Title:

Protocol for a systematic review of different antimicrobial treatment options for bovine respiratory disease complex in feedlot cattle, housed dairy calves, veal calves or beef calves using the incidence of retreatment as the outcome of interest

Registration:

This protocol will be registered at the Systematic Reviews for Animals & Food (http://www.syreaf.org/). It will also be made available on the website of the European Network for Optimization of Veterinary Antimicrobial Treatment (ENOVAT; https://enovat.eu/). The protocol follows the PRISMA-P guidelines (Moher et al., 2015).

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Authors' contributions:

Amendments:

None to date.

Support:

This systematic review aims at informing the guidelines for the antimicrobial therapy of bovine respiratory disease complex (BRDC). This project is supported by the COST Action CA18217 European Network for Optimization of Veterinary Antimicrobial Treatment (ENOVAT) in collaboration with the European Society of Clinical Microbiology and Infectious Diseases Study Group for Veterinary Microbiology (ESGVM).

INTRODUCTION:

Rationale:

Bovine respiratory disease complex (BRDC) is a major health problem for the cattle industry. Young feedlot cattle and calves around the time of weaning tend to be particularly affected (Griffin, 1997). Although BRDC is pathogenically multifactorial, bacteria are frequently involved in pneumonia, albeit as a primary or opportunistic pathogen (Panciera and Confer, 2010). This is also the reason that the cornerstone of bovine respiratory disease (BRD) treatment is antimicrobial therapy (Edwards, 2010). In fact, BRDC represents one of the main indications for antimicrobial use in cattle worldwide (USDA, 2013). Antimicrobial selection should be based on the intended clinical outcome, i.e. resolution of clinical signs, prevention of disease relapse or mortality. However, prudent use of antimicrobials to reduce the risk of emerging antimicrobial resistance, as well as financial aspects for the farmer, are also important factors to be taken into consideration by clinical veterinarians (WHO, 2015). To enable informed decision making on the prescription and use of antimicrobials for BRDC treatment, it is crucial to know the relative efficacy of different antimicrobials. Furthermore, when screening the antimicrobial treatment options, a choice should be made with the One Health approach in mind, i.e., choosing the formulation with the least negative effects on the closely interlinked complex of animal, human and ecosystem´s health.

Numerous randomized controlled trials have assessed the efficacy of different antimicrobials for BRDC treatments. In recent years, O'Connor and colleagues have summarized the information available on different antimicrobial treatments for BRDC using network meta-analysis (O'Connor et al., 2013, O'Connor et al., 2019). Their systematic reviews included all injectable antibiotics registered for use in North America for the treatment of undifferentiated BRDC. However, their population focus was on feedlot cattle only, a minor production system in the EU. The cattle industry comprises different production branches with specific herd and

management characteristics. While feedlot cattle represent the bovine population most frequently affected by BRDC and targeted with antimicrobials in North America, other production types, i.e. housed dairy calves, veal calves and beef calves, represent large populations of interest in the context of BRDC in Europe. The goal of the present project is to present evidence-based information on the best antimicrobial treatment options, in line with ENOVAT's aim to develop evidence-based veterinary practice guidelines to promote best practice for the management of key infectious diseases in veterinary medicine. This review will focus on the comparative efficacy of amoxicillin, ampicillin, erythromycin, ceftiofur, cloxacillin, danofloxacin, enrofloxacin, florfenicol, gentamycin, gentamicin, lincomycin, oxytetracyclin, penicillin, spectinomycin, sulfonamide, sulfamethoxazole, tilmicosin, trimethroprim, tulathromycin, tylosin, gamithromycin, tildipirosin, rated as the most relevant antimicrobial drugs in the BRDC context by a group of 14 international experts, including clinicians, microbiologists, epidemiologists and pharmacologists. To assess the importance of different substances the panel of experts looked at available guidelines, formularies and recommendations throughout Europe.

Objective:

This systematic review will evaluate the scientific evidence related to the question: What is the comparative efficacy (measured as incidence of retreatment) of the most relevant antimicrobials for the treatment of undifferentiated BRDC in feedlot cattle, dairy calves, veal calves and beef calves? The results of this systematic review will inform the development of clinical recommendations for antimicrobial treatment of BRDC.

METHODS:

Eligibility criteria:

Population: Feedlot cattle, dairy calves, beef calves, veal calves; including domestic cattle (*Bos taurus*) only; diagnosed with BRDC: Studies not providing criteria for defining BRDC cases in eligible animals will be excluded (example of an explicit definition of BRDC: "In the study reported herein, the case definition for bovine respiratory disease complex (BRDC) was an elevated rectal temperature (≥ 40.3°C) and a lack of abnormal clinical signs referable to organ systems other than the respiratory system."; example of a description not considered explicit: "In this study, cattle with BRDC were enrolled.").

Intervention: antimicrobial treatment (amoxicillin, ampicillin, erythromycin, ceftiofur, cloxacillin, danofloxacin, enrofloxacin, florfenicol, gentamycin, gentamicin, marbofloxacin, lincomycin, oxytetracyclin, penicillin, spectinomycin, sulfonamide, sulfamethoxazole, tilmicosin, trimethroprim, tulathromycin, tylosin, gamithromycin, tildipirosin)

Comparator: antimicrobial treatment (amoxicillin, ampicillin, erythromycin, ceftiofur, cloxacillin, danofloxacin, enrofloxacin, florfenicol, gentamycin, gentamicin, lincomycin, oxytetracyclin, penicillin, spectinomycin, sulfonamide, sulfamethoxazole, tilmicosin, trimethroprim, tulathromycin, tylosin, gamithromycin, tildipirosin) or control

Outcome: The primary outcome will be clinical failure of treatment defined as the necessity to retreat an animal for BRDC within 28 days of completion of initial treatment. Studies not providing a definition of treatment failure will be excluded (example of an explicit definition: "In the study reported herein, the case definition for treatment failure was an elevated rectal temperature (> or = 40.3°C) and a lack of abnormal clinical signs referable to organ systems other than the respiratory system no sooner than 3 days and 15 days after treatment ceased.";

example of a description of treatment failure not considered explicit (unless the authors explicitly define BRDC as previously described): “Cattle that still had signs of BRDC after 10 days were considered a treatment failure”. Mortality will be considered a potential secondary outcome.

Study design: Randomized or systematically allocated controlled trials containing at least two treatment arms (placebo [either no therapeutic or prophylactic treatment (e.g. antibiotic, anti-inflammatory)] and/or antimicrobial drug[s]).

Setting: Naturally occurring, Experimental BRD, undifferentiated BRDC

Years considered: 2000-2022

Language: English

Information sources:

The following electronic databases will be searched: Web of Science, CAB Direct, Scopus.

Search strategy:

The search strings will consist of the terms for “population of interest”, “bovine respiratory disease” and “antimicrobials”. These groups will be joined using AND. The search string will be adapted to the respective databases. We will search in “topic” in Web of Science (includes title, abstracts, author keywords, Keywords Plus), in “Article title, Abstract, Keywords” in Scopus and in “Article title”, “Abstract” and “Subject term” in CAB Direct.

The search string will be based on the following terms:

Population terms: "cow" OR "cows" OR "cattle" OR heifer* OR "steer" OR "steers" OR "bull" OR "bulls" OR "calf" OR "calves" OR "youngstock*" OR "young-stock*" OR "beef" OR "veal" OR "bovine" OR "bovidae"

BRDC terms: “respiratory disease*” OR “respiratory tract disease*” OR “shipping fever” OR “undifferentiated fever” OR “BRD” OR “BRDC” OR “*pneumonia*” OR “rhinitis” OR “tracheitis” OR “pneumoniti*” OR “pasteurellosis” OR “pasteurella multocida” OR “mycoplasma bovis” OR “mannheimia haemolytica” OR “haemophilus somnus” OR “histophilus somni”

Antimicrobial terms: “amoxicillin” OR “amoxycillin” OR “ampicillin” OR “erythromycin” OR “ceftiofur” OR “cloxacillin” OR “danofloxacin” OR “enrofloxacin” OR “florfenicol” OR “gentamycin” OR “gentamicin” OR “lincomycin” OR “oxytetracyclin” OR “penicillin” OR “spectinomycin” OR “sulfonamide” OR “sulfamethoxazole” OR “tilmicosin” OR “trimethroprim” OR “tulathromycin” OR “tylosin” OR “gamithromycin” OR “tildipirosin” OR “marbofloxacin”

STUDY RECORDS:

Data management:

Database records of recovered articles will be downloaded in a tagged format and loaded into Rayyan (Ouzzani et al., 2016). Deduplication and abstract screening will be done in Rayyan as well. Data extraction will be documented in Microsoft Excel.

Selection process:

Two reviewers will independently screen publications for eligibility in two stages: title/abstract and full text screening. Any conflicts about the selection of articles will be resolved during meetings between the two reviewers. Studies meeting inclusion criteria will pass to the next phase. Questions relating to inclusion or exclusion of papers will be answered with "Yes", "No" or "Unclear". The order of the questions may be rearranged if needed. Once a study is considered ineligible, screening is terminated. Prior to each screening stage, the protocol will be tested by the two reviewers by evaluating the first 20 abstracts/full texts. This is to ensure clarity of the questions and consistency of interpretation of questions among reviewers.

<u>First stage (title/abstract screening):</u>

1) Does the study involve in vivo assessment of antimicrobials' efficacy for the treatment of BRDC?

   No → Exclude

   Yes/Unclear → Next question

2) Is the study population identifiable as either beef cattle, housed dairy calves or veal calves?

   No → Exclude

   Yes/Unclear → Next question

<u>Second stage (full text screening):</u>

1) Is full-text available in English, German, French, Italian, Portuguese and Dutch?

   No → Exclude

   Yes → Include

2) Is the study population identifiable as either feedlot cattle, housed dairy calves, veal calves or beef calves?

   No/Unclear → Exclude

   Yes → Next question

3) Does the study involve assessment of antimicrobials for the treatment of BRDC?

   No/Unclear → Exclude

   Yes → Next question

4) Is there a case definition provided for the diagnosis of BRDC?

   No/Unclear → Exclude

   Yes → Next question

5) Does the study provide information about frequency of retreatment within 28 days of completion of initial treatment / successful treatment in the study groups or mortality?

   No/Unclear → Exclude

   Yes → Next question

6) Is treatment failure defined?

   No/Unclear → Exclude

   Yes → Next question

7) Is the study a field trial?

   No/Unclear → Exclude

   Yes → Next question

8) Are the animals randomly allocated to the intervention groups?

   No/Unclear → Exclude

   Yes → Next question

9) Is the unit of observation the individual animal?

   No/Unclear → Exclude

   Yes → Include/Data extraction

Data collection process:

Each data item (as listed below) will represent a header for a specific column in a Microsoft Excel spreadsheet. The data extraction template will be tested independently by both reviewers using 10 articles randomly selected for data extraction. Following this exercise, the data extraction tool will be modified as necessary to improve practicability and ensure completeness of extracted data. Once consensus is reached on the process, data extraction will be performed by two reviewers independently. Conflicts will be resolved by consensus or with the help of a third reviewer, if necessary.

If data presented in a study is unclear, inconsistent, missing or in a non-extractable format, the authors of this study will not be contacted for clarification.

Data items:

Data extraction will include:

- General information: Author(s), title, year of publication, journal name, funding information
- Study design: type of study, sample size, case definition
- Population characteristics: production type, age, sex, breed, number of animals per category
- Intervention and comparator: commercial/drug name, concentration, dose, route of administration
- Outcome: Numbers of animals with treatment failure and death

Outcomes and prioritization:

The primary outcome will be clinical failure of treatment defined as the necessity to retreat an animal for BRDC within 28 days of completion of initial treatment. Mortality will potentially be assessed as secondary outcome.

Risk of bias in individual studies:

Risk of bias will be assessed for controlled trials with natural disease exposure. Risk of bias will be evaluated using the Cochrane risk-of-bias tool for randomized trials (RoB 2; Higgins et al., 2021) with the signalling questions modified as necessary for the specific review question. Two reviewers will score each manuscript independently. A pilot run for determining agreement between the reviewers will be performed with five different studies to ensure adequate agreement.

DATA:

Synthesis:

Network meta-analysis will be done in STATA. A random effect model will be used and forest plots will be constructed. The tau-squared will be calculated to estimate the variance of the effect size parameters across the population of studies as well as the generalized I^2 statistic and the generalized heterogeneity statistic Q_{total} to test presence and to quantify heterogeneity in the network.

Publication bias(es):

Funnel plots will be used to assess potential publication bias by evaluating the symmetrical and normal distribution of studies as well as Egger test to explore whether the association between the study effect size and its standard error is greater than what might be expected by chance.

Sensitivity analysis

The aim of the sensitivity analysis is to show the influence of each study or of a group of studies (in particular studies of different methodological quality) on the pooled estimates.

Future endeavour: Confidence in cumulative evidence

Our overall objective is to propose evidence-based guidelines for the use of common antimicrobials applied for the treatment of BRDC, based on their clinical efficacy in terms of relapse and mortality. After this systematic review we hope to be able to draw practical conclusions for ranking their efficacy. The review results will be assessed for the risk of bias by using the GRADE approach.

References:

USDA (2013) Feedlot. Part iv: health and health management on us feedlots with a capacity of 1,000 or more head, NAHMS Feedlot Studies. Fort Collins: National Animal Health Monitoring System

Edwards, T.A., 2010. Control methods for bovine respiratory disease for feedlot cattle. Vet. Clin. North Am. - Food Anim. Pract. 26, 273–284. https://doi.org/10.1016/j.cvfa.2010.03.005

Griffin, D., 1997. Economic impact associated with respiratory disease in beef cattle. Vet. Clin. North Am. Food Anim. Pract. 13, 367–377. https://doi.org/10.1016/S0749-0720(15)30302-9

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1. doi: 10.1186/2046-4053-4-1

O'Connor, A.M., Coetzee, J.F., da Silva, N., Wang, C., 2013. A mixed treatment comparison meta-analysis of antibiotic treatments for bovine respiratory disease. Prev. Vet. Med. 110, 77–87. https://doi.org/10.1016/j.prevetmed.2012.11.025

O'Connor, A.M., Hu, D., Totton, S.C., Scott, N., Winder, C.B., Wang, B., Wang, C., Glanville, J., Wood, H., White, B., Larson, R., Waldner, C., Sargeant, J.M., 2019. A systematic review and network meta-analysis of injectable antibiotic options for the control of bovine respiratory disease in the first 45 days post arrival at the feedlot. Anim. Heal. Res. Rev. 20, 143–162. https://doi.org/10.1017/S1466252319000288

Ouzzani, M., Hammady, H., Fedorowicz, Z., Elmagarmid, A., 2016. Rayyan-a web and mobile app for systematic reviews. Syst. Rev. 5, 1–10. https://doi.org/10.1186/s13643-016-0384-4

Panciera, R.J., Confer, A.W., 2010. Pathogenesis and pathology of bovine pneumonia. Vet. Clin. North Am. - Food Anim. Pract. 26, 191–214. https://doi.org/10.1016/j.cvfa.2010.04.001

WHO, 2015. Global Action Plan on Antimicrobial Resistance.

Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.