurate description of the project and no important information or analyses are omitted.

## Sponsorship

This study was funded by Bayer Animal Health. The sponsor and sponsor designate had a role in developing the protocol to ensure that the review studied the target swine populations, interventions, outcomes, and study designs of interest. It was determined *a priori* (SM1: Protocol) that during the review process, if needed, the sponsor designate would provide feedback about potentially relevant studies only when the 2 main reviewers were in conflict about eligibility. The sponsor designate was otherwise not involved in eligibility assessment of citations retrieved by the search, data extraction, or conduct of the analysis. The first draft of the results was provided for the sponsor designate's interpretation of the results and the discussion. It was decided *a priori* (SM1: Protocol) that the sponsor had a role in developing the protocol, providing feedback on the draft of the discussion and conclusions, and, consistent with standards for authorship, should be listed as a co-author on any publications and conflicts of interest noted.

## Conflict of interest

Drs O'Connor and Totton were funded by Bayer Animal Health for the conduct of the review. Dr Shane is the sponsor designate and employed by Bayer Animal Health.

## Disclaimer

Scientific manuscripts published in the *Journal of Swine Health and Production* are peer reviewed. However, information on medications, feed, and management techniques may be specific to the research or commercial situation presented in the manuscript. It is the responsibility of the reader to use information responsibly and in accordance with the rules and regulations governing research or the practice of veterinary medicine in their country or region.

**Table 6:** Results of the indirect comparison for the consistency assumption.

| Comparison* | Dir, d (SD)† | MTC, d (SD)‡ | Rest, d (SD)§ | w (SD) | *P* value¶ |
|---|---|---|---|---|---|
| Enrofloxacin vs Enrofloxacin (2.5 mg/kg 3 days) | 1.16 (2.91) | 1.17 (0.80) | 1.17 (0.84) | -0.01 (3.03) | 1.00 |
| Enrofloxacin (7.5 mg/kg once or twice) vs Marbofloxacin | -0.04 (2.90) | -0.03 (1.06) | -0.02 (1.14) | -0.01 (3.11) | 1.00 |
| Enrofloxacin (7.5 mg/kg once or twice) vs Amoxicillin | -0.55 (2.94) | 0.96 (0.84) | 1.09 (0.88) | -1.64 (3.07) | 0.59 |
| Florfenicol vs Enrofloxacin (7.5 mg/kg once or twice) | 1.37 (3.03) | -0.43 (0.79) | -0.57 (0.82) | 1.93 (3.14) | 0.54 |
| Florfenicol vs Tulathromycin | 1.18 (3.17) | 0.33 (0.53) | 0.31 (0.54) | 0.87 (3.21) | 0.79 |
| Oxytetracycline vs Florfenicol | 1.00 (2.90) | -1.00 (0.86) | -1.19 (0.9) | 2.19 (3.04) | 0.47 |
| Tiamulin vs Tulathromycin | -1.16 (0.66) | -1.13 (0.48) | -1.1 (0.69) | -0.06 (0.95) | 0.95 |
| Tildipirosin vs Gamithromycin | 0.87 (2.93) | -0.92 (0.87) | -1.1 (0.91) | 1.97 (3.07) | 0.52 |
| Tulathromycin vs Tildipirosin | 0.04 (0.65) | -0.05 (0.41) | -0.11 (0.53) | 0.15 (0.84) | 0.86 |
| Tulathromycin vs Amoxicillin/clavulanic acid (7.0/1.75 mg/kg 3 days) | -0.31 (1.69) | 0.24 (0.64) | 0.33 (0.69) | -0.64 (1.83) | 0.73 |
| Non-active control vs Enrofloxacin | -3.73 (1.50) | -3.04 (0.48) | -2.96 (0.5) | -0.76 (1.58) | 0.63 |
| Non-active control vs Florfenicol | -1.39 (2.95) | -1.35 (0.62) | -1.35 (0.63) | -0.04 (3.02) | 0.99 |
| Non-active control vs Tildipirosin | -0.99 (2.88) | -1.07 (0.47) | -1.07 (0.48) | 0.08 (2.92) | 0.98 |
| Non-active control vs Tulathromycin | -1.05 (0.31) | -1.02 (0.29) | -0.82 (0.78) | -0.24 (0.84) | 0.78 |
| Non-active control vs Ceftiofur CFA | -0.44 (2.90) | -0.65 (0.64) | -0.66 (0.65) | 0.22 (2.97) | 0.94 |
| Non-active control vs Ceftiofur (MD) | -1.00 (0.65) | -0.76 (0.38) | -0.64 (0.47) | -0.36 (0.8) | 0.65 |
| Non-active control vs Ceftiofur HCl (5 mg/kg once) | 0.11 (2.95) | 0.08 (0.79) | 0.08 (0.82) | 0.03 (3.06) | 0.99 |
| Amoxicillin vs Florfenicol | -0.75 (2.96) | -0.52 (0.71) | -0.51 (0.73) | -0.25 (3.05) | 0.94 |
| Ceftiofur (HCl or NA) vs Florfenicol | -1.93 (3.22) | -1.92 (1.47) | -1.92 (1.66) | -0.01 (3.62) | 1.00 |
| Ceftiofur CFA vs Amoxicillin | -0.35 (3.01) | -0.19 (0.72) | -0.18 (0.74) | -0.17 (3.1) | 0.96 |
| Ceftiofur (MD) vs Tulathromycin | -0.49 (0.79) | -0.26 (0.34) | -0.21 (0.38) | -0.28 (0.87) | 0.75 |
| Ceftiofur NA (1-2 mg/kg 3 days) vs Ceftiofur NA (1-2 mg/kg 3 days) | 1.07 (2.93) | 0.00 (0.94) | -0.12 (1) | 1.19 (3.09) | 0.70 |
| Danofloxacin (1.25 or 2.5 mg/kg once) vs Gamithromycin | -0.68 (2.90) | -0.71 (1.23) | -0.72 (1.35) | 0.04 (3.2) | 0.99 |

* The first treatment listed is the reference (denominator) and the second treatment listed is the comparator (numerator).
† Posterior mean (d) and SD of log-odds ratio of treatment effects calculated using direct evidence only.
‡ Posterior mean (d) and SD of log-odds ratio of treatment effects calculated using all the evidence.
§ Posterior mean (d) and SD of log-odds ratio of treatment effects calculated using indirect evidence only.
¶ The Z distribution test was used.
Dir = direct evidence; d = posterior mean; MTC = all evidence; rest = indirect evidence; w = inconsistency estimate; CFA = crystalline free acid; MD = multidose; HCl = hydrochloride; NA = sodium.

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* Non-refereed references.

# 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 1$^{st}$ 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<br>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<br><br>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<br><br>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<br><br>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.<br><br>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<br><br>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<br><br>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<br><br>Efficacy of tulathromycin for the treatment of at risk nursery pigs [071.pdf] Matt Allerson; John Deen, DVM, MVSc, PhD; Stephanie Rutten, DVM<br><br>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<br><br>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.<br><br>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.<br><br>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]<br>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
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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.
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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.
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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.
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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.
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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.
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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.
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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.
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**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.

# Supplementary material 2

# 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.

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The citation searches began on October 5, 2017 and searching for new studies was completed on November 30, 2017 after all relevant studies had been identified and their bibliographies assessed. The Cambridge Agricultural and Biological Index search conducted is reported in Table S1. The search strategy was not peer-reviewed. Instead, we verified that 4 studies identified as likely to be relevant to the review were captured by the search. The Swine Information Library has an interface that makes Boolean searches difficult. Therefore, to identify relevant manuscripts, the webpage "find" function was used to search for titles that included the single word terms "treat", "trial", "efficacy", and the titles and abstracts with those terms evaluated for evidence. Those considered relevant were manually entered into a RIS file format. The New Animal Drug Application (NADA) and Abbreviated NADA (ANADA) numbers searched were as follows: NADA 97-505, NADA 111-636, NADA 113-232, NADA 140-338, NADA 140-890, NADA 141-209, NADA 141-235, NADA 141-244,NADA 141-264, NADA 141-288, NADA 141-328 ,NADA 141-334 , ANADA 200-066, ANADA 200-154, ANADA 200-128, NADA 141-206. This list included some NADA and ANADA that were only tangentially relevant regimes (ie, in feed for the same products); however, these were assessed in case a relevant treatment was used as a comparator. Duplication refers to multiple citations of the same publication. Duplicates were removed initially in the reference management software, then again in the systematic review management software (Distiller SR, Ontario, Canada). Linked publications, ie, the same studies reported in part or in full in different sources, were sometimes identified during the relevance screening but more commonly during data extraction. For linked publications, the more complete record was used as the citation. Reference lists from relevant reports and reviews were hand searched for additional relevant manuscripts. If these studies were published in years outside of our original search range, they were still included. When disagreements arose about the relevance of the study, the two reviewers consulted and made a determination. It was not found to be necessary to consult the sponsor designate during the eligibility assessment.

**Table S1:** CABI Web of Science search results for literature from 1970-2017†

| Search No. | Search string | No. of hits |
|---|---|---|
| #8 | #3 AND #4 AND #7 | 992 |
| #7 | #5 OR #6 | 48,073 |
| #6 | TS = (pneumonia OR pleuritis OR pleuropneumonia OR "respiratory disease" OR SRD) | 35,025 |
| #5 | TS = ("*Mycoplasma hyopneumoniae*" OR M. hyo OR "*Actinobacillus pleuropneumoniae*" OR APP OR "*Bordetella bronchiseptica*" OR "*Pasteurella multocida*" OR "*Streptococcus suis*" OR "*Haemophilus parasuis*" OR Glassers Disease OR "*Actinobacillus suis*") | 16,563 |
| #4 | 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*) | 509,424 |
| #3 | #2 OR #1 | 42,298 |
| #2 | 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) | 2221 |
| #1 | 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) | 41,624 |

† The search was performed on October 10, 2017.
CABI = Cambridge Agricultural and Biological Index; TS =Topic search string used by CABI to identify the type of search to conduct.

**Table S2:** Criteria for exclusion of 190 full text articles from the meta-analysis

| Reference | Exclusion criteria |
|---|---|
| The Upjohn Company *Naxcel Sterile Powder* **https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/469**. NADA 140-338 FOI Summary Supplemental New Animal Drug Application. Approved April 05, 1990. Accessed October 2017. | Level 2, Form level_2_screening_form, Population -> No-exclusion reason wrong population |
| Zoetis Inc. (original sponsor: Pharmacia & Upjohn Company A Division of Pfizer Inc) *NAXCEL Sterile Powder (ceftiofur sodium) to establish a 4-day pre-slaughter withdrawal time for swine* **https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/476**. NADA 140-338 FOI Summary Supplemental New Animal Drug Application. Approved June 18, 2004. Accessed October 2017. | Level 2, Form level_2_screening_form, Outcome: Does the study report treatm... -> No - treatment response not reported |
| The Upjohn Company. *Excenel® Sterile Suspension* (*ceftiofur hydrochloride*). **https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/516**. NADA 140-890 FOI Summary Original New Animal Drug Application. Approved April 26, 1996. Accessed October 2017. | Level 2, Form level_2_screening_form, Population -> No-exclusion reason wrong population |
| The Upjohn Company. *Excenel® Sterile Suspension* (*ceftiofur hydrochloride*). **https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/520**. NADA 140-890 FOI Summary Supplemental New Animal Drug Application. Approved June 18, 2004. Accessed October 2017. | Level 2, Form level_2_screening_form, Population -> No-exclusion reason wrong population |
| Pharmacia & Upjohn Co., a Division of Pfizer, Inc. *Excede for Swine. Ceftiofur Crystalline Free Acid Sterile Suspension Swine* **https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/777**. NADA 141-235 FOI Summary Supplemental New Animal Drug Application. Approved September 15, 2010. Accessed October 2017. | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |
| Pharmacia & Upjohn Co., a Division of Pfizer, Inc. *Excenel® RTU EZ Sterile Suspension*, *Ceftiofur hydrochloride*. *Sterile suspension for injection*. *Swine and cattle* (*beef, non-lactating dairy*, *and lactating dairy*) **https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/851**. NADA 141-288 FOI Summary Original New Animal Drug Application. Approved July 1, 2008. Accessed October 2017. | Level 2, Form level_2_screening_form, Population -> No-exclusion reason wrong population |
| Zoetis Inc. *Excenel® RTU EZ Ceftiofur Hydrochloride*. *Sterile Suspension*. *Swine and cattle* (*beef*, *non-lactating dairy*, *and lactating dairy*). **https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/852**. NADA 141-288 FOI Summary Original New Animal Drug Application. Approved September 13, 2013. Accessed October 2017. | Level 2, Form level_2_screening_form, Population -> No-exclusion reason wrong population |
| Schering-Plough Animal Health. *Nuflor® 2.3% Concentrate Solution* (*florfenicol*). **https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/724**. NADA 141-206 FOI Summary Original New Animal Drug Application. Approved September 04, 2002. Accessed October 2017. | Level 2, Form level_2_screening_form, Intervention: Does the paper appear t... -> No - Drug correct but regime not correct |
| Pennfield Oil Company. Pennox 200 Injection. **https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/990**. ANADA 200-154 Oxytetracycline 200 - original approval. Approved June 13, 2002. Accessed October 2017. | Level 2, Form level_2_screening_form, Population -> No-exclusion reason wrong population |
| Ferro A, Marca J, Navarrete E, Stipkovits L. The effect of the combination of benzylpenicillin + dihydrostreptomycin + Inmodulen® in the treatment of enzootic pneumonia. *Proc IPVS*. Melbourne, Australia. 2000;129. | Level 2, Form level_2_screening_form, Intervention: Does the paper appear t... -> No - Not a relevant drug |
| Kohn K, Neike EM. Excenel™ RTU (ceftiofur HCl) every-other-day treatment for acute pneumonia in pigs. *Proc IPVS*. Melbourne, Australia. 2000;134. | Level 2, Form level_2_screening_form, Intervention: Does the paper appear t... -> No - Drug correct but regime not correct |

**Table S2:** Continued

| Reference | Exclusion criteria |
|---|---|
| Grandemange E, Benzerrak S, Woehrle F, Boisrame B. Pharmacodynamic, pharmacokinetic and clinical properties of marbofloxacin in the treatment of respiratory diseases in fattening pigs. *Proc IPVS*. Melbourne, Australia. 2000;455. | Level 2, Form level_2_screening_form, Population -> Not at all relevant |
| Pallares FJ, Berrocal F, Sanchez A, Oliva JE, Munoz A, Martinez JS. Comparison of two different treatments against swine enzootic pneumonia in three sites production system. *Proc IPVS*. Melbourne, Australia. 2000;502. | Level 2, Form level_2_screening_form, Intervention: Does the paper appear t... -> No - Drug correct but regime not correct |
| Timmerman T, Dewulf J, Maes D, Catry B, de Kruif A. Antibiotics used for group treatment in Belgian pig herds. *Proc IPVS*. Hamburg,Germany. 2004;515. | Level 2, Form level_2_screening_form, Population -> Not at all relevant |
| McKelvie J, Nanjiani I, Sherington J, Rowan TG, Sutherland SJ. The efficacy of tulathromycin Draxxin® in the treatment of swine respiratory disease associated with *Mycoplasma hyopneumoniae*. *Proc IPVS*. Hamburg, Germany. 2004;528. | Level 2, Form level_2_screening_form, Population -> No- challenge study |
| Palzer A, Ritzmann M, Wolf G, Heinritzi K. Control of a treatment with tulathromycin (Draxxin®) by bronchoalveolar lavage. *Proc IPVS*. Copenhagen, Denmark. 2006:P.20-06. | Level 2, Form level_2_screening_form, Outcome: Does the study report treatm... -> No - treatment response not reported |
| Schuh HH, Detloff EM. Different methods of treatment to control bacterial diseases and losses in the wean to feeder period. *Proc IPVS*. Copenhagen, Denmark. 2006;P.38-14. | Level 2, Form level_2_screening_form, Is the full text available in English? -> No- no attachment so not available |
| Salvini F, Guadagnini, G Antibiotic treatments for prdc: field experience on the use of Draxxin®. *Proc IPVS*. Copenhagen, Denmark. 2006;P05.040 | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |
| Nanjiani I, Joaquin M, Carlos P, Pascale S, Jensen E Christian J. Metaphylaxis with tulathromycin (Draxxin®) and therapeutic use of ceftiofur (Naxcel®) against Swine Respiratory Disease and Polyserositis Complex in pigs: comparison with the use of in-feed Amoxycillin. *Proc IPVS*. Vancouver, Canada 2006;P364 | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |
| Carles V, Nuria G, Virginia A, Rozas A, Lorenzo F. Effect of marbofloxacin treatment on *Haemophilus parasuis* colonization. *Proc IPVS*. Jeju, Korea. 2012;145. | Level 2, Form level_2_screening_form, Outcome: Does the study report treatm... -> No - treatment response not reported |
| Lorenzo JL, Rosas ML, MenjÃ R, JimÃnez M, Bollo JM. Efficacy of Zuprevo 4% in the early treatment of an acute *H. parasuis* infection compared with another. *Proc IPVS*. Jeju, Korea. 2012;659. | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |
| Thiry J, de Haas V, Thomas E. Efficacy of a new florfenicol formulation administered once intramuscularly in the treatment of swine respiratory disease under field conditions. *Proc IPVS*. Jeju, Korea. 2012;777. | Level 2, Form level_2_screening_form, Intervention: Does the paper appear t... -> No - Drug correct but regime not correct |
| Voss T, Eggen , Rueden S, von Berg S. Efficacy of treatment with Tildipirosin (Zuprevo®) compared with Tulathromycin (Draxxin®) treatment or vaccination, in controlling *Haemophilus parasuis* infections. *Proc IPVS*. Jeju, Korea. 2012;PP032 | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |
| Macedo N, Torremorell M, Rovira A. Impact of early antibiotic treatment on *H. parasuis* disease, seroconversion and resistance to challenge. *Proc IPVS*. Cancun, Mexico. 2014;225. | Level 2, Form level_2_screening_form, Population -> No- challenge study |
| Unterweger C, Ruczizka U, Spergser J, Baums C, Hennig-Pauka I. Efficacy of early-life longtime Ceftiofur treatment in piglets on *Streptococcus suis* serotype 7 dynamics in a farm dealing with streptococcal diseases. *Proc IPVS*. Dublin, Ireland. 2016. | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |
| Hoeltig D, Rohde J, Brunner B, Hellmann K, Grandemange E, Waldmann KH. Efficacy of one-shot Marbofloxacin treatment on development of porcine pleuropneumonia. *Proc IPVS*. Dublin, Ireland. 2016;329. | Level 2, Form level_2_screening_form, Population -> No- challenge study |
| Kondo Y, Nakanishi N, Wakui Y, Richard-Mazet A, Kinoshita G, Jeannin P. Field efficacy of ZACTRAN® (gamithromycin injectable solution) for the treatment of *Mycoplasma hyopneumoniae* for swine in Japan. *Proc IPVS*. Dublin, Ireland. 2016;572. | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |

**Table S2:** Continued

| Reference | Exclusion criteria |
|---|---|
| Caldern Diaz JA, Diana A, Boyle LA, Teixeira D, Garcia Manzanilla E. Effects of antibiotic treatment during the weaner stage on pig performance and health during finishing. *Proc IPVS*. Dublin, Ireland. 2016;1343. | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |
| Gjestvang M, Lium B, Framstad T. A field trial to eradicate *actinobacillus pleuropneumoniae* from seropositive herds using double-dose injections with enrofloxacin (Baytril®) and in-feed medication with Tiamulin (Tiamutin®). *Proc IPVS*. Durbin, South Africa. 2008;OR.03.03. | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |
| Yuenyaw A, Nusupa W, Thongmak W, Navasakuljinda W, Urairong S. Field observation of efficacy of Draxxin® on nursery pig in farms in Thailand. *Proc IPVS*. Cancun, Mexico. 2014;271. | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |
| Kondo Y, Nakanishi N, Wakui Y, Richard-Mazet A, Tokuyama K, Kinoshita G, Jeannin P. Second-line therapeutic efficacy of ZACTRAN® (gamithromycin injectable solution) against Swine Respiratory Disease in a field trial in Japan. *Proc IPVS*. Dublin, Ireland. 2016;583. | Level 2, Form level_2_screening_form, Population -> No-exclusion reason wrong population |
| Schwartz KJ, Ewert KM. 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. *Proc AASV*. Indianapolis, Indiana. 2000:103. | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |
| Cardinal F. Use of Nuflor and Banamine for individual treatment of PMWS and PCV2 associated pneumonia. *Proc AASV*. Kansas City, Missouri. 2006:135-138. | Level 2, Form level_2_screening_form, Outcome: Does the study report treatm... -> No - treatment response not reported |
| Allerson M, Deen J, Rutten St. Efficacy of tulathromycin for the treatment of at risk nursery pigs. *Proc AASV*. Orlando, Florida. 2007:71-72. | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |
| Eubank J, Senn MK, R. Nutsch G, Wachowski MB, Taylor LP; Moyaert H; N. Wuyts N. Comparison of efficacy of tulathromycin (DRAXXIN®) and tildipirosin (ZUPREVO®) in the treatment of *Mycoplasma hyopneumoniae* infection in pigs. *Proc AASV*. San Diego, California. 2013:415-416. | Level 2, Form level_2_screening_form, Population -> No- challenge study |
| Nubia M, Holtcamp A, Maxim C. Effect of antibiotic treatment on the development of *Haemophilus parasuis* disease and seroconversion. *Proc AASV*. Dallas, Texas. 2014:73-74. | Level 2, Form level_2_screening_form, Population -> No- challenge study |
| Nutsch GR, Merlyn JL, Collard W. Safety of DRAXXIN® 25 injectable solution (tulathromycin 25 mg/mL) in swine for treatment and control of SRD. *Proc AASV*. Dallas, Texas. 2014:73-74. | Level 2, Form level_2_screening_form, Population -> Not at all relevant |
| Reynolds K, Poljak Z, Friendship RM, Dewey C. 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. *Proc AASV*. Omaha, Nebraska. 2010:333-334. | Level 2, Form level_2_screening_form, Outcome: Does the study report treatm... -> No - treatment response not reported |
| Johnson JC, Hoover T. Health and performance improvements in pigs treated with tulathromycin injectable solution (Draxxin®) for swine respiratory disease (SRD). *Proc AASV*. Dallas, Texas. 2009:155-156. | Level 2, Form level_2_screening_form, Outcome: Does the study report treatm... -> No - treatment response not reported |
| Hoover T, Johnson J. Clinical responses and performance of pigs treated with tulathromycin injectable solution (DRAXXIN®) for swine respiratory disease (SRD). *Proc Allen D. Leman Swine Conf*. Minneapolis, Minnesota. 2009. | Level 2, Form level_2_screening_form, Outcome: Does the study report treatm... -> No - treatment response not reported |
| Nutsch RG, Wachowski MB, Taylor LP, Moyaert H, Wuyts N. Comparison of efficacy of Tulathromycin (Draxxin®) and Tildipirosin (Zuprevo®) in the treatment of *Mycoplasma hyopneumoniae* infection in pigs. *Proc Allen D. Leman Conf*. Minneapolis, Minnesota. 2012:230. | Level 2, Form level_2_screening_form, Population -> No- challenge study |

**Table S2:** Continued

| Reference | Exclusion criteria |
|---|---|
| Nutsch RG, Lucas MJ, Collard W, Lesman SP, Boucher JF, Tena JKS, Senn M. Efficacy of Draxxin® 25 injectable solution (Tulathromycin 25 mg/ml) for treatment and control of swine respiratory disease. *Proc Allen D. Leman Conf*. Minneapolis, Minnesota. 2013:230. | Level 2, Form level_2_screening_form, Population -> Not at all relevant |
| Fleck R, Lechtenberg K, Schieber T, Seagren, Amodie D. Draxxin at weaning for control of swine respiratory disease in a natural infection. *Proc Allen D. Leman Conf*. Minneapolis, Minnesota. 2013:231. | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |
| Uffe N, Nybroe G. Efficacy evaluation of Draxxin in an acute outbreak of *Actinobacillus pleuropneumoniae* type 2 among weaner pigs in Denmark. *Proc Allen D. Leman Conf*. Minneapolis, Minnesota. 2005. | Level 2, Form level_2_screening_form, Intervention: Does the paper appear t... -> No - Not a relevant drug |
| Silva N, Sousa M. Is marbofloxacin a good candidate for treating pigs in Europe? *Vet Rec*. 2017;180:588-590. | Level 2, Form level_2_screening_form, Population -> Not at all relevant |
| Depondt W. Improving the outcome of antimicrobial treatment for respiratory disease. *Int Pig Top*. 2017;32:7-9. | Level 2, Form level_2_screening_form, Population -> Not at all relevant |
| Pepovich P, Nikolov B, Genova K, Hristov K, Tafradjiiska-Hadjiolova R, Nikolova E, Stoimenov G. The comparative therapeutic efficacy of antimicrobials in pigs infected with *Mycoplasma hyopneumoniae*. *Sci Works*. *Series C. Vet Med*. 2016;62:76-81. | Level 2, Form level_2_screening_form, Outcome: Does the study report treatm... -> No - treatment response measure at th... |
| Abramov SV. Solving the problem of streptococcosis - "Maymoxi 10 microcapsulat". *Svinovodstvo* (*Moskva*). 2016;7:51-52. | Level 2, Form level_2_screening_form, Is the full text available in English? -> No- no attachment so not available |
| Sala V, de Faveri E, Gusmara C, Costa A. 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 Anim Rev*. 2015;21:129-134. | Level 2, Form level_2_screening_form, Is the full text available in English? -> No- foreign language |
| Chen X, Wang W, Wu Q, Shen X, Qiu D, Dong B, Liang Z, Fang B, Zeng Z, Chen J. Preparation of polylactic acid microspheres containing lactones from Venenum Bufonis, its slow-release characteristics and therapeutic effects on mycoplasmal pneumonia of swine. *Chin J Vet Sci*. 2015;35:2014-2020. | Level 2, Form level_2_screening_form, Is the full text available in English? -> No- no attachment so not available |
| Azlor O, Collell M, Fraile L. The use of tildipirosin in treating porcine respiratory disease complex. *Int Pig Top*. 2015;30:11. | Level 2, Form level_2_screening_form, Population -> Not at all relevant |
| Sala V, Costa A, de Faveri E, Campiotti G. Field comparative evaluation of two quinolones in the treatment of acute respiratory bacteriosis of pig fattening [Valutazione comparativa in campo di due chinoloni nel trattamento delle batteriosi respiratorie acute del ciclo magronaggio-ingrasso del suino]. *Atti della Societa Italiana di Patologia ed Allevamento dei Suini*, *XL Meeting Annuale*, *Montichiari*, *Italia*.2014;279-286 | Level 2, Form level_2_screening_form, Is the full text available in English? -> No- foreign language |
| Hien ND, Thu HTV, Dung TTK, Bryant JE. Porcine reproductive and respiratory syndrome (PRRS): current situation in Cantho City, viral and bacterial co-infection and antibiotic treatments. *Proc APVSC*. Ho Chi Minh City, Vietnam. 2013;OR62. | Level 2, Form level_2_screening_form, Population -> Not at all relevant |
| Krejci R, Forget P, Guerra N, Lopez A. Resuspendability and syringeability of Vetrimoxin LA in comparison with other injectable amoxicillin products. *Proc APVSC*. Ho Chi Minh City, Vietnam. 2013;OR15. | Level 2, Form level_2_screening_form, Population -> Not at all relevant |
| Moon YC, Park JY, Lee JH, Jeong PS, Kong HC, Lee SY. Control strategies of bacterial pathogens in Danji (high pig dense area). *Proc APVSC*. Ho Chi Minh City, Vietnam. 2013;PO48. | Level 2, Form level_2_screening_form, Population -> Not at all relevant |

**Table S2:** Continued

| Reference | Exclusion criteria |
|---|---|
| Cabezas A, Abellana J, Tasnadi G, Menjon R, Jimenez M. Comparative efficacy of Zuprevo 4% in the early treatment of H. parasuis infection. *Proc 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. 2013;182. | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |
| Marco E, Perdido JA, Mora J, Martinez N, Roozen M. *Mycoplasma hyopneumoniae* eradication in a 800 sow herd by partial depopulation and medication with tylvalosin (Aivlosin), tulathromycin (Draxxin) and tiamulin. *Proc 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. 2013;183. | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |
| Palomo A, Jimenez M, Menjon R. 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. 2013;184. | Level 2, Form level_2_screening_form, Outcome: Does the study report treatm... -> No - treatment response measure at th... |
| Bongiovanni E, Minelli G, Luppi A, Martelli P. Comparison of the efficacy of the oral and injectable treatments in the control of the respiratory disease of pig [Valutazione di due approcci metafilattici nel controllo della malattia respiratoria del maiale]. *Atti della Societa Italiana di Patologia ed Allevamento dei Suini*, *XXXIX Meeting Annuale*. Piacenza, Italia. 2013;239-245. | Level 2, Form level_2_screening_form, Is the full text available in English? -> No- foreign language |
| Klimov AA, Tatarchuk OP, Biryukova AV. The pharmacological basis of regimes for antibiotic therapy of respiratory diseases in pigs. *Svinovodstvo* (*Moskva*). 2012;4:62-4. | Level 2, Form level_2_screening_form, Is the full text available in English? -> No- no attachment so not available |
| Grandia J, Berges AC, Jimenez M, Menjon R. Effectiveness of tildipirosin (Zuprevo trade) in the early treatment of CRP in pigs [Eficacia de la tildipirosina (Zuprevo) en el tratamiento temprano del CRP en lechonera]. *Suis*. 2012;93:82. | Level 2, Form level_2_screening_form, Is the full text available in English? -> No- no attachment so not available |
| Macedo N, Torremorell M, Rovira A, Holtcamp A. Enrofloxacin treatment affects the colonization stage of *Haemophilus parasuis* in weaned pigs. *Proc AASV*. Denver, Colorado. 2012;53-54. | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |
| Langhoff R, Stuckler T, Ladinig A, Barz A, Spergser J, Palzer A, Ritzmann M. Investigation about the effects of tulathromycin (Draxxin) against *Mycoplasma hyorhinis* in a field trial [Untersuchung der Wirksamkeit von Tulathromycin (Draxxin) gegen *Mycoplasma hyorhinis* in einem Feldversuch]. *Tierarztliche Umschau*. 2012;67:3-9. | Level 2, Form level_2_screening_form, Is the full text available in English? -> No- no attachment so not available |
| Ardigo P, Ferrari L, Morganti M, de Angelis E, Luppi A, Gherpelli Y, Merialdi G, Volta A, Gnudi G, Saleri R, Borghetti P, Martelli P. Study on the clinical signs, the anatomic changes and the inflammatory cytokine pattern in bronchoalveolar lavage fluids of pigs suffering from spontaneous acute respiratory disease caused by *Actinobacillus pleuropneumoniae* and therapeutic implications [Studio delle manifestazioni cliniche, delle modificazioni anatomiche e del pattern infiammatorio citochinico nel liquido bronco-alveolare in suini affetti da malattia respiratoria acuta spontanea da *Actinobacillus pleuropneumoniae*: implicazioni terapeutiche]. *Atti della Societa Italiana di Patologia ed Allevamento dei Suini*, *XXXVIII Meeting Annuale*. Parma, Italia. 2012;187-204. | Level 2, Form level_2_screening_form, Is the full text available in English? -> No- foreign language |
| Senn MK, Nutsch RG, Lucas M. EXCEDE for swine sterile suspension for the control of swine respiratory disease. *Proc AASV*. Phoenix, Arizona. 2011;249-252. | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |
| Surprenant C, Gottschalk M. A treatment protocol designed to control Mycoplasma hyorhinis infection in a commercial herd points to a potential association with *Streptococcus suis*. *Proc AASV*. Phoenix, Arizona. 2011;463-464. | Level 2, Form level_2_screening_form, Population -> No- meta-phalyxis - healthy pigs |

**Table S2:** Continued

| Reference | Exclusion criteria |
|---|---|
| GuoWang L, Zhao H, Miao Z. Effect of Chinese herbs on *mycoplasma pneumonia* of swine. *Guizhou Agri Sci*. 2011;169-170. | Level 2, Form level_2_screening_form, Is the full text available in English? -> No- no attachment so not available |
| Schmelz F. 3.0, an innovative approach to long-term treatment of bovine respiratory infections and flu in pigs [3.0 - ein innovativer Ansatz zur Langzeit-Behandlung von Rindergrippe und Atemwegsinfektionen beim Schwein]. *Praktische Tierarzt*. 2011;92:1108-1109. | Level 2, Form level_2_screening_form, Is the full text available in English? -> No- no attachment so not available |
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**Table S2:** Continued

| Reference | Exclusion criteria |
|---|---|
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**Table S2:** Continued

| Reference | Exclusion criteria |
|---|---|
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**Table S2:** Continued

| Reference | Exclusion criteria |
|---|---|
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**Table S2:** Continued

| Reference | Exclusion criteria |
|---|---|
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**Table S3:** Definitions of swine respiratory disease used by studies included in the meta-analysis

| Reference number | Swine respiratory disease definition |
|---|---|
| 1 | A pig with a rectal temperature ≥ 104.0° F, increased respiratory rate, labored or dyspneic breathing, and depressed attitude was considered sick and febrile. |
| 2 | Pigs with a depression score of ≥ 2 (on a scale of 0 [normal] to 3 [severe depression]) and a respiratory score ≥ 2 (on a scale from 0 [normal] to 3 [severe respiratory distress]) and a rectal temperature ≥ 104.0° F were weighed, randomized to treatment groups, and treated (Day 0). |
| 3 | Pigs experiencing natural occurrences of bacterial respiratory disease (bacterial pneumonia). |
| 4 | Pigs were enrolled if they showed signs of bacterial respiratory disease and met the entrance criteria – a combined general appearance and respiratory index score of 2 or greater, and a rectal temperature of ≥104.1° F. |
| 5 | Two hundred nineteen females and castrated males, with an average initial weight of 21 kg, were enrolled in the study when they showed pyrexia (40.3° or 40.5° C depending on the site) associated with dyspnea. |
| 6 | Pigs that exhibited markedly increased respiratory rate and a rectal temperature ≥ 39.8° C were enrolled (study day 1). |
| 7 | One hundred five grower pigs with symptoms of severe swine acute respiratory disease were randomly assigned to 2 treatment groups based on 2 inclusion criteria, (i) body temperature ≥ 40.0° C and (ii) a total clinical score > 3. |
| 8 | The criteria for inclusion in the study were the following: pyrexia ≥ 40° C, clinical disease index score (CDIS) ≥ 2, (0 = healthy, 1 = slightly ill, 2 = moderately ill, 3 = severely ill, 4 = dying), and dyspnea or depression ≥ 2 (0 = absent, 1 = mild, 2 = moderate, 3 = severe). |
| 9 | Pigs with moderate or severe respiratory disease and pyrexia (≥ 40° C) were treated with amoxicillin/clavulanic acid (Synulox RTU) at 7.0/1.75 mg/kg on days 0, 1 and 2 or tulathromycin at 2.5 mg/kg on day 0 only. |
| 10 | The inclusion criteria were: pyrexia (≥ 40.3° C), a ≥ 2 clinical disease score together with one of the following respiratory signs: at least moderate dyspnea (≥ 2 score), at least moderate depression (≥ 2 score) or at least moderate cough (≥ 2 score) with 0 = absent, 1 = mild, 2 = moderate, 3 = severe. |
| 11 | Pigs with rectal temperature ≥ 40.0° C, respiratory symptoms and depression according to pre-established scores were eligible for both studies. |
| 12 | Pigs evaluated by clinical scores including rectal temperature. |
| 13 | At study inclusion (Day 0), pigs had moderate (score 2) or severe (score 3) clinical signs of swine respiratory disease (depression, dyspnea, coughing and sneezing) in combination with pyrexia (rectal temperature ≥ 40.0° C). |
| 14 | On each test site, pigs from the same batch were included by assessing clinical signs of swine respiratory disease using clinical scores for respiratory condition, cough, physical activity, appetite and recording rectal temperature. Pigs having a minimum level of a composite clinical score and a body temperature of at least 39.5° C were enrolled in the study. |
| 15 | Each enrolled animal was clinically assessed daily for clinical signs including depression, respiratory scores, and rectal temperature. |
| 16 | Animals with rectal temperatures ≥ 104.5° F (40.3° C) were randomly assigned to one of three treatments groups. |
| 17 | After at least 14 days of antibiotic removal, pigs (N = 346, 9 locations; BW 3.6 - 24.5 kg) exhibiting clinical signs of swine respiratory disease were enrolled on study on day 0 when they scored 2 or greater for a combined respiratory index (4 category index) and general appearance (5 category index) and also had a body temperature ≥ 104° F. |
| 18 | Pigs meeting the following criteria were included in the study: Pyrexia ≥ 104.5° F, AND Depression ≥ 2 on a scale of 0 to 3, AND Dyspnea score ≥ 2 on a scale of 0 to 3. |

**Table S3: Continued**

| Reference number | Swine respiratory disease definition |
|---|---|
| 19 | Pigs that exhibited clinical signs of swine respiratory disease (respiratory or attitude scores > 1). Respiratory scoring criteria were as follows: 0 = normal; 1 = mild increase in respiratory effort and/or occasional cough; 2 = moderate increase in respiratory effort and/or obvious cough; 3 = dyspnea (eg, gasping or open-mouthed breathing) and/or cyanosis. Clinical attitude scoring was as follows: 0 = normal; 1 = mild depression, pig appears mildly depressed or lethargic prior to stimulation, upon stimulation appears normal; 2 = moderate depression, pig will rise upon stimulation but appear lethargic; 3 = severely depressed or moribund, unable to rise, resistant to stimulation but will rise, continues to look depressed, or seeks to lie down. Animals at each site were monitored until an outbreak of respiratory disease was confirmed, and affected pigs were then enrolled individually onto the study when they met pre-defined criteria of pyrexia (rectal temperature ≥ 40° C) and clinical signs of respiratory disease. |
| 20 | Animals with temperatures of ≥ 40.3° C (104.5° F) were randomly assigned to one of two treatments groups. |
| 21 | Enrollment criteria consisted of signs of swine respiratory disease that included a rectal temperature ≥ 40° C, abnormal respiration (respiratory score ≥ 2), and abnormal attitude (attitude score ≥ 2). |
| 22 | Pigs which had lost vigor and appetite and had respiratory symptoms - abdominal respiration, fever (40°-42° C), coughing, etc. |
| 23 | Thereafter, animals exhibiting clinical signs of acute pneumonia together with pyrexia (> 40° C) were weighed and randomly allotted on the basis of body weight and severity of illness, to receive either 1.25 mg/kg danofloxacin or 20,000 IU:25 mg/kg benzylpenicillin/dihydrostreptomycin (PC/DSM) by intramuscular injection in the neck, once daily for three consecutive days. |
| 24 | Pigs with moderate to severe clinical signs of respiratory disease were divided into 3 groups as indicated in the experimental design. |
| 25 | For an animal to be enrolled on day 0, it was required to have a temperature of ≥ 40.2° C and a minimum of moderate respiratory signs and moderate depression as determined by the blinded examining veterinarian. |

**Table S4:** Definitions of treatment success or failure

| Reference number | Outcome definition |
|---|---|
| 1 | A pig was considered a treatment success if it had a rectal temperature of < 104.0° F, normal respiratory character, and no or mild depression on Day 4. |
| 2 | Treatment success was defined as an animal that was not removed from the study for swine respiratory disease from Days 1 to 7, and that had a depression score ≤ 1 and a respiratory score ≤ 1 and a rectal temperature < 104° F on Day 7. |
| 3 | Gainers (pigs that survived and gained 5 pounds in 14 days) |
| 4 | Treatment was considered a success (clinical cure) if the sum of the general appearance score and respiratory index was 0 or 1 and body temperature was ≤ 104.0° F, on both Days 3 and 6. |
| 5 | Only failure was defined, however: Failure (pyrexia > 40.3° C associated with dyspnea) was assessed on days 4 and 9. [Note that the data was converted to success (no pyrexia) for the purposes of the data extraction.] |
| 6 | The primary variables of interest (decision variables) were cumulative mortality, lung lesion scores at study day 15, and percent growers (defined as pigs surviving the 15-day study period and gaining at least 2.5 kg). |
| 7 | Lack of dyspnea. Dyspnea was not defined by the authors. |
| 8 | Treatment success was defined as a temperature < 40° C and a 0 score in the studied variables (clinical disease index score, dyspnea, depression). |
| 9 | Animals were clinically examined and rectal temperatures recorded daily for 15 days and weighed on day 0 and day 14. Pigs that met the enrolment criteria on any two consecutive days from day 2 to 14 were classified as treatment failures and withdrawn to permit further medication. Successes were pigs free from clinical swine respiratory disease at day 14. |
| 10 | Percent Pyrexia: Defined as ≥ 40.3° C. [Note that the data was converted to success (no pyrexia) for the purposes of the data extraction.] |
| 11 | Efficacy criteria were the number of animals completing the study on day 14 without meeting predefined removal criteria during the daily examinations (rectal temperature ≥ 40° C, plus at least moderate respiratory symptoms and at least mild depression), cure rate on day 5, reduction of rectal temperature, respiratory and depression score compared to baseline, mortality, and weight gain. |
| 12 | Based on daily observation and specific criteria, pigs became either treatment failures (withdrawals) or remained on study until final evaluation on day 10. |
| 13 | The primary efficacy variable was the cure rate on day 14 with the objective to demonstrate non-inferiority of tulathromycin compared to tildipirosin based on percentage of clinical cure (swine respiratory disease score ≤ 1) on day 14. |
| 14 | A clinical improvement index was calculated for each pig using the clinical scores recorded on day 0 and day 7. The proportion of improved pigs for each treatment was compared using a non-inferiority hypothesis test (non-inf. margin = 0.15). |
| 15 | Each enrolled animal was assessed daily for clinical signs including depression, respiratory scores, and rectal temperature. On day 10, all remaining animals were evaluated as treatment success or failure. |
| 16 | Florfenicol-treated pigs were statistically significantly improved over the negative control pigs with regard to mortality rate, dyspnea, rectal temperature, depression, illness index score, weight gain, and lung lesion scores. |
| 17 | Clinical cure rate was defined as the percentage of pigs that had a combined general appearance score and respiratory score of either 0 or 1 and a body temperature of less than 104° F on both days 3 and 6 post-enrollment. |
| 18 | Failure was declared based on day 6 observations when the following criteria were met: Rectal temperature ≥ 104° F or depression score ≥ 2 or dyspnea score ≥ 2 or mortality/moribund with euthanasia before day 6. [Note that the data was extracted as "Success".] |

**Table S4:** Continued

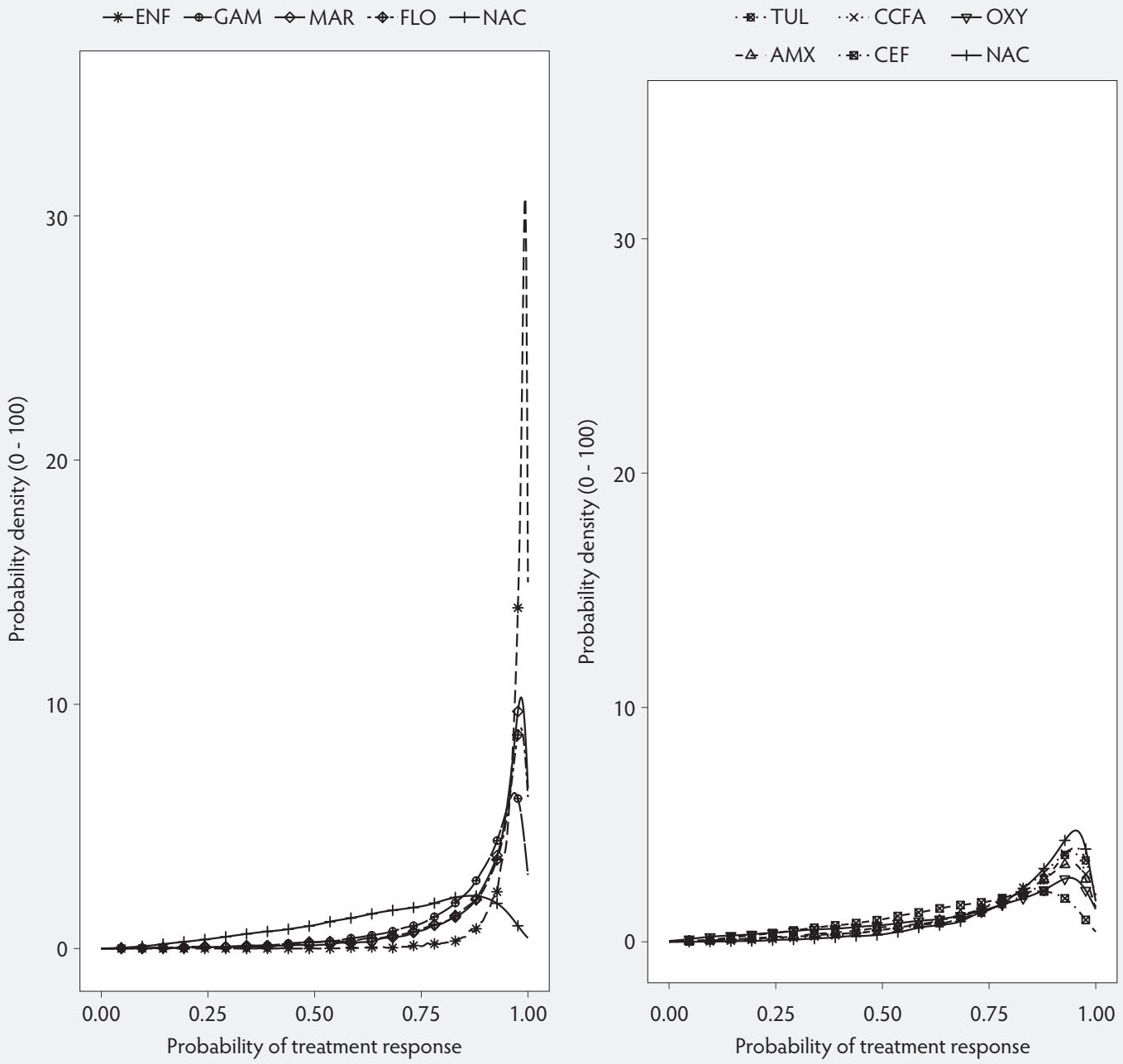
| Reference number | Outcome definition |
|---|---|
| 19 | On day 7 following treatment, surviving animals were considered cured if they were not removed because of disease other than swine respiratory disease, did not have a respiratory or attitude score > 1, or a rectal temperature ≥ 40° C. Efficacy was assessed on the basis of changes in rectal temperature, severity and prevalence of clinical signs of respiratory disease, and the number of animals completing the study to day 10. |
| 20 | Success rate was not explicitly defined. However, it appears that coughing, dyspnea, rectal temperature, and depression were examined. |
| 21 | Treatment success on day 10 was defined as: respiratory score < 2, and attitude score of < 2, and rectal temperature < 40° C. |
| 22 | Efficacy rate is assumed to mean the percent of animals with an "Excellent" ("The total score the day after completion of medication was improved by 80% or more from that on the first day of medication.") or "Good" ("The total score three days after completion of medication was improved by 80% or more from that on the first day of medication.") clinical outcome. |
| 23 | Pigs having an excellent response (85% to 100% reduction in clinical illness score) or good response (70% to 84% reduction in clinical illness score) to treatment, as measured by reduction in illness scores by day 4. |
| 24 | Percent cured. Based on the text of the Results and Table 1, it appears only the pigs in the "highly effective" category were considered cured ["...only 43% of diseased animals were cured when a 1 mg/kg dosage of ceftiofur was used."] |
| 25 | Cure was defined as normal rectal temperature (≤ 40° C) and absence of clinical signs of depression and absence of respiratory signs. |

**Table S5:** Summary of probability of treatment response

| | Mean | Median | Minimum | Maximum | 25 quantile | 97.5 quantile |
|---|---|---|---|---|---|---|
| Non-active control | 0.68 | 0.72 | 0.03 | 0.99 | 0.21 | 0.96 |
| Amoxicillin | 0.79 | 0.86 | 0.02 | 1.00 | 0.28 | 0.99 |
| Ceftiofur CFA | 0.77 | 0.83 | 0.04 | 1.00 | 0.27 | 0.99 |
| Ceftiofur (MD) | 0.79 | 0.85 | 0.06 | 1.00 | 0.34 | 0.98 |
| Enrofloxacin | 0.96 | 0.98 | 0.31 | 1.00 | 0.82 | 1.00 |
| Florfenicol | 0.86 | 0.91 | 0.06 | 1.00 | 0.44 | 0.99 |
| Gamithromycin | 0.90 | 0.95 | 0.01 | 1.00 | 0.47 | 1.00 |
| Marboflaxacin | 0.88 | 0.94 | 0.03 | 1.00 | 0.42 | 1.00 |
| Oxytetracycline | 0.72 | 0.79 | 0.01 | 1.00 | 0.15 | 0.99 |
| Tildipirosin | 0.83 | 0.88 | 0.07 | 1.00 | 0.39 | 0.99 |
| Tulathromycin | 0.83 | 0.88 | 0.08 | 1.00 | 0.41 | 0.99 |

CFA = crystalline free acid; MD = multidose.

**Figure S1:** Probability of treatment response for treatment regimens included in Table S4. ENF = enrofloxacin; MAR = marbofloxacin; TIL = tilidipirosin; GAM = gamithromycin; FLO = florfenicol; NAC = non-active control; TUL = tulathromycin; CCFA = ceftiofur crystalline free acid; OXY = oxytetracycline; AMX = amoxicillin; CEF = ceftiofur.



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*1. Bayer HealthCare LLC Animal Health Division. *Baytril 100 Enrofloxacin injectable solution swine for the treatment and control of swine respiratory disease (SRD) associated with* Actinobacillus pleuropneumoniae*,* Pasteurella multocida*,* Haemophilus parasuis*, and* Streptococcus suis*.* **https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/605**. NADA 141-068 FOI Summary Supplemental New Animal Drug Application. Approved March 14, 2008. Accessed October 2017.

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