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Systematic review and meta-analysis on efficacy of Fostera PRRSV Modified Live Virus vaccine studies in growing pigs

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Abstract

Porcine reproductive and respiratory syndrome virus (PRRSV) is one of the most economically important health challenges that currently exists in the global swine industry. PRRSV is an enveloped, single-stranded, positive-sense RNA virus belonging to genus Arterivirus. A PRRSV infection is clinically characterized by reproductive failure in sows and/or respiratory disease in growing pigs, causing significant economic losses (Zimmerman et al., 2012). RNA viruses have relatively high mutation rates compared to DNA viruses, mainly due to the low fidelity of viral RNA-dependent RNA polymerases (Arnold et al., 2005; Vignuzzi et al., 2008). This rapid high mutation rate usually leads to the generation of genetically and antigenically variable virus strains in the field, which can hinder the development of effective vaccines. PRRSV is currently classified into two distinct genotypes, type 1 and type 2 which differs significantly in term of their clinical, and genetic properties (Kapur et al., 1996; Labarque et al., 2004; Nelson et al., 1993). Within type 2, it has been proposed a further subdivision into 9 genetic lineages (Shi et al., 2010). The extensive heterogeneity of PRRSV presents challenges for the efficacy vaccines, which are currently based on a single virus strain. Consequently, the current commercially vaccines confer partial cross-protection against heterologous PRRSV strains (Kimman et al., 2009; Li et al., 2014; Murtaugh and Genzow, 2011), which is sufficient to significantly decrease duration and magnitude of viremia, shedding, and lung lesions. In previous cross-protection studies, type 2 PRRSV modified live vaccine have not been effective when applied to control pigs against type 1 PRRSV (Labarque et al., 2003; van Woensel et al., 1998; Labarque et al., 2000). Cross-protection discoursed by type 2 PRRSV vaccine against type 1 PRRSV is an important clinical issue in many Asian countries because of the emergence of type 1 PRRSV (Chen et al., 2011; Nam et al., 2009; Thanawongnuwech et al., 2004). A modified live type 2 PRRSV vaccine (Fostera PRRS, Zoetis, Parsippany, NJ, USA) was introduced in the US in 2012, and is profess to be efficacious to protect pigs against heterologous type 2 PRRSV challenge (Park et al., 2014), and has been licensed to produce better cross-protection against heterologous PRRSV challenge. Fostera PRRS is an attenuated PRRSV vaccine, passaged first on pig kidney cells engineered to constitutively express the porcine CD163 PRRS receptor, then on baby hamster kidney cells that were also engineered to express porcine CD163. The commercial modified live PRRS vaccines were attenuated by passage on African green monkey kidney cells (cell line MA-104 and derivatives), which inappropriately express the macrophage-specific CD163 PRRS receptor. Adaptation of the virus to use the monkey CD163 receptor contributes to the observed attenuation phenotype of at least some of these vaccines, namely a reduced ability of the vaccine virus to infect the host target cell, primary porcine alveolar macrophages (Pearce et al., 2014). In contrast, the Fostera PRRSv is passaged only on cells expressing porcine CD163, and thus potentially maintaining its ability to replicate to high titer on primary porcine alveolar macrophages. This fundamental difference in attenuation may play a role in the dynamics of viremia in pigs, following challenge with PRRS viruses from genotypes 1 (Charoenchanikran et al., 2016; Choi et al., 2016; Do et al., 2015; Park et al., 2015, 2014; Savard et al., 2016; Tian et al., 2015).

Disciplines

Agricultural Economics | Large or Food Animal and Equine Medicine | Veterinary Pathology and Pathobiology | Veterinary Preventive Medicine, Epidemiology, and Public Health

1 **Title**

2 Systematic review and meta-analysis on efficacy of Fostera PRRSV Modified Live Virus

3 vaccine studies in growing pigs.

4 **Registration**

APPROVED
By O'Connor, Annette M [VDPAM] at 8:09 am, Apr 10, 2018

Gaurav Rawal, April 10, 2018 at 9:03 am

Daniel Linhares, April 11, 2018 at 15:34h

5 NA

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14 **Contributions**

15 G. Rawal contributed the question and the development of all parts of the protocol. G. Rawal

16 assessed the adequacy of the terms for identifying relevant challenge study. J. Angulo

17 contributed to assessing the updating the search, redesign of the screening tools and design of

18 data extraction tools. A. O'Connor and D.C.L. Linhares assess the adequacy of the proposed

systematic review, meta-analysis methods and reviewing of manuscript.

Amendments

NA

Support

NA

Introduction

Rationale

Porcine reproductive and respiratory syndrome virus (PRRSV) is one of the most economically important health challenges that currently exists in the global swine industry. PRRSV is an enveloped, single-stranded, positive-sense RNA virus belonging to genus Arterivirus. A PRRSV infection is clinically characterized by reproductive failure in sows and/or respiratory disease in growing pigs, causing significant economic losses (Zimmerman et al., 2012). RNA viruses have relatively high mutation rates compared to DNA viruses, mainly due to the low fidelity of viral RNA-dependent RNA polymerases (Arnold et al., 2005; Vignuzzi et al., 2008). This rapid high mutation rate usually leads to the generation of genetically and antigenically variable virus strains in the field, which can hinder the development of effective vaccines. PRRSV is currently classified into two distinct genotypes, type 1 and type 2 which differs significantly in term of their clinical, and genetic properties (Kapur et al., 1996; Labarque et al., 2004; Nelson et al., 1993). Within type 2, it has been proposed a further subdivision into 9 genetic lineages (Shi et al., 2010). The extensive heterogeneity of PRRSV presents challenges for the efficacy vaccines, which are currently based on a single virus strain. Consequently, the current commercially vaccines confer partial cross-protection against heterologous PRRSV strains (Kimman et al., 2009; Li et al., 2014; Murtaugh and Genzow, 2011), which is sufficient to significantly decrease

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Objectives

The objective of this study was to summarize the efficacy of a type 2 modified live PRRSV vaccine (Fostera PRRS, Zoetis, Parsippany, NJ, USA) against heterologous PRRSV challenge in growing pigs. The primary outcome of interest was magnitude of macroscopic lung lesions, and the secondary outcome variables included viremia levels and average daily gain.

For the purpose of this study, efficacy was described using the mean macroscopic lung score, representing an estimate of the percentage of lung affected by pneumonia. Each lung lobe was assigned a number to reflect the approximate volume percentage of the entire lung represented by that lobe.

Methods

Eligibility criteria:

Population

The population of the interest was peer reviewed manuscripts, and proceeding papers about clinical trials on the efficacy of Fostera PRRSV vaccine (Zoetis, Parsippany, NJ, USA). Age of the enrolled pigs, or country where trials were carried out will not be used as an exclusion factor.

Intervention

Eligible intervention is Fostera modified live PRRSV type 2 vaccine.

Comparator

Unvaccinated challenged pigs.

Outcome

The primary outcome of interest is macroscopic lung lesion mean score, and the secondary outcome of interest are level of viremia (log_{10} $TCID_{50}$/mL), duration of viremia and average daily gain (ADG) at different days' post challenge with wild type heterologous PRRSV.

Studies:

Eligible studies will be randomized controlled parallel trials that allocate individual level study population of swine. At least one treatment arm i.e. challenged and vaccinated with Fostera PRRSV vaccine (Zoetis, Parsippany, NJ, USA), and a concurrent comparison arm i.e. challenged and unvaccinated. They should have at least one of the three outcomes reported.

Information sources:

MEDLINE and the Centre for Biosciences and Agriculture International (CABI) databases will be searched using the Iowa State University (ISU) Web of Science interface. The search strategy will be restricted from January 2012 to March 2018 because this type 2 PRRSV vaccine (Fostera PRRS, Zoetis, Florham Park, NJ, USA) was not available before 2012. Reference lists of relevant manuscripts and the table of contents from the last 6 years of the proceedings of the American Association of Swine Veterinarians (AASV), James McKean Iowa State University Swine Disease Conference, Allen D. Leman Swine Conference, North American PRRS symposium, and International Pig Veterinary Society Congress (IPVS) will be also searched for eligible studies. The search will involve searching for the term "Fostera" only for the Swine Information Library (SIL) excluding Journal of Swine Health & Production (JSHAP) text and abstracts, web pages, and AASV news. For this resource the title will be screened, and if it appears relevant, the paper will be evaluated. Recent review manuscripts of Fostera MLV PRRSV will be examined for additional reports potentially missed by our database search. The bibliography of relevant manuscripts will also be assessed for relevant manuscripts.

Search strategy:

An example search strategy is listed in Table 1. The search will not be restricted by language but we will be restricted by years (2012-2018).

Search Number	Search string	No of Results
1	TS= (pig OR porcine OR swine OR hog)	185,099
2	TS= (Fostera OR Modified live virus vaccine OR MLV OR porcine reproductive respiratory syndrome virus modified live virus vaccine OR PRRSV MLV OR Attenuated PRRSV)	1,898
3	#1 AND #2	523

Table1. Search Strategy using the ISU Web of Science interface from 2012-2018

Study records:

Data management

End note reference management will be used to store Research Information System (RIS) files, and the 1st duplication will be conducted in this software. As it is not possible to extract RIS file from SIL, we will only import the relevant references into distiller list, noting separately how many were retrieved by the actual search. We will retain the number of items returned by the "Fostera" term and the number that were considered relevant. An online systematic review software will be used to manage literature records and data.

Selection process

At least two reviewers will independently read all abstracts/summaries identified from the search. Full reports will be acquired if one reviewer identifies the abstract as potentially relevant. The full manuscripts will be further assessed by at least two reviewers and if again deemed relevant, all data will be extracted.

The 1st level (abstract/title) screening question:

1. Does the title or abstract indicate primary research describing a challenge trial for the Fostera MLV PRRSV or treatment in growing pigs?

The 2nd level (full text) screening questions:

1. Is the full text available in English?

2. Does the study have at least 2 arms and one is Fostera administered per the label and another is challenged and unvaccinated?

3. Does the study contain at least one of the three outcomes or interest: macroscopic lesion mean score, level of viremia, duration of viremia and/or average daily gain (ADG)?

Data collection process:

Study level information

1. What is the study id?
2. What was the year of the publication?
3. What was the year of study conduct?
4. What was the country of trial?

5. Describe the Age and weight units at enrollment?
6. What was the gender composition?
7. What was breed or genetic line?
8. Number of groups in the design?
9. Pigs were challenged before or after vaccination?
10. Time from acquisition to vaccination(days)?
11. Number of days between vaccination and challenge?
12. Frequency of vaccination?
13. Vaccination route(s)?
14. Challenge route(s)?
15. Dose of challenge?
16. Which PRRSv strain was used as inoculum?
17. Report percentage genetic similarity of challenged strain with Fostera vaccine strain?
18. Days between PRRSv challenge and necropsy?
19. What outcome was reported?
20. What is the next outcome you want to report?

Arm level information

1. Number of treatment groups?
2. What method was used for randomization?
3. How many pigs were allocated in Fostera vaccinated and challenged group?
4. How many pigs were allocated in unvaccinated and challenged i.e. control group?
5. How many pigs were allocated in another group?
6. How many weeks of age, they were vaccinated?

7. What was the mean macroscopic lung lesion score in Fostera vaccinated and challenged group?
8. What was the mean macroscopic lung lesion score in unvaccinated and challenged group?
9. What was the level of viremia in Fostera vaccinated and challenged group?
10. What was the level of viremia in unvaccinated and challenged group?
11. What was the duration of viremia in Fostera vaccinated and challenged group?
12. What was the duration of viremia in unvaccinated and challenged group?
13. What was the mean average daily weight gain in Fostera vaccinated and challenged group?
14. What was the mean average daily weight gain in unvaccinated and challenged group?

Data collection process

Data extraction will be completed independently by at least two reviewers from all eligible manuscripts. In the event, same study is obtained from multiple sources (i.e. conference proceedings and a manuscript from MEDLINE), the different sources will be combined to obtain the most complete trail description.

Data items

Source of heterogeneity

The source of heterogeneity will be PRRSV challenged strain as inoculum, age of pigs when they are purchased, source from where they are purchased, breed of pigs, weight of pig before the start of trial, number of days for acclimation before the start of trial, number of pigs per

group, number of groups, challenge dose, route of challenge, individually housed or group housed.

Study level information

Country where study was conducted, year of conduct, pig mean age, mean weight, gender composition, breed or genetic line of pigs involved, duration of study observation period.

Arm level information

Interventions used in each arm (PRRSV strain, dose, route, duration) total number of pigs in trial arm, number of events (high lung lesion score) in trial arm at the end of study period, mean lung lesion score outcome per trial arm, mean score of lung lesion score outcome per trial arm, pharmaceutical sponsorship of treatment, description of blinding of outcome assessment included (yes/no), description of use of randomization to group (yes/no), use of systematic allocation to treatment arm (yes/no), and use of allocation restrictions (blocking by time, blocking by weight, stratification by severity, stratification by sex).

Outcomes and prioritization

The primary outcome of interest is mean score of macroscopic lung lesions, and secondary outcomes of interest are level of viremia, duration of viremia and average daily gain (ADG).

Risk of bias in individual studies

The Cochrane Risk of Bias Scale for intervention studies will be used to assess bias for all outcomes together (macroscopic, magnitude and duration of viremia, and ADG) as these are all considered objective outcomes (Higgins et al., 2011). The bias domains include selection bias (sequence generation and allocation concealment), detection bias (outcome assessor blinding),

attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other potential sources of bias. Two reviewers will be independently assessing all sources of bias as "high risk", "low risk", or "unclear". This information will be used as a source of heterogeneity in the meta-analysis.

Data Synthesis

We propose to conduct a meta-analysis using a pair-wise comparison. The suitability of the dataset for this method will be determined when data has been extracted in consultation with a statistician. Unit of analysis will be handled by exclusion as all studies must have the individual as the unit of allocation. Studies with missing data will be excluded from the meta-analysis and identified as such in the results.

Subgroup analysis will include assessment of factors associated with methodological and clinical heterogeneity. The methodological factors (sponsorship and blinding) will be used to assess the systematic bias between studies where the null hypothesis is the beta estimates of the trial factors equal zero. We expect the potential sources of clinical heterogeneity to be the PRRSV strain, number of pigs per group, number of groups, challenge dose, route of challenge, calculation of outcomes, lung lesion evaluation DPC. We will assess this including these factors as indicator variables in the model where the null hypothesis is the beta estimates of the trial factors equal zero.

If quantitative synthesis is determined to be unfeasible, a systematic narrative synthesis paired with descriptive pairwise forest plots will be produced explaining the characteristics and findings within and between included studies.

Meta-bias(es)

To assess publication bias, we will attempt use a selection model based on study size, study design, estimated effect size, and sponsorship to determine estimates of propensity for publication (Mavridis et al., 2014). Based on previous reviews, it is unclear how many different study designs (e.g. active-to-active, placebo-controlled trials, three arm trials) will be observed and thus publication bias will be difficult to ascertain.

Confidence in cumulative evidence

We will summarize the data using the GRADE approach, with a summary of findings tables and evidence profiles for the multiple outcomes. All the outcomes are considered important or critical.

Title

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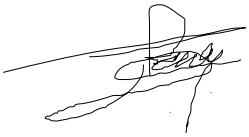
Registration

NA

Authors



Approved by Jose Angulo Apr 29,2018

Gaurav Rawal[1], grawal@iastate.edu; Jose Angulo[2], jose.angulo@zoetis.com; Daniel C.L. Linhares[1], linhares@iastate.edu; A.M. O'Connor[1,3]oconnor@iastate.edu;

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Contributions

G. Rawal contributed the question and the development of all parts of the protocol. G. Rawal assessed the adequacy of the terms for identifying relevant challenge study. J. Angulo contributed to assessing the updating the search, redesign of the screening tools and design of data extraction tools. A. O'Connor and D.C.L. Linhares assess the adequacy of the proposed

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Amendments

NA

Support

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Intervention

Eligible intervention is Fostera modified live PRRSV type 2 vaccine.

Comparator

Unvaccinated challenged pigs.

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Data collection process:

Study level information

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3. What was the year of study conduct?
4. What was the country of trial?

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6. What was the gender composition?
7. What was breed or genetic line?
8. Number of groups in the design?
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10. Time from acquisition to vaccination(days)?
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13. Vaccination route(s)?
14. Challenge route(s)?
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16. Which PRRSv strain was used as inoculum?
17. Report percentage genetic similarity of challenged strain with Fostera vaccine strain?
18. Days between PRRSv challenge and necropsy?
19. What outcome was reported?
20. What is the next outcome you want to report?

Arm level information

1. Number of treatment groups?
2. What method was used for randomization?
3. How many pigs were allocated in Fostera vaccinated and challenged group?
4. How many pigs were allocated in unvaccinated and challenged i.e. control group?
5. How many pigs were allocated in another group?
6. How many weeks of age, they were vaccinated?

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12. What was the duration of viremia in unvaccinated and challenged group?
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14. What was the mean average daily weight gain in unvaccinated and challenged group?

Data collection process

Data extraction will be completed independently by at least two reviewers from all eligible manuscripts. In the event, same study is obtained from multiple sources (i.e. conference proceedings and a manuscript from MEDLINE), the different sources will be combined to obtain the most complete trail description.

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group, number of groups, challenge dose, route of challenge, individually housed or group housed.

Study level information

Country where study was conducted, year of conduct, pig mean age, mean weight, gender composition, breed or genetic line of pigs involved, duration of study observation period.

Arm level information

Interventions used in each arm (PRRSV strain, dose, route, duration) total number of pigs in trial arm, number of events (high lung lesion score) in trial arm at the end of study period, mean lung lesion score outcome per trial arm, mean score of lung lesion score outcome per trial arm, pharmaceutical sponsorship of treatment, description of blinding of outcome assessment included (yes/no), description of use of randomization to group (yes/no), use of systematic allocation to treatment arm (yes/no), and use of allocation restrictions (blocking by time, blocking by weight, stratification by severity, stratification by sex).

Outcomes and prioritization

The primary outcome of interest is mean score of macroscopic lung lesions, and secondary outcomes of interest are level of viremia, duration of viremia and average daily gain (ADG).

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The Cochrane Risk of Bias Scale for intervention studies will be used to assess bias for all outcomes together (macroscopic, magnitude and duration of viremia, and ADG) as these are all considered objective outcomes (Higgins et al., 2011). The bias domains include selection bias (sequence generation and allocation concealment), detection bias (outcome assessor blinding),

attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other potential sources of bias. Two reviewers will be independently assessing all sources of bias as "high risk", "low risk", or "unclear". This information will be used as a source of heterogeneity in the meta-analysis.

Data Synthesis

We propose to conduct a meta-analysis using a pair-wise comparison. The suitability of the dataset for this method will be determined when data has been extracted in consultation with a statistician. Unit of analysis will be handled by exclusion as all studies must have the individual as the unit of allocation. Studies with missing data will be excluded from the meta-analysis and identified as such in the results.

Subgroup analysis will include assessment of factors associated with methodological and clinical heterogeneity. The methodological factors (sponsorship and blinding) will be used to assess the systematic bias between studies where the null hypothesis is the beta estimates of the trial factors equal zero. We expect the potential sources of clinical heterogeneity to be the PRRSV strain, number of pigs per group, number of groups, challenge dose, route of challenge, calculation of outcomes, lung lesion evaluation DPC. We will assess this including these factors as indicator variables in the model where the null hypothesis is the beta estimates of the trial factors equal zero.

If quantitative synthesis is determined to be unfeasible, a systematic narrative synthesis paired with descriptive pairwise forest plots will be produced explaining the characteristics and findings within and between included studies.

Meta-bias(es)

To assess publication bias, we will attempt use a selection model based on study size, study design, estimated effect size, and sponsorship to determine estimates of propensity for publication (Mavridis et al., 2014). Based on previous reviews, it is unclear how many different study designs (e.g. active-to-active, placebo-controlled trials, three arm trials) will be observed and thus publication bias will be difficult to ascertain.

Confidence in cumulative evidence

We will summarize the data using the GRADE approach, with a summary of findings tables and evidence profiles for the multiple outcomes. All the outcomes are considered important or critical.