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

Sarah C. Totton[a,*], Jonah N. Cullen[b], Jan M Sargeant[c,d,e], Annette M. O'Connor[b]

[a] 63 College Avenue West, Guelph, Ontario, N1G 1S1, Canada

[b] Department of Veterinary Diagnostic and Production Animal Medicine, College of Veterinary Medicine, Iowa State University, Ames, Iowa, 50011-3619, USA

[c] Department of Population Medicine, Ontario Veterinary College, University of Guelph, 50 Stone Road East, Guelph, Ontario, N1G 2W1, Canada

[d] Centre for Public Health and Zoonoses, University of Guelph, 50 Stone Road East, Guelph, Ontario, N1G 2W1, Canada

[e] Arrell Food Institute, University of Guelph, 50 Stone Road East, Guelph, Ontario, N1G 2W1, Canada

∗ Corresponding author at: 63 College Avenue West, Guelph, Ontario, N1G 1S1, Canada

Email address: sarah.totton@gmail.com (Sarah C. Totton)

Author contributions statements

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JC- extraction of data, data analysis, and preparation of the manuscript

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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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P.S., Ramirez, A., Sischo, W., Smith, D.R., Snedeker, K., Sofos, J.N., Ward, M.P., Wills, R., Consensus Meeting, P., 2010e. The REFLECT statement: methods and processes of creating reporting guidelines for randomized controlled trials for livestock and food safety. J. Food Prot. 73, 132–139.

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Simera, I., Moher, D., Hirst, A., Hoey, J., Schulz, K.F., Altman, D.G., 2010. Transparent and accurate reporting increases reliability, utility, and impact of your research: reporting guidelines and the EQUATOR Network. BMC Med. 8, 24. doi: 10.1186/1741-7015-8-24.

Sweet, J.J., 2014. Editorial. EQUATOR - reporting guidelines for "Enhancing the QUality and Transparency Of health Research". Clin. Neuropsychol. 28, 547–548. doi: 10.1080/13854046.2014.934019.

Torres, S., Thomson, D.U., Bello, N.M., Nosky, B.J., Reinhardt, C.D., 2013. Field study of the comparative efficacy of gamithromycin and tulathromycin for the control of undifferentiated bovine respiratory disease complex in beef feedlot calves at high risk of developing respiratory tract disease. Am. J. Vet. Res. 74, 839–846. doi: 10.2460/ajvr.74.6.839.

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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.

Van Donkersgoed, J., Berg, J., Hendrick, S., 2008. Comparison of florfenicol and tulathromycin for the treatment of undifferentiated fever in Alberta feedlot calves. Vet. Ther. 9, 275–281.

Wellman, N.G., O'Connor, A.M., 2007. Meta-analysis of treatment of cattle with bovine respiratory disease with tulathromycin. J. Vet. Pharmacol. Ther. 30, 234–241. doi: 10.1111/j.1365-2885.2007.00846.x.

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.

Search no.	Search string	No. hits
1	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)	933,061
2	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)	90,838
3	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)	168,066
4	#1 AND #2 AND #3	2193

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.

Question text	Answer type	Answer options
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)?	Radio	Yes No Can't tell (unclear) Can't tell (no abstract) Potentially relevant review
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.

Question text	Answer type	Answer options
Q1. Is the full text available in English? If not in English, please indicate language.	Radio	Yes No (not in English) No (unable to obtain .pdf of full text) No (Reference cites tables that were not in the manuscript.)
Q2. Does the trial describe primary research on weaned beef calves in the USA and/or Canada on a cattle feedlot published in a journal?	Radio	Yes No
Q3. 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.	Radio	Yes No Unclear
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

- No
- Unclear

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, <u>for the BRD outcome(s) only</u>, 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.

Reference	Reason for exclusion
D Nash. A comparison of three therapeutic programs for the treatment of shipping fever in weaned calves. Bovine Respiratory Disease: A Symposium; Ed by R Loan, College Station, Texas A&M University Press 1984. 471-472.	Not published in a journal
Enrico Fiore, Leonardo Armato, Massimo Morgante, Michele Muraro, Matteo Boso, Matteo Gianesella. Methaphylactic effect of tulathromycin treatment on rumen fluid parameters in feedlot beef cattle. *Canadian journal of veterinary research.* 2016. 80: 60-5.	Study occurred in Italy.
Robert G. Nutsch, Terry L. Skogerboe, Kathleen A. Rooney, Daniel J. Weigel, Kimberly Gajewski, Kelly F. Lechtenberg. Comparative efficacy of tulathromycin, tilmicosin, and florfenicol in the treatment of bovine respiratory disease in stocker cattle. *Veterinary Therapeutics: research in applied veterinary medicine.* 2005. 6:167-79.	Study took place on pastures, not feedlot.
B. Elitok, O. M. Elitok. Clinical efficacy of carprofen as an adjunct to the antibacterial treatment of bovine respiratory disease. *Journal of veterinary pharmacology and therapeutics.* 2004. 27:317-20.	Turkish study
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	The authors did not assess the relationship between antimicrobial treatment and a BRD outcome.

on respiratory disease, serum antioxidant status, and serum concentrations of lipid peroxidation biomarkers in beef cattle. *American journal of veterinary research.* 2004. 65:860-4.	
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. *Veterinary Therapeutics : research in applied veterinary medicine.* 2002. 3:252-61.	Study had multiple arms and at least one arm is an FDA-registered antibiotic(s) available in the USA or Canada? No
G. H. Frank, R. E. Briggs, R. W. Loan, C. W. Purdy, E. S. Zehr. Effects of tilmicosin treatment on *Pasteurella haemolytica* organisms in nasal secretion specimens of calves with respiratory tract disease. *American journal of veterinary research.* 2000. 61:525-9.	There was only one arm in this study.
H. Schmidt, H. Philipp, U. Hamel, J. F. Quirke. Treatment of acute respiratory tract diseases in cattle with Bisolvon in combination with either enrofloxacin, cefquinome, ceftiofur or florfenicol. *Tierarztliche Praxis. Ausgabe G, Grosstiere/Nutztiere.* 1998. 26:127-32.	Study in German
T. V. Balmer, P. Williams, I. E. Selman. Comparison of carprofen and flunixin meglumine as adjunctive therapy in bovine respiratory disease. *Veterinary journal (London, England : 1997).* 1997. 154:233-41.	Study in the United Kingdom
T. Katoh, J. Sakai, Y. Ogata, Y. Urushiyama. Effect of a combination of antimicrobial agents for the treatment of respiratory disease in cattle. *The Journal of veterinary medical science.* 1996. 58:783-5.	Not a US or Canadian study

P. R. Scott, M. McGowan, N. D. Sargison, C. D. Penny, B. G. Lowman. Use of tilmicosin in a severe outbreak of respiratory disease in weaned beef calves. *Australian veterinary journal.* 1996. 73:62-4.	Not a US or Canadian study
P. R. Scott. Efficacy of strategic tilmicosin injection during an outbreak of respiratory disease in housed beef calves. *The British veterinary journal.* 1995. 151:587-9.	Not a US or Canadian study
J. Deleforge, E. Thomas, J. L. Davot, B. Boisrame. A field evaluation of the efficacy of tolfenamic acid and oxytetracycline in the treatment of bovine respiratory disease. *Journal of veterinary pharmacology and therapeutics.* 1994. 17:43-7.	Not a US or Canadian study
H. P. Heckert, W. Hofmann. Clinical indications of an auxiliary effect of antihistamines (parenteral Benadryl) in the treatment of RSV infections of cattle. *Berliner und Munchener tierarztliche Wochenschrift.* 1993. 106:230-5.	Study in German
B. Genicot, F. Mouligneau, F. Rollin, J. K. Lindsey, R. Close, P. Lekeux. Economic, clinical and functional consequences of a treatment using metrenperone during an outbreak of shipping fever in cattle. *The Veterinary record.* 1993. 132:245-7.	Not a US or Canadian study
J. W. Allen, L. Viel, K. G. Bateman, S. Rosendal. Changes in the bacterial flora of the upper and lower respiratory tracts and bronchoalveolar lavage differential cell counts in feedlot calves treated for respiratory diseases. *Canadian journal of veterinary research = Revue canadienne de recherche veterinaire.* 1992. 56:177-83.	Case-control study
T. Picavet, E. Muylle, L. A. Devriese, J. Geryl. Efficacy of tilmicosin in treatment of pulmonary infections in calves. *The Veterinary record.* 1991. 129:400-3.	Not a US or Canadian study

P. Gustin, F. J. Landser, F. Lomba, P. Lekeux. Assessment of respiratory diseases and therapeutic intervention by the forced oscillation technique in feedlot cattle. *Research in veterinary science.* 1990. 49:319-22.	Not a US or Canadian study
D. J. McKenna, G. D. Koritz, C. A. Neff-Davis, V. C. Langston, L. L. Berger. Field trial of theophylline in cattle with respiratory tract disease. *Journal of the American Veterinary Medical Association.* 1989. 195:603-5.	Unable to obtain full text
P. Lekeux, T. Art. Effect of enrofloxacin therapy on shipping fever pneumonia in feedlot cattle. *The Veterinary record.* 1988. 123:205-7.	Not a US or Canadian study
A. R. Peters. Use of a long-acting oxytetracycline preparation in respiratory disease in young beef bulls. *The Veterinary record.* 1985. 116:321.	Not a US or Canadian study
G. R. Sampson, R. A. Sauter, R. P. Gregory. Evaluation of injectable tylosin in cattle. *Modern veterinary practice.* 1974. 55:10.	Unable to obtain full text
R. E. Messersmith, S. W. Anderson, L. N. Brown, F. J. Hussey. Respiratory disease in recently-shipped Minnesota steers (a clinical study). *Veterinary medicine, small animal clinician : VM, SAC.* 1972. 67:1011-6.	Unable to obtain full text
L. E. Fazzio, M. J. Giuliodori, W. R. Galvan, N. Streitenberger, M. F. Landoni. A metaphylactic treatment with double dose oxytetracycline reduces the risk of bovine respiratory disease in feedlot calves. *Revista Veterinaria.* 2015. 26:89-92.	Not a US or Canadian study
Kumar Pankaj, A. Dey, Kumar Neeraj, Kumar Sanjiv. Clinical management of respiratory disease and septicemia in calves. *Intas Polivet.* 2015. 16:90-93.	Not a US or Canadian study

R. Urban-Chmiel, R. Stachura, P. Hola, A. Puchalski, M. Dec, A. Wernicki. Effects of flunixin and florfenicol combined with vitamins E and/or C on selected immune mechanisms in cattle under conditions of adaptive stress. *Bulletin of the Veterinary Institute in Pulawy.* 2015. 59:295-301.	Not a US or Canadian study
R. Compiani, G. Baldi, M. Bonfanti, D. Fucci, G. Pisoni, S. Jottini, S. Torres. Comparison of tildipirosin and tulathromycin for control of bovine respiratory disease in high-risk beef heifers. *Bovine Practitioner.* 2014. 48:114-119.	Not a US or Canadian study
T. J. Miller, D. U. Thomson, C. D. Reinhardt, C. A. Loest, M. E. Hubbert. Comparison of the metaphylactic efficacy of gamithromycin, tilmicosin and tulathromycin in beef calves at high risk for BRD. *Proceedings of the 46th Annual Conference of the American Association of Bovine Practitioners, Milwaukee, Wisconsin, USA, 19-21 September 2013.* 2014. Pp. 144.	Not published in a journal
A. P. R. Saber, B. F. Hoshyar, F. Sadigi, B. A. Asgharzade, D. Bakhshi, M. Aghapour, S. Babaei, J. Kkhanzade. Evaluation the effects of penicillin in control of clinical pneumonia in calves. *Annals of Biological Research.* 2013. 4:174-178.	Not a US or Canadian study
D. Bednarek, K. Lutnicki, K. Dudek, J. Marczuk, L. Kurek, R. Mordak, P. A. Stewart. The effect of the combined use of a long-acting antibiotic with NSAID on the clinical status and cellular immune response in calves affected with bovine respiratory disease. *Cattle Practice.* 2013. 21:91-97.	Not a US or Canadian study
J. T. Richeson, J. G. Powell, E. B. Kegley, J. A. Hornsby. Evaluation of an ear-mounted tympanic thermometer device for bovine respiratory disease diagnosis. *Research*	Not published in a journal

Series - Arkansas Agricultural Experiment Station. 2012. pp. 40-42.	
D. Fucci, R. Compiani, G. Baldi, C. A. S. Rossi. Incidence of respiratory diseases and growth performance of high risk BRD newly received beef cattle treated at arrival Incidenza di problematiche respiratorie e performance di crescita di bovini da ristallo ad alto rischio BRD sottoposti a trattamento anti-infettivo d'arrivo. *Large Animal Review.* 2012. 18:171-175.	Study in Italian
Y. Ozkanlar, M. S. Aktas, O. Kaynar, S. Ozkanlar, E. Kirecci, L. Yildiz. Bovine respiratory disease in naturally infected calves: clinical signs, blood gases and cytokine response. *Revue de Medecine Veterinaire.* 2012. 163:123-130.	Not a US or Canadian study
J. V. Gonzalez-Martin, L. Elvira, M. Cervino Lopez, N. Perez Villalobos, E. C. Lopez-Guerrero, S. Astiz. Reducing antibiotic use: selective metaphylaxis with florfenicol in commercial feedlots. *Livestock Science.* 2011. 141:173-181.	Not a US or Canadian study
M. Jezdimirovic, N. Aleksic, A. Barac-Basevic, M. Zutic, V. Ivetic, O. Radanovic, N. Jezdimirovic. Comparative investigation on the efficacy of tulathromycin and florfenicol in the treatment of bronchopneumonia in feedlot calves Uporedno ispitivanje efikasnosti tulatromicina i florfenikola u lecenju bronhopneumonije junadi. *Veterinarski Glasnik.* 2011. 65:153-178.	Study in Serbian
L. E. Fazzio, M. F. Landoni. Comparison of the effectiveness of a metaphylactic treatment with oxytetracycline and tilmicosin on bovine respiratory disease in feed lot calves Comparacion de la eficacia de oxitetraciclina y tilmicosina en el tratamiento metafilactico de la enfermedad	Study in Spanish

respiratoria bovina en animales de feed lot. *Analecta Veterinaria.* 2010. 30:35-40.	
I. Aytekin, N. Mamak, A. C. Onmaz, F. Sarin, S. Aslan. Effects of tulathromycin and tilmicosin application in the treatment of bovine respiratory disease in cattle. *Yuzuncu yil Universitesi Veteriner Fakultesi Dergisi.* 2010. 21:159-162.	Not a US or Canadian study
Tilmicosin, an effective tool against BRS. *Bovine & Ovine.* 2010. #volume#:50-52, 70.	Study in Arabic
J. Embrechts, W. Lohlein, O. Wolf, M. Ocak, J. de Busser. An innovative long acting florfenicol formulation for the treatment of bovine respiratory disease. *Cattle Practice.* 2010. 18:195-196.	Not a US or Canadian study
H. Coetzee, M. Apley. BRD treatment in cattle. Large animal. Proceedings of the North American Veterinary Conference, Orlando, Florida, USA, 16-20 January 2010. 2010. Pp. 1-4.	Not primary research
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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.

Search no	Search string	# Hits
1	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)	443,367
2	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)	198,197
3	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)	443,841
4	#1 AND #2 AND #3	676

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.

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

[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.

Item 3.2. In the Methods, did the investigators report study unit (animal) eligibility? Yes	42/67 (63%)	18/28 (64%)	1.03 (0.74, 1.43)
Item 3.3. In the Methods, was the setting where the data were collected described? Yes	42/67 (63%)	26/28 (93%)	1.48 (1.2, 1.83)
Item 4. 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	54/67[6] (81%)	26/28[7] (93%)	1.15 (0.99, 1.35)
Item 5.1. Did the investigators report the specific objectives of the study? Yes	64/67 (96%)	27/28 (96%)	1.01 (0.92, 1.10)
Item 5.2. Did the investigators report the specific hypotheses of the study? Yes	6/67 (9.0%)	9/28 (32%)	3.59 (1.41, 9.13)
Item 6. 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	21/67 (31%)	10/28 (36%)	1.14 (0.62, 2.10)
Item 7. Did the investigators report how the sample size was determined and, when applicable, give an explanation of any interim analyses and stopping rules? Yes	10/67 (15%)	5/28 (18%)	1.20 (0.45, 3.18)
Item 8. Did the investigators report the method used to generate the random allocation sequence at the relevant	15/45[8] (33.3%)	8/21[9] (38.1%)	1.14 (0.58, 2.27)

[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			
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	0/45 (0%)	0/21 (0%)	2.091 (0.04, 101.9)
Item 10.1. Did the investigators report who generated the allocation sequence? Yes[10]	10[11]/45 (22.2%)	9[12]/21 (42.9%)	1.93 (0.92, 4.03)
Item 10.2. Did the investigators report who enrolled study units? Yes	1/67 (1.5%)	3/28 (11%)	7.18 (0.78, 66.1)
Item 10.3. Did the investigators report who assigned study units to their groups at the relevant level of the organizational structure? Yes	1[13]/67 (1.5%)	0/28 (0%)	0.78 (0.03, 18.6)
Item 11.1. Did the investigators report whether or not those administering the interventions were blinded? Yes	6[14]/67 (9%)	7[15]/28 (25%)	2.79 (1.03, 7.57)

[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	4[16]/67 (6%)	2[17]/28 (7%)	1.20 (0.23, 6.20)
Item 11.3. Did the investigators report whether or not those assessing the outcomes were blinded? Yes	37[18]/67 (55%)	24[19]/28 (86%)	1.55 (1.19, 2.02)
Item 11.4. Did the investigators report whether or not those analyzing the data were blinded? Yes	0/67 (0%)	0/28 (0%)	2.34 (0.05, 115)
Item 11.5. Did the investigators report blinding (or the absence of blinding) at all? Yes	40/67 (60%)	26/28 (93%)	1.56 (1.25, 1.94)
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	46[20]/67 (69%)	24/28 (86%)	1.25 (1.00, 1.57)
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	45/67 (67%)	17/28 (61%)	0.90 (0.64, 1.27)
Item 14. Did the investigators report dates defining the periods of recruitment and follow-up? Yes	33/67 (49%)	21/28 (75%)	1.52 (1.10, 2.11)

[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.

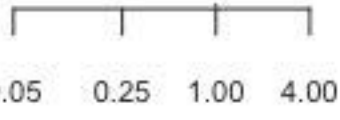
[20] For 5 studies (not included in the 46), the way the animals were housed was not described in enough detail to determine if clustering by pen should have been taken into account in the analysis or not.

Item 15. 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	27/67 (40%)	15/28 (55%)	1.33 (0.85, 2.09)
Item 16. 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	43/67 (64%)	18/28 (64%)	1.00 (0.72, 1.39)
Item 17. 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	15/67 (22%)	7/28 (25%)	1.12 (0.51, 2.44)
Item 18. 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[21]	3[22]/34 (8.8%)	0/7 (0%)	0.63 (0.04, 10.93)
Item 19. Did the investigators report all important adverse events or side effects in each intervention group? Yes	11/67 (16%)	4/28 (14%)	0.87 (0.30, 2.50)

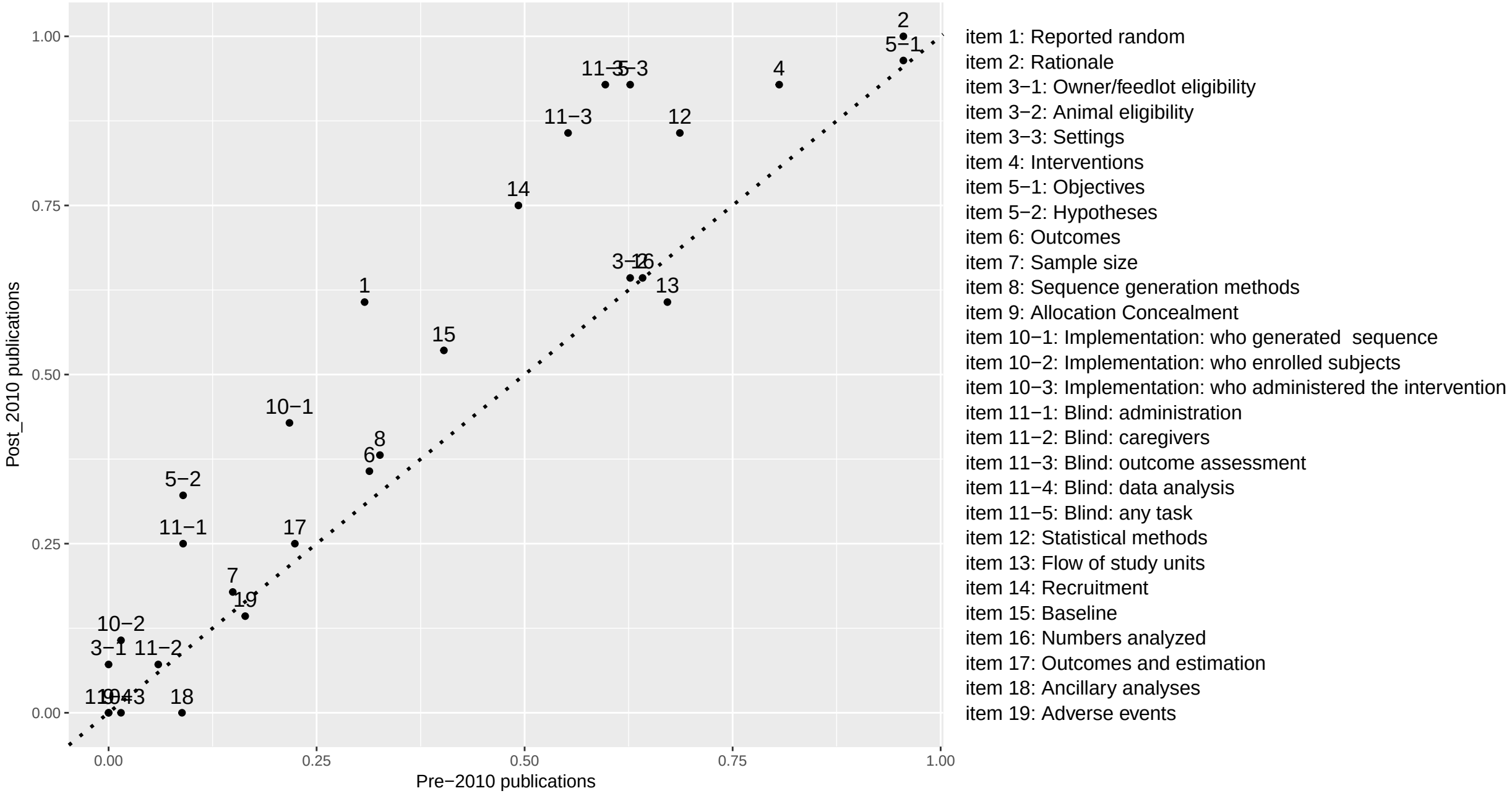
[21] The denominators comprise only those studies with 3 or more arms. A study was scored Yes if Tukey's test, Ducan's multiple range test, Fisher's LSD, or the Bonferroni method were reported with respect to BRD outcomes only.

[22] All 3 studies reported using Duncan's multiple range test.

Item Number	Pre-2010 Yes	Pre-2010 No	Post-2010 Yes	Post-2010 No	Prevalence Ratio [95% CI]
Item_1	20	45	17	11	1.97 [1.23 , 3.16]
Item_3_2	42	25	18	10	1.03 [0.74 , 1.43]
Item_3_3	42	25	26	2	1.48 [1.20 , 1.83]
Item_4	54	13	26	2	1.15 [0.99 , 1.35]
Item_5_1	64	3	27	1	1.01 [0.92 , 1.10]
Item_5_2	6	61	9	19	3.59 [1.41 , 9.13]
Item_6	21	46	10	18	1.14 [0.62 , 2.10]
Item_7	10	57	5	23	1.20 [0.45 , 3.18]
Item_8	15	30	8	13	1.14 [0.58 , 2.27]
Item_10_1	10	35	9	12	1.93 [0.92 , 4.03]
Item_10_2	1	66	3	25	7.18 [0.78 , 66.08]
Item_11_1	6	61	7	21	2.79 [1.03 , 7.57]
Item_11_2	4	63	2	26	1.20 [0.23 , 6.16]
Item_11_3	37	30	24	4	1.55 [1.19 , 2.02]
Item_11_5	40	27	26	2	1.56 [1.25 , 1.94]
Item_12	46	21	24	4	1.25 [1.00 , 1.56]
Item_13	45	22	17	11	0.90 [0.64 , 1.27]
Item_14	33	34	21	7	1.52 [1.10 , 2.10]
Item_15	27	40	15	13	1.33 [0.85 , 2.09]
Item_16	43	24	18	10	1.00 [0.72 , 1.39]
Item_17	15	52	7	21	1.12 [0.51 , 2.44]
Item_19	11	56	4	24	0.87 [0.30 , 2.50]



(Pre-2010) Prevalence Ratio (Post-2010)


Post_2010 publications
Pre−2010 publications
0.00
0.25
0.50
0.75
1.00
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