The reporting characteristics of bovine respiratory disease clinical intervention trials published prior to and following publication of the REFLECT statement

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The reporting characteristics of bovine respiratory disease clinical intervention trials published prior to and following publication of the REFLECT statement

Abstract
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Author contributions statements

ST- development of the study proposal, extraction of data, data analysis, and preparation of the manuscript

JC- extraction of data, data analysis, and preparation of the manuscript
AOC, JS—development of the study proposal, data analysis, and reviewed drafts of the manuscript

The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
Abstract

The goal of the REFLECT Statement (Reporting guidElines For randomized controLled trials in livEstoCk and food safeTy) (published in 2010) was to provide the veterinary research community with reporting guidelines tailored for randomized controlled trials for livestock and food safety. Our objective was to determine the prevalence of REFLECT Statement reporting of items 1 to 19 in controlled trials published in journals between 1970 and 2017 examining the comparative efficacy of FDA-registered antimicrobials against naturally acquired BRD (bovine respiratory disease) in weaned beef calves in Canada or the USA, and to compare the prevalence of reporting before and after 2010, when REFLECT was published. We divided REFLECT Statement, items 3, 5, 10, and 11 into subitems, because each dealt with multiple elements requiring separate assessment. As a result, 28 different items or subitems were evaluated independently. We searched MEDLINE® and CABI (CAB Abstracts® and Global Health®) (Web of Science™) in April 2017 and screened 2327 references. Two reviewers independently assessed the reporting of each item and subitem. Ninety-five references were eligible for the study. The reporting of the REFLECT items showed a point estimate for the prevalence ratio > 1 (i.e. a higher proportion of studies published post-2010 reported this item compared to studies published pre-2010), apart from items 10.3, i.e., item 10, subitem 3 (who assigned study units to the interventions), 13 (the flow of study units through the study), 16 (number of study units in analysis), 18 (multiplicity), and 19 (adverse effects). Fifty-three (79%) of 67 studies published before 2010 and all 28 (100%) papers published after 2010 reported using a random allocation method in either the title, abstract, or methods (Prevalence ratio = 1.25; 95% CI (1.09,1.43)). However, 8 studies published prior to 2010 and 7 studies published post-2010 reported the term "systematic randomization" or variations of this term (which is not true randomization) to
describe the allocation procedure. Fifty-five percent (37/67) of studies published pre-2010 reported blinding status (blinded/not blinded) of outcome assessors, compared to 24/28 (86%) of studies published post-2010 (Prevalence ratio = 1.5, 95% CI (1.19, 2.02)). The reporting of recommended items in journal articles in this body of work is generally improving; however, there is also evidence of confusion about what constitutes a random allocation procedure, and this suggests an educational need. As this study is observational, this precludes concluding that the publication of the REFLECT Statement was the cause of this trend.
1. Introduction

1.1. Rationale

In science, including veterinary science, there has been a movement toward improving the reporting of research protocols, conduct, and results (Altman et al., 2008; Begley, 2013; Groves and Godlee, 2012; Keiding, 2010; Simera et al., 2010; Simera and Altman, 2009; Sweet, 2014). The rationale for these efforts is to enable the maximum value to be extracted from research results. Randomized controlled trials (RCTs) that are clearly reported allow the clinician to properly assess the efficacy of tested interventions and incorporate that information into making the best therapeutic and preventive decisions for patients. To improve the reporting of RCTs in human health, the CONSORT Statement (Consolidated Standards of Reporting Trials) was originally developed in 1996 and has been subsequently revised, with the latest version being published in 2010 (Moher et al., 2010; Schulz et al., 2010). The goal of reporting guidelines is to provide authors, reviewers, and editors with a list of items that should be included in a publication to encourage comprehensive reporting.

In 2010, the REFLECT Statement (Reporting guidElines For randomized controLled trials in livEstoCk and food safeTy) was also published. The goal of the REFLECT Statement was to provide the veterinary research community with a reporting guideline tailored for randomized controlled trials conducted in the fields of livestock and food safety (O'Connor et al., 2010b; Sargeant et al., 2010b). The rationale for a livestock-specific reporting guideline was that, although it is feasible to use the CONSORT Statement for RCTs in animals, authors, reviewers and editors might find the reporting guideline easier to adopt if the examples and terminology used were more consistent with livestock production; additionally, there are some features of livestock trials (such as complex organizational levels (e.g., pens, feedlots), different categories
of participants (i.e., owners/managers and animals), etc.) that CONSORT does not address. In 2010, the REFLECT Statement was published in 5 journals, and several presentations were made to publicize the goal of the work (O'Connor et al., 2010a; O'Connor et al., 2010b; O'Connor et al., 2010c; O'Connor et al., 2010d; O'Connor et al., 2010e; Sargeant et al., 2010a; Sargeant et al., 2010b). Further, a website devoted to the REFLECT Statement was developed and maintained (www.reflect-statement.org). One of the motivators for the REFLECT Statement was empirical evidence of poor reporting in livestock trials (Brace et al., 2010; O'Connor et al., 2010f; Sargeant et al., 2009; Wellman and O'Connor, 2007). Given the goal of reporting guidelines to improve comprehensive reporting, it is of interest to assess if such approaches have made an impact.

1.2. Objectives

Therefore, one objective of this study was to determine the prevalence of reporting of REFLECT items 1 to 19, with respect to clinical trials conducted in Canada and/or the USA examining the comparative efficacy of FDA-registered antimicrobials against naturally acquired BRD (bovine respiratory disease) in weaned beef calves, published in journals between 1970 and 2017. The rationale for assessing this area was that a large number of RCTs were conducted, and we had previously evaluated the reporting of these studies and discussed the need for improvement (O'Connor et al., 2010f). Although we evaluated the first 19 items of the REFLECT Statement for the current study, items 3, 5, 10, and 11 had to be split into subitems, because each of these dealt with multiple elements that needed to be assessed separately. As a result, a total of 28 different items and subitems were evaluated independently. Further, although not an item on the REFLECT checklist (which assumes the study uses a random allocation method) it is clearly of broad interest to know if more authors are describing their allocation method. Therefore, another objective was to describe the number of studies pre- and post-2010...
reporting any type of allocation method. This latter objective was not intended as an assessment of the validity of the allocation approach, i.e. not a risk-of-bias assessment; rather, the objective was only concerned with whether the authors described the method of allocation.

2. Methods

2.1. Study population

The current study was an observational survey. The population of interest was published controlled trials on naturally occurring bovine respiratory disease in weaned beef calves in Canadian and/or US feedlots. The interventions of interest were FDA-registered antimicrobials, and the outcome of interest was naturally occurring BRD (i.e., challenge trials were not relevant to this study). The study design of interest was controlled clinical trials. Our focus was further limited to journal publications, rather than technical reports or research reports, because efforts to improve reporting have mainly focused on journals.

2.2. Study selection

The literature search comprised three concepts to capture studies of interest: population, outcome, and intervention (search strings 1, 2, and 3, respectively, in Table 1) and was conducted on 15 April 2017 in MEDLINE® (Web of Science™) (Table 1) and CABI (CAB Abstracts® and Global Health®) (Web of Science™)(Supplementary Material 1). Search dates were restricted to 1970 to 2017, with no language or document-type restrictions. All search results were exported to DistillerSR® (Ottawa, ON, Canada), where they were de-duplicated. Additionally, the reference lists of relevant reviews captured by the original search were hand-searched for potentially relevant references. Two additional relevant publications were found via a Google search while searching for PDF copies of previously identified studies. These two
articles were published in *The Professional Animal Scientist* journal; therefore, the index of this journal was also searched.

Two reviewers screened each record for relevance in DistillerSR®. Eligible citations were manuscripts that described:

1) Primary research published in journals,

2) A study population of cattle housed in feedlots in Canada or the USA,

3) At least one treatment arm with a product registered with the FDA for the prevention or treatment of naturally occurring BRD, and,

4) A comparison arm (placebo or active control) i.e., controlled trials.

Two levels of screening were used to identify eligible manuscripts. The exact screening questions are presented in Supplementary Material 2 and Supplementary Material 3. Conflicts between reviewers were resolved by discussion or, when consensus could not be reached, by consulting a third reviewer (AOC).

2.3. **Comprehensive reporting assessment**

The comprehensive reporting assessment form (Supplementary Material 4) was based on the REFLECT Statement guidelines (O'Connor et al., 2010a). Only the reporting of the first 19 items of the REFLECT Statement were assessed, as items 20, 21, and 22 were thought to be too subjective for simple assessment. Each of the 19 items in the REFLECT Statement was reworded into the form of a Yes/No question, for evaluative purposes (e.g. item 10 of REFLECT: "Who generated the allocation sequence…?" was modified to: "Did the authors describe who generated the allocation sequence?"). Also, some REFLECT items were split into multiple questions because they concerned more than one piece of information (e.g. item 10 states "Who generated the allocation sequence, who enrolled study units, and who assigned study units to their groups at
the relevant level of the organizational structure?"). This item was split into three separate
subitems (see Table 2). For nomenclature purposes, subitems were given decimal designations,
i.e., subitem 3 of item 10 is referred to as "item 10.3". As REFLECT assumes that authors
randomized, an additional question was needed to assess if the authors used the term
randomization or its variations anywhere in the manuscript, not simply in the title or abstract.

The comprehensive reporting assessment form was not pre-tested; however, the
reviewers made minor revisions to the form for clarity during the assessment of the first 6
references. Two reviewers assessed each publication. If a publication contained a description of
more than one trial, data from the first relevant trial were extracted. The reviewers were not blind
to publication dates, because the date on which the study was conducted was part of the
assessment of reporting (item 14).

2.4. Statistical analysis

Prevalence ratios and 95% confidence intervals for each of the items of the REFLECT
Statement were calculated using OpenEpi (Dean et al., 2013). The mean difference (and 95%
confidence interval) for the percent of "yes" answers per article was calculated and reported i.e.,
average proportion of "yes" post-2010 minus average proportion of "yes" pre-2010. A positive
number indicates that the proportion of "yes" responses increased post-2010.

A forest plot of the pre- and post-2010 prevalence ratios was created using the meta
package (Schwarzer, 2007) in R 3.4.1 (R-Core-Team, 2017). A plot was also created in R
comparing the prevalence of checklist items pre-2010 and post-2010. This type of graph allows
comparison of the point estimates and better illustrates the underlying prevalence of reporting for
the time periods (pre- and post-2010).
The denominator for items 1, 8, 9, and 10.1, was conditioned on randomization i.e., studies that reported randomizing the experimental units to the interventions. Studies that described quasi-randomization methods i.e., systematic randomization, were not included in the denominator.

Regarding item 18, because multiplicity takes many forms and the need for adjustment is debated, we limited our evaluation of multiplicity to the BRD outcome for treatment arms using multiple comparisons methods such as Tukey's test, Duncan's new multiple range test, Fisher's least significant difference, and the Bonferroni method. Such studies might naturally be expected to consider multiple pairwise comparisons between treatment groups, and therefore a clearer case can be made for authors to discuss multiple testing.

We also anticipated comparing the number of items reported in journals that did and did not encourage authors to use the REFLECT Statement after 2010; however, there were too few articles published in journals that endorsed the REFLECT Statement to conduct that analysis. We also anticipated comparing the count of items reported before and after 2010 for each journal; however, this was only feasible for the journal, *The Bovine Practitioner*, because the remaining journals had such sparse data (see Table 3).

3. Results

3.1. Screening references for eligibility

The number of records found per database searched is reported in Table 1 and Supplementary Material 1 for the MEDLINE® and CABI searches, respectively. After de-duplication in DistillerSR®, 2279 records remained. An additional 48 records were found by searching the reference lists of relevant review articles (DeDonder and Apley, 2015a, b;
O'Connor et al., 2010b; O'Connor et al., 2016) and The Professional Animal Scientist journal. In total, 2327 records underwent screening based on the title and abstract (i.e., Level 1), and of these, 1998 were excluded, so that 329 records proceeded to the second level of screening (Level 2), based on the full text.

Of the 329 records that underwent screening based on the full text, 234 were excluded because:

1) the full text was not available in English (131 references),
2) the full text could not be obtained (6 references),
3) the paper referred to tables that were not in the manuscript itself, preventing direct evaluation (1 reference),
4) the study did not take place in the USA or Canada (47 references),
5) the study was not published in a journal (20 references),
6) the study was a review (9 references),
7) the study was not conducted at a feedlot (11 references),
8) the study was a challenge trial (1 reference),
9) the study was not a controlled clinical trial assessing the efficacy of two or more interventions against BRD (8 references).

A list of all references excluded at Level 2 screening, with the reasons, is given in Supplementary Material 5. Therefore, 95 references proceeded to the reporting assessment phase of the review (see Supplementary Material 6 for a list of these references).

3.2. Characteristics of the controlled clinical trials

Of the 95 manuscripts assessed, 67 were published prior to 2010 (date range: 1971 to 2009), while 28 were published from 2011 to 2017. The trials were published in a variety of
journals with the most common journal being *The Bovine Practitioner*, a publication of the American Association of Bovine Practitioners (AABP). This journal does not provide authors with guidance to use any reporting guidelines, including the REFLECT Statement. However, one of the authors of the current study, and other groups, have presented at the annual conference for the AABP about reporting of controlled clinical trials several times. It is interesting to note that *Veterinary Therapeutics: Research in Applied Veterinary Medicine* was a common publication vehicle for many studies prior to 2010. No articles relevant to our survey were published in that journal since 2009, which is unsurprising as the journal was discontinued in 2010.

3.3. **Comprehensive reporting assessment**

   Reporting of the allocation method at the study level

   The authors reported (in the title, abstract, or methods section) the method used (random or non-random) to allocate the experimental units to the interventions in 56/67 (83.6%) and 28/28 (100%) studies published prior to and following 2010, respectively.

   Fifty-three (79%) of 67 studies published before 2010 and all 28 (100%) papers published after 2010 reported using a random allocation method in either the title, abstract, or methods section (prevalence ratio (PR) = 1.25; 95% CI (1.09,1.43)). However, it should be noted that 8 studies published prior to 2010 and 7 studies published after 2010 reported the term "systematic randomization" or variations thereof. Additionally, 5 studies, all published before 2010, explicitly reported a non-random allocation method (one study used the term "systematic" alone; the remaining four studies used alternate allocation, i.e., giving the same intervention to every other animal).

   Reporting of REFLECT checklist items
The reporting characteristics of the 95 extracted studies for the REFLECT checklist items are shown in Table 2. The forest plot displaying the prevalence ratios and corresponding 95% confidence intervals is shown in Fig. 1. Fig. 2 depicts the prevalence comparison plot; however, precision estimates are not included for clarity, and such information can be derived from Table 2.

Overall, there were positive changes post-2010 in the proportion of studies reporting the REFLECT items (i.e., All estimates within the 95% confidence interval of the prevalence ratio were above 1.) for the following items: reporting of randomization in the title and abstract (item 1), the description of the setting (item 3.3), specification of the hypothesis (item 5.2), reporting of blinding of the person(s) administering the intervention (item 11.1), blinding of outcome assessment (item 11.3), reporting whether or not blinding was done (item 11.5), descriptions of statistical methods (item 12), and reporting of the dates over which the study took place (item 14). The reporting of all of the other REFLECT items showed a point estimate of the prevalence ratio that was > 1 (apart from item 10.3 (who assigned study units to the interventions), item 13 (the flow of study units through the study), item 16 (number of study units used in analysis), item 18 (multiplicity), and item 19 (adverse effects)), although the 95% confidence intervals also included values ≤ 1. This suggests a trend toward better reporting in trials published subsequent to the publication of the REFLECT Statement as indicated by increasing prevalence.

Concealment of the allocation sequence (item 9) was not reported for any of the 95 manuscripts.

Comparing the mean percent of items reported before and after 2010 for each article in The Bovine Practitioner resulted in a point estimate for mean difference of +12% (95% CI (-0.006, 0.25)). The mean percent of items reported before 2010 was 40% and after 2010 was 52%.
Item 18 was only assessed for trials with 3 or more study arms. There were 41 such studies in total. Seven of the 41 studies were published after 2010, and none of these described the adjustment for multiple pairwise comparisons. Of the 34 studies published prior to 2010, 3 included adjustment for pairwise comparisons. This should not be interpreted as incorrect analysis by the non-reporting studies, as there is a debate as to whether adjustment for multiple comparisons is needed (Rothman, 2014). However, there is less debate about the need to report whether or not multiple adjustment tests were used to calculate p-values or variance estimates.

4. Discussion

The results suggest that reporting of published controlled clinical trials that assess antibiotic efficacy for the prevention or treatment of BRD is improving, apart from item 10.3, (who assigned study units to the interventions), item 13 (the flow of study units through the study), item 16 (number of study units used in analysis), item 18 (multiplicity), and item 19 (adverse effects).

The largest improvements appear to be occurring in items that already had a moderate level of reporting prior to 2010. Items that were poorly reported (i.e., < 5%) prior to 2010 continue to be poorly reported (items 3.1, 9, 10.2, 10.3, and 11.4), while there was little room for improvement for some items, which were already well reported (items 2, 4, and 5.1). This can be seen in the prevalence comparison plot (Fig. 2).

Although there is still room for improvement, it is encouraging that in 100% of studies published post-2010, the authors described an allocation method. It is also encouraging that authors are including the word "random" or some variation thereof in the title or abstract, which makes retrieval of RCTs easier in citation indices. It should be noted that in some of the studies
quasi-randomization approaches were used. For instance, "Systematic randomization was used to assign 2 animals to receive metaphylaxis (META) for every 1 receiving no metaphylaxis (NO META) at processing." (Hendrick et al., 2013, p. 1147), and "Cattle were systematically randomized to the treatment groups within each feedlot. A coin was flipped to determine whether the first animal in the trial would be treated with florfenicol or tulathromycin. The next animal was treated with the other drug. This pattern continued systematically until the desired sample size of 250 head/group was achieved." (Van Donkersgoed et al., 2008, p. 277).

It is important to acknowledge that systematic allocation approaches are not truly random, and therefore are less likely to achieve the goals of randomization i.e., exchangeability (ignorability) of groups (Greenland and Robins, 2009). While systematic allocation can help to ensure that study units are allocated at the desired ratio to each intervention, it does make knowledge of the allocation sequence more difficult to conceal, which may introduce bias (Di Girolamo et al., 2017; Higgins et al., 2016). For example, if intervention and placebo are given to alternate animals as they pass through a processing chute, an investigator may have an unconscious bias towards putting thinner-looking animals through the chute such that they will receive the preferred intervention. It remains to be studied if quasi-randomization approaches are associated with bias in trials in veterinary science. The answer will almost certainly be topic-specific. For this reason, use of true randomization methods would remove concerns. Because random allocation is often confused with haphazard or quasi-random (systematic) allocation, reporting of key elements of randomization (such as those required in items 8, 9, and 10) would increase confidence that allocation was a valid random procedure (Altman and Bland, 1999). The reporting of blinding (use or absence) (item 11.5) has improved overall. That authors are more commonly recognizing that good reporting includes reporting that a study was not blinded is a
reassuring observation. As with reporting the allocation procedure so that reviewers can
determine that non-random allocation was employed, this level of transparency enables the
reader to determine if this is a source of bias, which in some cases it might not be. More
education of authors, reviewers, and editors is needed on the importance of reporting items 3.2
(animal eligibility criteria), 5.2 (hypotheses), 6 (primary and secondary outcomes), 10.1 (who
generated the allocation sequence), 11.1 (blinding of intervention allocation), 17 (effect size and
precision), and in particular reporting items 3.1 (owner/manager/feedlot eligibility criteria), 7
(sample size calculations), 8 (method used to achieve randomization), 9 (allocation
concealment), 10.2 (who enrolled study units), 10.3 (who assigned study units to interventions),
11.2 (blinding of caregivers), 11.4 (blinding of data analyst), 18 (multiplicity), and 19 (adverse
events).

We did not assess the effect of journal endorsement of the REFLECT Statement on
improved reporting, because only 2 relevant studies were published in endorsing journals after
2010. The REFLECT group of authors has not devoted a large amount of time to seeking
endorsement, as our impression was that journals are unsure of the impact of reporting or are
concerned that authors will be hesitant to submit manuscripts to journals with additional
submissions requirements. We are unaware of any journal that requires a REFLECT Statement
checklist with submission.

As far as we know, this is the first comparative assessment of reporting in veterinary
science. However, in human health, because the CONSORT reporting guidelines are so widely
endorsed (at the time of the current study, the count was over 585 journals), the impact of
reporting guidelines is more readily assessed (CONSORT, 2017). A systematic review published
in 2012 summarized the results of 53 publications reporting 16,604 RCTs (median per evaluation
123 (interquartile range (IQR) 77 to 226) published in a median of six (IQR 3 to 26) journals (Turner et al., 2012). That systematic review asked three questions about the:

1) Completeness of reporting of RCTs published in journals that have and have not endorsed the CONSORT Statement,

2) Completeness of reporting of RCTs published in CONSORT-endorsing journals before and after endorsement, or

3) Completeness of reporting of RCTs before and after the publication of the CONSORT Statement (1996 or 2001).

The latter point is similar to our question of interest, and the findings of that aspect of the review were consistent with our study. The authors included statistical significance testing, and concluded that six outcomes had statistically significant results, suggesting that these items were more completely reported after the publication of the CONSORT Statement. These items were: complete reporting of sample size, sequence generation, allocation concealment, statistical methods, participant flow, and baseline data. As with our study, there was a strong overall trend towards more comprehensive reporting, but there was still room for improvement.

O'Connor et al. (2010f) previously assessed and reported comprehensive reporting of controlled trials assessing antibiotics used for BRD prior to 2010. The study population was slightly different from the one used here (i.e., only individual allocation treatment studies); however, the reporting assessment for the pre-2010 studies was very similar. In that study, at the study level, 36 (87%) of 41 studies reported using a random method of treatment allocation, which was higher than the pre-2010 group in the current study but still lower than the post-2010 group (28/28: 100%) in the current study. Only 20 of 41 studies reported that staff performing
outcome assessment were blinded to treatment group. These results were similar to the current study's pre-2010 group (37/67: 55%) compared to 24/28 (86%) post-2010.

The trends in reporting observed in this study are positive, but they may be attributable to many factors independent of the publication of the REFLECT Statement, such as changes to journal submission guidelines, improved author knowledge of statistical techniques and options, and the overall increased awareness of reporting that goes along with efforts in scientific publication.

A major limitation of this study is that it was observational, rather than the result of an RCT itself. Ideally, we would have worked with journals to randomize authors to be required to provide a REFLECT checklist upon submission, or randomized reviewers to use the REFLECT checklist. Such a study would have been able to control for the numerous confounders discussed above that limit the inference we can make about the "impact of REFLECT". Another source of bias is that the reviewers in this study were not blinded to the identities of the authors, journal, or year of publication of the studies from which data were extracted. This may have resulted in a bias away from the null. The steps taken to address this concern were dual independent review and open access to the data so that others can determine if they agree with our assessment.

5. Conclusions

There are generally positive trends toward improved reporting in controlled trials that assess the use of antibiotic(s) for the treatment and prevention of bovine respiratory disease. There is still room for improvement of reporting. We propose that it is critical to determine how we can raise awareness of authors to available guidelines that can save time and effort. Education of investigators is needed to clarify the difference between "systematic randomization" and true
randomization, particularly with respect to the risk of bias when using "systematic random" allocation procedures.
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the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. Cochrane Database Syst. Rev. 11, MR000030. doi: 10.1002/14651858.MR000030.pub2.


Figure captions

**Fig. 1.** Forest plot of the prevalence ratios and associated 95% confidence intervals of items 1 to 19 from the REFLECT Statement (O'Connor et al., 2010b) from a survey of controlled clinical trials conducted in Canada and/or the USA examining the comparative efficacy of at least one FDA-registered antimicrobial against naturally acquired BRD in weaned beef calves. Missing are items 2, 3.1, 9, 10.3, 11.4, and 18 because they had at least 1 zero value in the 2 X 2 table.

**Fig. 2.** Prevalence comparison plot of items 1 to 19 from the REFLECT Statement (O'Connor et al., 2010b) from a survey of controlled clinical trials conducted in Canada and/or the USA examining the comparative efficacy of at least one FDA-registered antimicrobial against naturally acquired BRD in weaned beef calves. The y-axis represents the post-2010 prevalence of the REFLECT item, and the x-axis represents the pre-2010 prevalence of the REFLECT item. The dotted line indicates equivalent prevalence. Items above the dotted line had a higher prevalence post-2010 compared to pre-2010, while below the dotted line, the prevalence of that item is lower post-2010 compared to pre-2010.
**Supplementary Materials**

**Supplementary Material 1.** Results of a search conducted in CABI (CAB Abstracts® and Global Health®) (Web of Science™) on 15 April 2017 for a survey of clinical trials conducted in Canada and/or the USA examining the comparative efficacy of at least one FDA-registered antimicrobial against naturally acquired BRD in weaned beef calves. The search dates were restricted to 1970 to Present (2017), and there were no language or document-type restrictions.

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<th>Search string</th>
<th>No. hits</th>
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<tr>
<td>1</td>
<td>TS=(beef OR bovine OR calf OR calves OR cattle OR cow OR cows OR dairy OR Hereford OR Holstein OR ruminant OR ruminants OR steer OR steers)</td>
<td>933,061</td>
</tr>
<tr>
<td>2</td>
<td>TS=(bovine respiratory disease OR Bovine viral diarrhea OR Bovine viral diarrhea virus OR undifferentiated fever OR BRD OR BVD OR BVDV OR <em>Haemophilus somnus</em> OR <em>Histophilus somni</em> OR IBR OR Infectious bovine rhinotracheitis OR <em>Mannheimia hemolytica</em> OR <em>Pasteurella multocida</em> OR Pasteurellosis OR respiratory disease OR undifferentiated bovine respiratory disease)</td>
<td>90,838</td>
</tr>
<tr>
<td>3</td>
<td>TS=(amoxicillin OR ampicillin OR antibiotic OR antibiotics OR antimicrobial OR antimicrobials OR erythromycin OR ceftiofur OR cloxacin 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)</td>
<td>168,066</td>
</tr>
<tr>
<td>4</td>
<td>#1 AND #2 AND #3</td>
<td>2193</td>
</tr>
</tbody>
</table>
Supplementary Material 2. First-level relevance screening question (based on the title and/or abstract) for a survey of clinical trials conducted in Canada and/or the USA examining the comparative efficacy of at least one FDA-registered antimicrobial against naturally acquired BRD in weaned beef calves.

<table>
<thead>
<tr>
<th>Question text</th>
<th>Answer type</th>
<th>Answer options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1. Does the title or abstract indicate primary research (published in journals rather than FDA submissions or technical reports) describing a trial for an FDA-registered treatment of BRD in feedlot calves within North America (Canada and/or USA only)?</td>
<td>Radio</td>
<td>Yes, No, Can't tell (unclear), Can't tell (no abstract), Potentially relevant review</td>
</tr>
</tbody>
</table>

Comments Text
**Supplementary Material 3.** Second-level relevance screening questions (based on the full text of the reference) for a survey of clinical trials conducted in Canada and/or the USA examining the comparative efficacy of at least one FDA-registered antimicrobial against naturally acquired BRD in weaned beef calves.

<table>
<thead>
<tr>
<th>Question text</th>
<th>Answer type</th>
<th>Answer options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Q1.</strong> Is the full text available in English? If not in English, please indicate language.</td>
<td>Radio</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No (not in English)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No (unable to obtain .pdf of full text)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No (Reference cites tables that were not in the manuscript.)</td>
</tr>
<tr>
<td><strong>Q2.</strong> Does the trial describe primary research on weaned beef calves in the USA and/or Canada on a cattle feedlot published in a journal?</td>
<td>Radio</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td><strong>Q3.</strong> Does the study have multiple arms with at least one arm as an FDA-registered antibiotic(s) available in the USA or Canada? It can be either metaphylaxis to prevent BRD or treatment for BRD.</td>
<td>Radio</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unclear</td>
</tr>
</tbody>
</table>

Additional comments: Text
**Supplementary Material 4.** Reporting assessment form for a survey of clinical trials conducted in Canada and/or the USA examining the comparative efficacy of at least one FDA-registered antimicrobial against naturally acquired BRD in weaned beef calves. This form is based on the REFLECT Statement (O'Connor et al. 2010).

**Q1.** In the Title and/or Abstract, did the investigators report that the study units were randomly allocated to the interventions (e.g. "random allocation", "randomized", or "randomly assigned")?

- Yes
- No
- Unclear

**Q2.** In the Introduction, did the investigators provide a scientific background of the topic and a rationale (explanation) for the study?

- Yes
- No
- Unclear

**Q3.** In the Methods, did the investigators report eligibility criteria for owner(s)/manager(s)/feedlot(s) and study units (i.e., how they were selected) at each level of the organizational structure, and did they describe the settings and locations where the data were collected?

- Yes (animal and feedlot eligibility criteria were reported and setting was described)
- No (animal and feedlot eligibility criteria were reported but setting was not described)
- No (animal and feedlot eligibility criteria not reported but setting was described)
- No (neither animal/feedlot eligibility criteria were reported nor was setting described)
- Unclear

**Q4.** In the Methods, did the investigators give precise details of the interventions intended for each group, the level at which the intervention was allocated, and how and when interventions were actually administered? Dose and route are the minimum information required.
- Yes (fully reported)
- No (list details missing) _________________
- Unclear

**Q5.** Did the investigators report the specific objectives and hypotheses of the study (a statistical hypothesis, not a working hypothesis, which is like an objective)?
- Yes (objectives and hypotheses reported)
- Yes (only objectives were reported, not hypotheses)
- Yes (only hypotheses were reported, not objectives)
- No (neither hypotheses nor objectives were reported)
- Unclear

**Q6.** Did the investigators give clearly defined primary and secondary outcome measures and the levels at which they were measured, and, when applicable, any methods used to enhance the quality of the measurements? The primary outcome is the one based on which the sample size
was calculated. In the absence of sample size calculations, authors must use the term "primary" or "main" to indicate a primary objective.

- Yes
- No
- Unclear

Q7. Did the investigators report how the sample size was determined and, when applicable, give an explanation of any interim analyses and stopping rules? Sample-size considerations should include sample-size determinations at each level of the organizational structure and the assumptions used to account for any non-independence among groups or individuals within a group.

- Yes
- No
- Unclear

Q8. Did the investigators report the method used to generate the random allocation sequence at the relevant level of the organizational structure, including details of any restrictions (e.g., blocking, stratification)?

- Yes
- No
- Unclear
Q9. Did the investigators report the method used to implement the random allocation sequence at the relevant level of the organizational structure, (e.g. numbered containers), clarifying whether the sequence was concealed until interventions were assigned?
   - Yes
   - No
   - Unclear

Q10. Did the investigators report who generated the allocation sequence, who enrolled study units, and who assigned study units to their groups at the relevant level of the organizational structure?
   - Yes
   - No (Indicate what's missing) ______________________
   - Unclear

Q11. Did the investigators report whether or not those administering the interventions, caregivers, and those assessing the outcomes were blinded to group assignment? If done, was the success of blinding evaluated? Did the investigators provide justification for not using blinding if it was not used? Check all that apply:
   - Yes (people giving the intervention)
   - Yes (caregivers. The term "caregivers" or "caretakers" or "care takers" must be used.)
   - Yes (outcome assessors)
   - Yes (people analyzing the data)
   - No (Investigators did not report whether or not anyone was blinded.)
• Unclear

**Q12.** Were statistical methods used to compare groups for all BRD outcome(s)? Did the investigators clearly state the level of statistical analysis and methods used to account for the organizational structure (where applicable)? Were the methods for additional analyses, such as subgroup analyses and adjusted analyses reported? (Only consider the BRD outcomes.)

- Yes
- No (Specify what's missing/not accounted for) ____________
- Unclear

**Q13.** In the Results, did the investigators report the flow of study units through each stage for each level of the organization structure of the study? A diagram is strongly recommended. Specifically, for each group, did the investigators report the numbers of study units randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome (The primary outcome is the one for which the sample size was calculated.)? Did the investigators describe protocol deviations from study as planned, together with reasons, if applicable?

- Yes
- No
- Unclear

**Q14.** Did the investigators report dates defining the periods of recruitment and follow-up?

- Yes
Q15. Did the investigators report the baseline demographic and clinical characteristics of each group, explicitly providing information for each relevant level of the organizational structure? Data should be reported in such a way that secondary analysis, such as risk assessment, is possible. If the study was done on 3 feedlots, we want the results reported by feedlot, not pooled.

- Yes
- No
- Unclear

Q16. Did the investigators report the number of study units (denominator) in each group included in each analysis? Did the investigators state the results in absolute numbers when feasible (e.g., 10/20, not 50%)?

- Yes
- No
- Unclear

Q17. Did the investigators, for the BRD outcome(s) only, report a summary of results for each group, accounting for each relevant level of the organizational structure, and the estimated effect size and its precision (e.g., 95% confidence interval): 1) on the primary outcome, if there was one (primary outcome is the one for which sample size calculation was made) and 2) if not, report on the main health outcome (likely BRD or 1st pull rate)?
• Yes
• No
• Unclear

Q18. Did the investigators address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory?
  • Yes (specify) ______________________
  • No
  • Unclear

Q19. Did the investigators report all important adverse events or side effects in each intervention group? If they didn't report anything, the answer is "No". They need to separate it out by group; if it says 3 adverse events BUT they don't report how many per group then the answer is "No".
  • Yes
  • No
  • Unclear
**Supplementary Material 5.** References excluded at the second level of screening (based on the full text) for a survey of clinical trials conducted in Canada and/or the USA examining the comparative efficacy of at least one FDA-registered antimicrobial against naturally acquired BRD in weaned beef calves.

<table>
<thead>
<tr>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not published in a journal</td>
</tr>
<tr>
<td>Study occurred in Italy.</td>
</tr>
<tr>
<td>Study took place on pastures, not feedlot.</td>
</tr>
<tr>
<td>Turkish study</td>
</tr>
<tr>
<td>Norbert K. Chirase, L. Wayne Greene, Charles W. Purdy, Raymond W. Loan, Brent W. Auvermann, David B. Parker, Earl F. Walborg, Donald E. Stevenson, Yong Xu, James E. Klaunig. Effect of transport stress</td>
</tr>
<tr>
<td>The authors did not assess the relationship between antimicrobial treatment and a BRD outcome.</td>
</tr>
</tbody>
</table>
on respiratory disease, serum antioxidant status, and serum concentrations of lipid peroxidation biomarkers in beef cattle. 


Beth Hibbard, Edward J. Robb, Michael D. Apley, S. Theodore Chester, Kenneth J. Dame. Feedlot performance of steers treated concurrently with ceftiofur crystalline-free acid subcutaneously in the posterior aspect of the ear and a growth-promoting implant. 


T. V. Balmer, P. Williams, I. E. Selman. Comparison of carprofen and flunixin meglumine as adjunctive therapy in bovine respiratory disease. 


Tilton et al./Revised Manuscript/Page 44


Tilmicosin, an effective tool against BRS. *Bovine & Ovine*. 2010. #volume#:50-52, 70.


L. E. Fazzio, M. F. Landoni. Comparative study on the efficacy of oxitetracicline at 40 mg/kg dose and tilmicosin both combined to meloxicam in the treatment of respiratory bovine disease in fed lot animals. Estudio comparativo de la eficacia de oxitetraciclina a la dosis de 40 mg/kg y tilmicosina, combinadas con meloxicam, en el tratamiento de la enfermedad respiratoria bovina en animales de feed lot. *Analecta Veterinaria*. 2009. 29:20-24.

A. Hentzen, W. Schultheiss, B. Herrig, J. Swinkels. Clinical efficacy and safety of a

Not a US or Canadian study

Study in Arabic

Not a US or Canadian study

Not primary research

Not a US or Canadian study

Study in Spanish

Not a US or Canadian study


P. Lekeux, P. Boutet, J. Coghe. Implementing therapeutic strategies aimed at...


H. Schmidt, H. Philipp, E. Salamon, K. Okkinga. Effects of Metacam (Meloxicam) on the course of acute respiratory diseases in cattle. Effekte der zusatzlichen Gabe von Metacam (Meloxicam) auf den Krankheitsverlauf bei Rindern mit akuten


T. Pobel, P. Zanello, H. Spennick. Spectinomycin (SPECTAMG.A.) in therapy of bovine respiratory diseases due to *Pasteurella haemolytica* or *Pasteurella multocida* associated or not with *Mycoplasma bovis* Comparaison de l'administration quotidienne ou


P. W. D. Lockwood, V. D. De Haas, T. M. S. Katz, K. J. Varma. Clinical efficacy of florfenicol in the treatment of shipping fever Study in English
in cattle in the USA


**Veterinaire Pratique de France.** 1993. 77:339...351.


C. Faixa, C. Alaman. Field study: evaluation of the efficacy of injectable amoxicillin-clavulanic acid, with a single antibiotic treatment or combined with tylosin Experiencia de campo: evaluacion de la eficacia de la amoxicilina-acido clavulanico inyectable, como unico tratamiento antibiotico o combinado con tilosina, frente a una combinacion multiple antibiotica-antiinflamatoria. *Medicina Veterinaria.* 1993. 10:610-615.


J. Hunkenmoller. Comparison of the efficacy of enrofloxacin and gentamicin in cattle with infections of the respiratory and digestive systems, under clinic conditions and in practice. Vergleichende Untersuchungen zur Wirksamkeit von Enrofloxacin (Baytril, BAY VP 2647, Bayer) und Gentamicin bei Infektionen des Atmungs- und Verdauungsapparates des Rindes in Klinik und Praxis. 1991. 135 pp. Study in German


V. de Haas, J. L. Abric, D. B. Anderson, W. B. Young. A flunixin-meglumine oxytetracycline combination in the treatment of pneumonia in calves. *Interet de l'association d'un anti-inflammatoire non*
steroiden (AINS), la flunixine meglumine, a
un antibiotique dans le traitement d'une
pneumonie chez le veau. *Maladies
respiratoires des jeunes bovins.* Paris, 24-25

C. Rindlisbacher. Treatment of bacterial
diseases in calves by sulfonamide-
trimethoprim combinations: comparison of the clinical effect of two preparations
*Behandlung bakterieller Kalberkrankheiten mit Sulfonamid-Trimethoprim-

S. Siebert. Comparative studies on the efficacy of two non-steroid anti-
inflammatory agents (acetylsalicylic acid and UH-AC 62-Boehringer) in combination with conventional antibacterial therapy in enzootic bronchopneumonia of cattle

M. Vucko, M. Potocnjak. Prevention of bronchopathies in beef cattle (with a long-
acting i.m. oxytetracycline preparation)
*Prilog preveniranju bronhopatija tovne junadi.* *Veterinarski Glasnik.* 1988. 42:647-
651.

R. Bauditz. Results from clinical studies with Baytril (Bay Vp 2674) in cattle
*Study in German*


V. Aldrovandi, F. Caleffi. First observations in the use of salbutamol in respiratory diseases of calves Prime osservazioni sull'uso del salbutamolo nelle malattie


R. Priefler. Treatment of respiratory diseases in calves and young cattle with a
combination of antibiotics and the expectorant Bisolvon (bromhexine)


Study in German

Study in Spanish

Not a feedlot study. Antibiotic used was not identified.


Study in Serbo-Croatian


Study in German


Study in Russian


Not published in a journal


Study in French

J. P. Raynaud, J. Y. Meaude. Intravenous oxytetracycline for acute respiratory diseases of microbial origin in cattle. Traitement des affections respiratoires aigues d'origine microbienne des bovins par
la Terramycine (N.D.) 100 mg/ml en intra veineuse. Proceedings of the 20th World Veterinary Congress, Thessaloniki. 1975. 3:1881-1884.


**Supplementary Material 6.** References included in a survey of clinical trials conducted in Canada and/or the USA examining the comparative efficacy of at least one FDA-registered antimicrobial against naturally acquired BRD in weaned beef calves (oldest to most recent).


Schunicht, O.C., Booker, C.W., Guielc, P.T., Jim, G.K., Wildman, B.K., Hill, B.W., Ward, T.I., Bauck, S.W., 2002. An evaluation of the relative efficacy of a new formulation of


Booker, C.W., Schunicht, O.C., Guichon, P.T., Jim, G.K., Wildman, B.K., Pittman, T.J., Perrett, T.,


Johnson, J.C., Bryson, W.L., Barringer, S., Hunsaker, B.D., 2008. Evaluation of on-arrival versus prompted metaphylaxis regimes using ceftiofur crystalline free acid for feedlot heifers at risk of


Van Donkersgoed, J., Merrill, J.K., 2013. Efficacy of tilmicosin for on-arrival treatment of bovine
respiratory disease in backgrounded winter-placed feedlot calves. The Bovine Practitioner 47, 7–12.


Reference cited in supplementary material

Table 1

Results of a database search conducted in MEDLINE® (Web of Science™) on 15 April 2017 for a survey of clinical trials conducted in Canada and/or the USA examining the comparative efficacy of at least one FDA-registered antimicrobial against naturally acquired BRD in weaned beef calves. Search dates were restricted to 1970 to present (2017). There were no language or document-type restrictions.

<table>
<thead>
<tr>
<th>Search no</th>
<th>Search string</th>
<th># Hits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TS=(beef OR bovine OR calf OR calves OR cattle OR cow OR cows OR dairy OR Hereford OR Holstein OR ruminant OR ruminants OR steer OR steers)</td>
<td>443,367</td>
</tr>
<tr>
<td>2</td>
<td>TS=(bovine respiratory disease OR Bovine viral diarrhea OR Bovine viral diarrhea virus OR undifferentiated fever OR BRD OR BVD OR BVDV OR Haemophilus somnus OR Histophilus somni OR IBR OR Infectious bovine rhinotracheitis OR Mannheimia hemolytica OR Pasteurella multocida OR Pasteurellosis OR respiratory disease OR undifferentiated bovine respiratory disease)</td>
<td>198,197</td>
</tr>
<tr>
<td>3</td>
<td>TS=(amoxicillin OR ampicillin OR antibiotic OR antibiotics OR antimicrobial OR antimicrobials 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)</td>
<td>443,841</td>
</tr>
<tr>
<td>4</td>
<td>#1 AND #2 AND #3</td>
<td>676</td>
</tr>
</tbody>
</table>
Table 2

Reporting characteristics from a survey of clinical trials conducted in Canada and/or the USA examining the comparative efficacy of at least one FDA-registered antimicrobial against naturally acquired BRD in weaned beef calves.

<table>
<thead>
<tr>
<th>REFLECT reporting item</th>
<th>Published pre-2010</th>
<th>Published post-2010</th>
<th>PR(^1) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In the Title and/or Abstract, did the investigators report that the study units were randomly allocated to the interventions? Yes(^2)</td>
<td>20/65(^3) (31%)</td>
<td>17(^4)/28 (61%)</td>
<td>1.97 (1.23, 3.16)</td>
</tr>
<tr>
<td>2. In the Introduction, did the investigators provide a scientific background of the topic and a rationale (explanation) for the study? Yes</td>
<td>64/67(^5) (95.5%)</td>
<td>28/28 (100%)</td>
<td>1.04 (0.96, 1.12)</td>
</tr>
<tr>
<td>3.1. In the Methods, did the investigators report eligibility criteria for the owner/manager/feedlot(s)? Yes</td>
<td>0/67 (0%)</td>
<td>2/28 (7.1%)</td>
<td>11.7 (0.58, 237)</td>
</tr>
</tbody>
</table>

\(^1\) Prevalence ratio (calculated as for Risk Ratio). If any cell in the 2 X 2 table had a zero value, 0.5 was added to the value in each cell in the 2 X 2 table prior to calculating the prevalence ratio, as per the recommendation at OpenEpi: http://www.openepi.com/TwobyTwo/TwobyTwo.htm.

\(^2\) This question was scored "Yes" if the authors used any form of the term "random" including systematic randomization.

\(^3\) Two references (not included in the denominator) did not have an abstract. Of the 65 papers included in the denominator, 14 did not mention randomizing the study units to the intervention groups anywhere in the paper, and they therefore may not have been randomized clinical trials.

\(^4\) One of these studies reported in the Abstract that the study units were "systematically randomized" to the interventions.

\(^5\) One of these 67 references did not have an Introduction section.
<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Yes</th>
<th>No</th>
<th>Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item 3.2</td>
<td>In the Methods, did the investigators report study unit (animal) eligibility? Yes</td>
<td>42/67 (63%)</td>
<td>18/28 (64%)</td>
<td>1.03 (0.74, 1.43)</td>
</tr>
<tr>
<td>Item 3.3</td>
<td>In the Methods, was the setting where the data were collected described? Yes</td>
<td>42/67 (63%)</td>
<td>26/28 (93%)</td>
<td>1.48 (1.2, 1.83)</td>
</tr>
<tr>
<td>Item 4</td>
<td>In the Methods, did the investigators give precise details of the interventions intended for each group, the level at which the intervention was allocated, and how and when interventions were actually administered? Yes</td>
<td>54/67 (81%)</td>
<td>26/28 (93%)</td>
<td>1.15 (0.99, 1.35)</td>
</tr>
<tr>
<td>Item 5.1</td>
<td>Did the investigators report the specific objectives of the study? Yes</td>
<td>64/67 (96%)</td>
<td>27/28 (96%)</td>
<td>1.01 (0.92, 1.10)</td>
</tr>
<tr>
<td>Item 5.2</td>
<td>Did the investigators report the specific hypotheses of the study? Yes</td>
<td>6/67 (9.0%)</td>
<td>9/28 (32%)</td>
<td>3.59 (1.41, 9.13)</td>
</tr>
<tr>
<td>Item 6</td>
<td>Did the investigators give clearly defined primary and secondary outcome measures and the levels at which they were measured, and, when applicable, any methods used to enhance the quality of the measurements? Yes</td>
<td>21/67 (31%)</td>
<td>10/28 (36%)</td>
<td>1.14 (0.62, 2.10)</td>
</tr>
<tr>
<td>Item 7</td>
<td>Did the investigators report how the sample size was determined and, when applicable, give an explanation of any interim analyses and stopping rules? Yes</td>
<td>10/67 (15%)</td>
<td>5/28 (18%)</td>
<td>1.20 (0.45, 3.18)</td>
</tr>
<tr>
<td>Item 8</td>
<td>Did the investigators report the method used to generate the random allocation sequence at the relevant</td>
<td>15/45 (33.3%)</td>
<td>8/21 (38.1%)</td>
<td>1.14 (0.58, 2.27)</td>
</tr>
</tbody>
</table>

---

6 Route of administration of the intervention was not reported in 11 of the 67 references; dose of the intervention was not reported in 3 of the 67 references.

7 Route of administration of the intervention was not reported in 2 of the 28 references.

8 14 of the references published prior to 2010 did not mention randomization and 8 studies that mentioned that the study units were systematically randomized to the interventions were not included in the denominator.

9 7 studies that reported systematic randomization were not included in the denominator.
level of the organizational structure, including details of any restrictions? Yes

<table>
<thead>
<tr>
<th>Item 9. Did the investigators report the method used to implement the random allocation sequence at the relevant level of the organizational structure, (e.g. numbered containers), clarifying whether the sequence was concealed until interventions were assigned? Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/45 (0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item 10.1. Did the investigators report who generated the allocation sequence? Yes$^{10}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>10$^{11}$/45 (22.2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item 10.2. Did the investigators report who enrolled study units? Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/67 (1.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item 10.3. Did the investigators report who assigned study units to their groups at the relevant level of the organizational structure? Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^{13}$/67 (1.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item 11.1. Did the investigators report whether or not those administering the interventions were blinded? Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>6$^{14}$/67 (9%)</td>
</tr>
</tbody>
</table>

$^{10}$ Denominators calculated as per item 8.

$^{11}$ For all 10 studies, a computer was used to generate the sequence. The identity of the person operating the computer was not reported.

$^{12}$ The random sequence was generated by a biostatistician (3 studies), the study investigator (1 study), the study monitor (1 study), and by a computer (computer operator not reported) (4 studies).

$^{13}$ This was done by the study investigator (1 study).

$^{14}$ In 3 of these 6 studies, the authors reported that the people giving the intervention were not blinded. The reason for this was not explained.

$^{15}$ In 6 of these 7 studies, the authors reported that the people giving the intervention were not blinded. For 2 of these 6 studies, the authors explained that lack of blinding was due to the staff needing to know which drug to administer; for the remaining 4 studies, the authors did not give a reason for the lack of blinding.
Item 11.2. Did the investigators report whether or not caregivers were blinded? Yes

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>416/67</td>
<td>217/28</td>
</tr>
<tr>
<td></td>
<td>(6%)</td>
<td>(7%)</td>
</tr>
<tr>
<td></td>
<td>(0.23,</td>
<td>(6.20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Item 11.3. Did the investigators report whether or not those assessing the outcomes were blinded? Yes

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3718/67</td>
<td>2419/28</td>
</tr>
<tr>
<td></td>
<td>(55%)</td>
<td>(86%)</td>
</tr>
<tr>
<td></td>
<td>(1.19,</td>
<td>(2.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Item 11.4. Did the investigators report whether or not those analyzing the data were blinded? Yes

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0/67</td>
<td>0/28</td>
</tr>
<tr>
<td></td>
<td>(0%)</td>
<td>(0%)</td>
</tr>
<tr>
<td></td>
<td>(0.05,</td>
<td>(115)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Item 11.5. Did the investigators report blinding (or the absence of blinding) at all? Yes

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40/67</td>
<td>26/28</td>
</tr>
<tr>
<td></td>
<td>(60%)</td>
<td>(93%)</td>
</tr>
<tr>
<td></td>
<td>(1.25,</td>
<td>(1.94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Item 12. Were statistical methods used to compare groups for all BRD outcome(s) and did the investigators clearly state the level of statistical analysis and methods used to account for the organizational structure (where applicable)? Yes

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4620/67</td>
<td>24/28</td>
</tr>
<tr>
<td></td>
<td>(69%)</td>
<td>(86%)</td>
</tr>
<tr>
<td></td>
<td>(1.00,</td>
<td>(1.57)</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

Item 13. In the Results, did the investigators report the flow of study units through each stage for each level of the organization structure of the study? Yes

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>45/67</td>
<td>17/28</td>
</tr>
<tr>
<td></td>
<td>(67%)</td>
<td>(61%)</td>
</tr>
<tr>
<td></td>
<td>(0.64,</td>
<td>(1.27)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Item 14. Did the investigators report dates defining the periods of recruitment and follow-up? Yes

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>33/67</td>
<td>21/28</td>
</tr>
<tr>
<td></td>
<td>(49%)</td>
<td>(75%)</td>
</tr>
<tr>
<td></td>
<td>(1.10,</td>
<td>(2.11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

16 For 1 of these 4 studies, the caregivers were reported to not be blinded, and a reason was given.

17 For 1 of these 2 studies, the caregivers were not blinded. The authors did not report a reason for this.

18 For 2 of these 37 studies, the outcome assessors were reported to not be blinded and a reason was given in each case.

19 For 7 of these 24 studies, at least one of the outcome assessors was reported to be not blinded. For 3 of 7 of these studies, a reason was reported for the absence of blinding.

20 For 5 studies (not included in the 46), the way the animals were housed was not described in enough detail to determine if clustering by pen should have been taken into account in the analysis or not.
<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Subitem</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Ratio</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Did the investigators report the baseline demographic and clinical characteristics of each group, explicitly providing information for each relevant level of the organizational structure? Yes</td>
<td>27/67 (40%)</td>
<td>15/28 (55%)</td>
<td>1.33</td>
<td>(0.85, 2.09)</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Did the investigators report the number of study units (denominator) in each group included in each analysis and the results in absolute numbers when feasible? Yes</td>
<td>43/67 (64%)</td>
<td>18/28 (64%)</td>
<td>1.00</td>
<td>(0.72, 1.39)</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Did the investigators, for the BRD outcome(s) only, report a summary of results for each group, accounting for each relevant level of the organizational structure, and the estimated effect size and its precision (e.g., 95% confidence interval)? Yes</td>
<td>15/67 (22%)</td>
<td>7/28 (25%)</td>
<td>1.12</td>
<td>(0.51, 2.44)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Did the investigators address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory? Yes</td>
<td>3/34 (8.8%)</td>
<td>0/7 (0%)</td>
<td>0.63</td>
<td>(0.04, 10.93)</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Did the investigators report all important adverse events or side effects in each intervention group? Yes</td>
<td>11/67 (16%)</td>
<td>4/28 (14%)</td>
<td>0.87</td>
<td>(0.30, 2.50)</td>
<td></td>
</tr>
</tbody>
</table>

21 The denominators comprise only those studies with 3 or more arms. A study was scored Yes if Tukey's test, Ducan's multiple range test, Fisher's LSD, or the Bonferroni method were reported with respect to BRD outcomes only.

22 All 3 studies reported using Duncan's multiple range test.
<table>
<thead>
<tr>
<th>Item Number</th>
<th>Pre-2010 Yes</th>
<th>Pre-2010 No</th>
<th>Post-2010 Yes</th>
<th>Post-2010 No</th>
<th>Prevalence Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item_1</td>
<td>20</td>
<td>45</td>
<td>17</td>
<td>11</td>
<td>1.97 [1.23, 3.16]</td>
</tr>
<tr>
<td>Item_3_2</td>
<td>42</td>
<td>25</td>
<td>18</td>
<td>10</td>
<td>1.03 [0.74, 1.43]</td>
</tr>
<tr>
<td>Item_3_3</td>
<td>42</td>
<td>25</td>
<td>26</td>
<td>2</td>
<td>1.48 [1.20, 1.83]</td>
</tr>
<tr>
<td>Item_4</td>
<td>54</td>
<td>13</td>
<td>26</td>
<td>2</td>
<td>1.15 [0.99, 1.35]</td>
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<tr>
<td>Item_5_1</td>
<td>64</td>
<td>3</td>
<td>27</td>
<td>1</td>
<td>1.01 [0.92, 1.10]</td>
</tr>
<tr>
<td>Item_5_2</td>
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<td>61</td>
<td>9</td>
<td>19</td>
<td>3.59 [1.41, 9.13]</td>
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<tr>
<td>Item_6</td>
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<td>46</td>
<td>10</td>
<td>18</td>
<td>1.14 [0.62, 2.10]</td>
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<tr>
<td>Item_7</td>
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<td>57</td>
<td>5</td>
<td>23</td>
<td>1.20 [0.45, 3.18]</td>
</tr>
<tr>
<td>Item_8</td>
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<td>30</td>
<td>8</td>
<td>13</td>
<td>1.14 [0.58, 2.27]</td>
</tr>
<tr>
<td>Item_10_1</td>
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<td>35</td>
<td>9</td>
<td>12</td>
<td>1.93 [0.92, 4.03]</td>
</tr>
<tr>
<td>Item_10_2</td>
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<td>66</td>
<td>3</td>
<td>25</td>
<td>7.18 [0.78, 66.08]</td>
</tr>
<tr>
<td>Item_11_1</td>
<td>6</td>
<td>61</td>
<td>7</td>
<td>21</td>
<td>2.79 [1.03, 7.57]</td>
</tr>
<tr>
<td>Item_11_2</td>
<td>4</td>
<td>63</td>
<td>2</td>
<td>26</td>
<td>1.20 [0.23, 6.16]</td>
</tr>
<tr>
<td>Item_11_3</td>
<td>37</td>
<td>30</td>
<td>24</td>
<td>4</td>
<td>1.55 [1.19, 2.02]</td>
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<tr>
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<td>27</td>
<td>26</td>
<td>2</td>
<td>1.56 [1.25, 1.94]</td>
</tr>
<tr>
<td>Item_12</td>
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<td>21</td>
<td>24</td>
<td>4</td>
<td>1.25 [1.00, 1.56]</td>
</tr>
<tr>
<td>Item_13</td>
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<td>22</td>
<td>17</td>
<td>11</td>
<td>0.90 [0.64, 1.27]</td>
</tr>
<tr>
<td>Item_14</td>
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<td>34</td>
<td>21</td>
<td>7</td>
<td>1.52 [1.10, 2.10]</td>
</tr>
<tr>
<td>Item_15</td>
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<td>40</td>
<td>15</td>
<td>13</td>
<td>1.33 [0.85, 2.09]</td>
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<tr>
<td>Item_16</td>
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<td>24</td>
<td>18</td>
<td>10</td>
<td>1.00 [0.72, 1.39]</td>
</tr>
<tr>
<td>Item_17</td>
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<td>52</td>
<td>7</td>
<td>21</td>
<td>1.12 [0.51, 2.44]</td>
</tr>
<tr>
<td>Item_19</td>
<td>11</td>
<td>56</td>
<td>4</td>
<td>24</td>
<td>0.87 [0.30, 2.50]</td>
</tr>
</tbody>
</table>
item 1: Reported random
item 2: Rationale
item 3−1: Owner/feedlot eligibility
item 3−2: Animal eligibility
item 3−3: Settings
item 4: Interventions
item 5−1: Objectives
item 5−2: Hypotheses
item 6: Outcomes
item 7: Sample size
item 8: Sequence generation methods
item 9: Allocation Concealment
item 10−1: Implementation: who generated sequence
item 10−2: Implementation: who enrolled subjects
item 10−3: Implementation: who administered the intervention
item 11−1: Blind: administration
item 11−2: Blind: caregivers
item 11−3: Blind: outcome assessment
item 11−4: Blind: data analysis
item 11−5: Blind: any task
item 12: Statistical methods
item 13: Flow of study units
item 14: Recruitment
item 15: Baseline
item 16: Numbers analyzed
item 17: Outcomes and estimation
item 18: Ancillary analyses
item 19: Adverse events