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The efficacy of bacterial vaccines to prevent respiratory diseases in swine: A protocol for a systematic review

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Abstract

The treatment and prevention of infectious diseases in pigs is an important aspect of swine production worldwide. The prudent use of antimicrobials and other therapeutic drugs is a primary responsibility of swine producers and veterinarians and decisions surrounding the use of drug therapy include considerations such as cost, efficacy, and food safety. The World Health Organization has published numerous reports urging all stakeholders concerned with both food-producing animals and humans to establish recommended steps to enhance the prudent use of antimicrobials (WHO, 2015). Similarly, the Organization for Animal Health has also published recommendations and position statements regarding prudent use and risk management related to antimicrobial use in animals (OIE, 2017).

Antibiotic therapy is used to treat and prevent respiratory diseases in pigs and there are numerous pathogenic organisms involved in all of the predominant swine respiratory diseases (Karriker, et al, 2012). In addition to antibiotics, vaccines targeted towards respiratory pathogens have been used extensively in swine production and are often used in combination with other approaches to reduce the incidence of disease. The usefulness of a vaccine or vaccine program varies from herd to herd and the complex interactions between host, agent and environment in swine production makes the design of a vaccine program challenging for veterinarians. There are many studies that have assessed the efficacy of antibiotics and vaccines for the treatment and prevention Mycoplasma hyopneumonia, for example, however, they often report conflicting results adding to the complexity of the decision-making process (Thacker and Minion, 2012).

Understanding the efficacy of these vaccines products is essential to optimizing their use in order to decrease reliance on antibiotics for both treatment and prevention of swine respiratory disease. Systematic reviews of randomized controlled trials in these areas will yield the highest level of evidence for efficacy of treatment under field conditions (Sargeant and O'Connor, 2014). Although vaccines exist for both viral and bacterial causes of respiratory diseases of swine, and antibiotics often are used in the treatment of both, this review will focus on bacterial causes for logistical reasons.

Disciplines

Large or Food Animal and Equine Medicine | Veterinary Infectious Diseases | Veterinary Microbiology and Immunobiology

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Author contributions:
All authors contributed to the development of the review question and the methodology described in this proposal. JMS drafted the protocol, with input and final approval of all co-authors.

Registration:
This protocol is archived in the University of Guelph's institutional repository (The Atrium; https://atrium.lib.uoguelph.ca/xmlui/handle/10214/10046) and published online with Systematic Reviews for Animals and Food (SYREAF) available at: http://www.syreaf.org/. The systematic review will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (Liberati et al., 2009). This protocol is reporting using the items (headings) recommended in the PRISMA-P guidelines (Moher et al., 2015).

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Introduction.

Rationale:

The treatment and prevention of infectious diseases in pigs is an important aspect of swine production worldwide. The prudent use of antimicrobials and other therapeutic drugs is a primary responsibility of swine producers and veterinarians and decisions surrounding the use of drug therapy include considerations such as cost, efficacy, and food safety. The World Health Organization has published numerous reports urging all stakeholders concerned with both food-producing animals and humans to establish recommended steps to enhance the prudent use of antimicrobials (WHO, 2015). Similarly, the Organization for Animal Health has also published recommendations and position statements regarding prudent use and risk management related to antimicrobial use in animals (OIE, 2017).

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Objectives: The objective of this protocol is to describe the methods for a systematic review – network meta-analyses to address the efficacy of bacterial vaccines to prevent respiratory disease in swine.

The specific PICO elements, which will define the eligibility criteria, are as follows:

i. *Population:* Live swine at any stage of production.
ii. *Intervention:* Vaccines (commercially available or commercially produced injectable autogenous vaccines derived from culture) for bacterial pathogens associated with respiratory diseases in swine, including *Mycoplasma hyopneumoniae, Actinobacillus pleuropneumoniae, Actinobacillus suis, Bordetella bronchiseptica, Pasteurella multocida, Streptococcus suis, Haemophilus parasuis* and *Mycoplasma hyorhinis*.
iii. *Comparator:* Negative control group or sham treatment.
iv. *Outcomes:* The outcomes of interest are respiratory-related morbidity (as defined by the authors), mortality, and total antibiotic use.

Methods

Eligibility criteria: In addition to eligibility criteria inherent in the PICO elements described above, eligibility includes publication in English. Both journal articles and other forms of research reports are eligible, provided they report the results of a primary research study with a concurrent comparison group using an eligible study design and a full text of more than 500 words.

Study designs eligible: Controlled trials with natural disease exposure will be eligible for inclusion, although we will document the number of controlled trials with deliberate disease

challenge and analytical observational studies at full text screening and also will identify the vaccines used and whether any of the outcomes of interest were assessed for studies of these designs.

Information sources:

We will conduct the literature search in a range of relevant bibliographic databases and other information sources containing both published and unpublished literature. Table 1 presents the resources to be searched.

Table 1: Databases and information sources to be searched

Database / information source	Interface / URL
MEDLINE	PubMed
CAB Abstracts	CAB Interface
Science Citation Index	Web of Science
Conference Proceedings Citation Index – Science	Web of Science
Agricola	Proquest

The AASV maintains a searchable digital library of proceedings from the prominent swine conferences through the American Association of Swine Veterinarians website (Swine Information Library http://www.aasv.org/library/swineinfo/). Selected proceedings, as noted below, will be search using the key words:
(Vaccine OR vaccination) AND
(bacterial OR *hyopneumoniae OR Mycoplasma OR Actinobacillus OR pleuropneumoniae OR Actinobacillus OR "A. suis" OR Bordetella OR bronchiseptica OR Pasteurella OR multocida OR "Streptococcus suis" OR "Strep. suis" OR "S. suis" OR Haemophilus OR parasuis OR hyorhinis*)
Resources to be searched on this site include proceedings from:
o AASV Annual Meeting (1999-2018)
o AASV Pre-Conference Seminars (2007-2018)
o International Pig Veterinary Society Congress (2000, 2002, 2004, 2006, 2008, 2010, 2012, 2014, 2016, 2018)

Search strategy:

A Science Citation Index (Web of Science) search strategy designed to identify studies of vaccine efficacy for bacterial vaccines for respiratory disease in swine is presented in Table 2. The search strategy employs a multi-stranded approach to maximize sensitivity. The conceptual structure is as follows:

- Swine at any stage of production;

AND

- Vaccines;

AND

- Bacteria associated with respiratory disease in swine

AND

- Respiratory outcomes

Table 2: Search strategy to identify studies of bacterial vaccines for respiratory diseases of swine in Science Citation Index (Web of Science)

#1 TS= (swine OR pig* OR piglet* OR gilt* OR boar* OR sow* OR hog* OR weane* OR porcine NOT guinea) 877,032

#2 TS = (vaccine OR vaccination OR bacterin) 286,956

#3 TS = (hyopneumoniae OR Mycoplasma OR Actinobacillus OR "atrophic rhrinitis" OR suis OR Bordetella OR bronchiseptica OR Pasteurella OR Pasteurellosis OR multocida OR Streptococcus OR Haemophilus OR Glasser's OR Glassers OR parasuis OR hyorhinis) 159,419

TS = (pneumonia OR pleuritis OR pleuropneumonia OR pleuropneumoniae OR respiratory OR SRD) 492,040

#1 AND #2 AND #3 AND #4 743

The search strategies will not be limited by date, language, or publication type.

We will conduct searches using each database listed in the protocol, translating the strategy appropriately to reflect the differences in database interfaces and functionality.

Study records:

Data management: We will download the results of searches in a tagged format and load them into bibliographic software (EndNote). The results will be de-duplicated using several algorithms. We will save results from resources that do not allow export in a format compatible with EndNote in Word or Excel documents as appropriate and manually de-duplicate. The de-duplicated search results will be uploaded into online systematic review software (DistillerSR®, Ottawa, ON, Canada). Reviewers will have training in epidemiology and in systematic review methods. Prior to both abstract and full-text screenings, data extraction, and risk of bias assessment, the reviewers assigned to each step will undergo training to ensure consistent data collection using the forms created in DistillerSR®.

Selection process: In the first round of screening, abstracts and titles will be screened for eligibility. Two reviewers will independently evaluate each citation for relevance using the following questions:

1) Does the study evaluate the use of vaccines for bacterial causes of respiratory disease in live swine?
   YES (neutral response), NO (EXCLUDE), UNCLEAR (neutral response)
2) Is there a concurrent comparison group? (i.e. controlled trial with natural or deliberate disease exposure or analytical observational study)?
   YES (neutral response), NO (EXCLUDE), UNCLEAR (neutral response)
3) Is the full text available in English?
   YES (include for full text screening), NO (EXCLUDE), UNCLEAR (include for full text screening)

Citations will be excluded if both reviewers responded "no" to any of the questions. Any disagreements will be resolved by consensus. If consensus cannot be reached, the article will be marked as "unclear" and will advance to full text screening. A pre-test will be conducted by all reviewers on the first 250 abstracts to ensure clarify of questions and consistency of understanding of the questions.

Following title/abstract screening, eligibility will be assessed through full-text screening, using the questions included below. Two reviewers will independently evaluate the full text articles, with any disagreements resolved by consensus. If consensus cannot be reached, a third reviewer will be used. A pre-test will be conducted by all reviewers on the first 10 full texts to ensure clarify of questions and consistency of understanding of the questions.

1) Is the full text available with > 500 words?
   YES (neutral response), NO (EXCLUDE)
2) Is the full text available in English?
   YES (neutral response), NO (EXCLUDE)
3) Eligible population: Does the study evaluate live swine?
   YES (neutral response), NO (EXCLUDE)
4) Eligible intervention: Does the study assess the use of a monovalent or polyvalent commercially available vaccine or a commercially produced injectable autogenous vaccine derived from culture) for one or more of the following bacterial pathogens associated with respiratory diseases in swine: *Mycoplasma hyopneumoniae, Actinobacillus pleuropneumoniae, Actinobacillus suis, Bordetella bronchiseptica, Pasteurella multocida, Streptococcus suis, Haemophilus parasuis* or *Mycoplasma hyorhinis*.
5) Are at least one of the following outcomes described: respiratory disease related morbidity, mortality, antibiotic use.
   YES (neutral response), NO (EXCLUDE)
6) Is there a concurrent comparison group? (i.e. controlled trial with natural or deliberate disease exposure or analytical observational study)?
   YES (neutral response), NO (EXCLUDE)

7) Eligible study design: Is the study a controlled trial with natural disease exposure?
   Yes (moves to data extraction stage),
   No, the study is a controlled trial with deliberate disease induction (indicate the bacterial vaccine(s) used, but exclude from data extraction)
   No, the study is an observational study (indicate the bacterial vaccine(s) used but exclude, from data extraction)

Data collection process: Data will be extracted by two reviewers working independently. Any disagreements will be resolved by consensus or, if consensus cannot be reached, a third reviewer will be used. Authors will not be contacted to request missing data or to clarify published results. A form for data extraction will be created for this review in DistillerSR® and pre-tested on 4 full text articles to ensure question clarity.

Data items:

Study level data to be extracted include:

- Country where trial was conducted (if not stated, use country affiliation of corresponding author)
- Commercial versus research trials
- Number of herds enrolled in study
- Year(s) the study was conducted
- Months of data collection
- Stage of production for allocation of the vaccine
- Stage(s) of production where the outcome was measured
- Reason for vaccinating: endemic disease, prevention of clinical disease, in response to a disease outbreak, not reported

Arm level data collected:

- Vaccine name as reported by investigators
- Target bacteria for the vaccine
- Dose / route / frequency of administration of the vaccine
- Unit of allocation of the vaccine (individual, pen)
- Description of comparison group (no treatment, sham vaccine)
- Number of animals enrolled
- Number of pens enrolled
- Number of animals / pens lost to follow up
- Number of animals / pens analyzed
- Any additional concurrent treatments given to the intervention groups.
- The approach used in the analysis to account for non-independent observations (not applicable, not reported, random effects, GEE, other.

Outcomes and prioritization:

- Respiratory-related morbidity,
- Mortality,
- Total antibiotic use,

These outcomes were prioritized based on their impact on animal health and welfare and their economic importance. Formal evaluation of these criteria for prioritization was not undertaken.

The specific outcome data, as described below, will be extracted only for experimental studies with natural disease exposure.

Outcome data to be collected:

1) Respiratory-related morbidity
    a. Case definition
    b. Time period for assessing outcome, frequency of outcome assessment
    c. Level at which outcome data were measured (animal / pen / herd)

2) Mortality
    a. Level at which outcome data were measured (animal / pen / herd)
    b. Time period for assessing outcome

3) Total antibiotic use
    a. Measure used to define outcome
    b. Time period for assessing outcome
    c. Antibiotic(s) used

For each outcome, we will extract the possible metrics in the following order:

- 1st priority: Adjusted summary effect size ($_{adjusted}$ risk ratio or $_{adjusted}$ odds ratio, mean differences for continuous outcomes) and variables included in adjustment and corresponding precision estimate
- 2nd priority: Unadjusted summary effect size
- 3rd priority: Arm level risk of the outcome, or arm level mean of the outcome (continuous outcomes)
- Variance components.

Risk of bias in individual studies: Risk of bias will only be assessed for controlled trials with natural disease exposure. Risk of bias assessment will be performed at the outcome level for each outcome using the Cochrane risk of bias instrument (Higgins et all, 2016), with the signaling questions modified as necessary for the specific review question. The ROB-2.0 for

clustered RCTs and individual RCTs will be used depending on the study design (Higgins et al., 2016). These tools are available at https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool.

Data synthesis:

Network meta-analysis. Network meta-analysis (aka mixed treatment comparison meta-analysis) will be conducted for each outcome, and separately for vaccines for each of the selected bacterial diseases. Network meta-analysis will use the approach described by NICE Decision Support Unit technical document (Dias et al., 2014; O'Connor et al., 2013, O'Connor et al., 2016). The approach to reporting will use the PRISMA- NMA (http://www.prisma-statement.org/Extensions/NetworkMetaAnalysis.aspx). Planned a priori sub-group analyses will be conducted for randomized versus non-randomized trials.

Meta-bias(es): Small study effects ("publication bias") will be assessed for all vaccines where there are at least 10 studies in the meta-analysis. If feasible, we will use approaches to assessing publication bias in the network of evidence using previously proposed approaches (Mavridis et al., 2013; Mavridis et al., 2014).

Confidence in cumulative evidence: The quality of evidence for each outcome will be assessed using the approach proposed by GRADE (GRADE, 2015, Puhan et al., 2014), while also considering the nature of the network meta-analysis (Jansen et al., 2011). If feasible, we will use the framework from the CINeMA platform for conveying the impact of risk of bias on the network performance.

Discussion:

This systematic review will provide a synthesis of the current evidence regarding the efficacy of vaccines to prevent bacterial diseases causing respiratory diseases in swine. Results will be helpful for veterinarians and swine producers when making evidence-informed decisions regarding management options to reduce respiratory illness and death caused based bacteria, and potentially reduce the need to use antibiotics to treat respiratory diseases. The results also will be helpful for identifying specific gaps in knowledge related to the efficacy of these vaccine for targeting additional research.

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