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Minireview

MINIREVIEW

Do antimicrobial mass medications work? A systematic review and meta-analysis of randomised clinical trials investigating antimicrobial prophylaxis or metaphylaxis against naturally occurring bovine respiratory disease

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One sentence summary: A systematic review and meta-analysis of randomised clinical trials investigating antimicrobial prophylaxis or metaphylaxis against naturally occurring bovine respiratory disease.
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ABSTRACT

A distinct difference between veterinary and human medicine is the routine use of antimicrobial mass medications (prophylaxis, metaphylaxis) to healthy individuals. The need for antimicrobial mass medications is based on beliefs that group/s of animals will contract a bacterial disease (i.e. morbidity) and/or die (i.e. mortality). Bovine respiratory disease (BRD) represents the major indication for cattle antimicrobials worldwide. The objectives were to perform a systematic review and meta-analysis of randomised controlled clinical trials (RCTs) for naturally occurring BRD investigating antimicrobial prophylaxis/metaphylaxis to prevent morbidity/mortality. In total, 58 publications met the inclusion criteria summarizing 169 individual RCTs, spanning 50 years (1966–2016). Antimicrobial prophylaxis and metaphylaxis demonstrated moderate, yet highly variable relative risk reductions in BRD morbidity. These were dependent on the antimicrobial classes used, dependent on metaphylaxis definition, BRD attack rates and duration of the RCTs. Best relative risk reductions were from broad-spectrum critically important antimicrobials, or combinations. BRD prophylaxis/metaphylaxis represents major antimicrobial consumption for highly variable short-term gains in absolute risk reduction of morbidity/mortality. Despite widespread use of prevention products, the need for antimicrobial mass medications should be re-evaluated since the underlying problem is more likely the segmented infrastructure of the feedlot and veal calf industries compared to the disease itself.

Keywords: antimicrobial; prophylaxis; metaphylaxis; bovine

INTRODUCTION

Bovine respiratory disease (BRD) complex is the most common and extensively studied cattle disease of all ages, especially feedlot cattle and veal calves. BRD represents the major indication for cattle antimicrobials worldwide, especially for prophylaxis and metaphylaxis. Coupled with mortalities, treatment costs, decreased performance and reduced carcass value, BRD leads to major economic losses for cattle feeders (Ives and Richeson 2015).

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The complex of viral, bacterial and/or mycoplasmal infections is described with blanket terms, 'enzootic pneumonia', 'shipping fever' or 'bovine respiratory disease complex', often used without precise definitions. Viruses and other stressors predispose cattle to opportunistic bacterial pneumonias, including bovine respiratory syncytial virus, parainfluenzavirus-3, infectious bovine rhinotracheitis virus, bovine herpes virus-1 and possibly bovine coronavirus (O'Neill *et al.* 2014). These viruses trigger BRD by damaging upper respiratory tract mucosa and/or modifying host pro- and anti-inflammatory immune responses. Bacterial BRD pathogens include *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, Arcanobacterium pyogenes*, *Mycoplasma dispar* and *M. bovis* that exist commonly as commensals, often as biofilms within the upper respiratory tract and tonsils.

Classical BRD field diagnosis are visual signs, including depression, anorexia, nasal and/or ocular discharge, coughing, laboured breathing (Buhman *et al.* 2000) or a semi-objective four-point clinical illness score (Perino and Apley 1998). This is subjective, non-standardised but the typical basis for deciding on further antimicrobials treatments, or combined with rectal temperature, although bovine fever thresholds vary throughout the scientific literature (Ives and Richeson 2015). Comparing BRD field diagnostics to pulmonary lesions evident at slaughter reveals several cattle (e.g. >50%) with lung lesions, not previously identified and treated for BRD (Thompson, Stone and Schultheiss 2006; Tennant *et al.* 2014). These limitations contribute largely to the justification for routine antimicrobial prophylaxis/metaphylaxis in place of identifying, pulling and treating sick calves/cattle. The culmination of stressors (e.g. recently weaned, auctioned, transported, environmental/nutritional changes, co-mingling, castrated) results in each cohort of feedlot cattle/veal calves expressing the majority of visual BRD cases (up to 90%) within the first 27 days after arrival (Edwards 1996; Buhman *et al.* 2000).

Soon after the introduction of antimicrobial agents, their growth-promoting effects were discovered in animals (Moore *et al.* 1946). Antimicrobials were approved for growth promotion in the USA since 1949 and since 1953 in the UK (Swann 1969). However, mounting evidence about antimicrobial resistance and transference of resistance genes from animal to human microbiota led to a full withdrawal of antimicrobial growth promoters in the European Union, since 2006 (Regulation 1831/2003). The European support to recommendations of the World Health Organization (WHO), the Food and Agriculture Organization (FAO) and the World Organization or Animal Health for a ban on antimicrobial growth promoters has encouraged other countries to follow (e.g. Canada, USA, South Korea). Since the ban, then antimicrobial 'mass medications' for the purposes of disease prevention has become the most common use in healthy food animals.

Different terms describe 'mass medication' concepts in food animals, such as prophylaxis, prevention and metaphylaxis. Antimicrobial prophylaxis for BRD first appeared in the scientific literature in the 1950s (King *et al.* 1955), and metaphylaxis appeared later in the 1980s. Both concepts are believed to still be heavily used, but exact consumption figures for food animal antimicrobial mass medications are largely unknown.

Various definitions describe prophylaxis, prevention and metaphylaxis. Prophylaxis and prevention are defined similarly as the administration of a veterinary medicinal product (VMP) to healthy animals to prevent infection/s based on risk or possible consequences (ECDC/EFSA/EMA 2015; EMA 2016). Typically, the risk is neither clearly defined nor quantified, but common reasons include:

I. previous history of herd outbreaks
II. traditional herd management practices or attitudes:
    a. introduction of new animals into groups (e.g. 'welcome shots')
    b. high stocking densities (i.e. increased 'risk' of disease)
    c. scheduled events in the production animal cycle (e.g. dry-off cow period, transport)
    d. stressful events (e.g. weaning, parturition, castration, dehorning)
    e. diet quality problems or diet changes
    f. intercurrent disease—e.g. viral or protozoal diseases

Originally, 'metaphylaxis' was defined the same as prophylaxis, the difference being that prophylaxis was applied to individuals and metaphylaxis was for whole groups/flocks/herds (Urban-Chmiel and Grooms 2012). Now, others re-define 'metaphylaxis' as mass medication of healthy animals when the disease of interest is present within the group/flock/herd (EMA 2016). Others define as, 'Metaphylaxis is indicated for high-risk individuals, when the number of clinical cases within a group reaches a *threshold*, the remainder of the in-contact animals are treated simultaneously in order to restrict the spread and impact of the disease' (Lees and Shojaee Aliabadi 2002). According to Edwards (2010) and Smith *et al.* (2001), the criterion for antimicrobial metaphylaxis occurs when morbidity (i.e. attack rate) exceeds 10% for two to three consecutive days. Thus, prophylaxis/prevention and metaphylaxis involves administering antimicrobials to 'healthy' individuals to 'prevent' infections, but for prophylaxis/prevention there is a perceived 'risk', whereas metaphylaxis could be a definable 'hazard'.

Routine antimicrobial prophylaxis/metaphylaxis are uniquely veterinary concepts since equivalent modern examples in human medicine of routine antimicrobial mass medications to healthy individuals would be difficult to specify. Routine prophylaxis/metaphylaxis leads to substantial antimicrobial consumption since 'healthy' individuals will always outnumber sick individuals, in all but exceptional situations. Many food animal antimicrobial VMP formulations are designed for easy mass medication, for dissemination in either bulk animal feed or common drinking water. Since it is considered 'inconvenient' or impractical to separate diseased from healthy animals, under intensive livestock production conditions, then routine prophylaxis/metaphylaxis is employed commonly, even if unintended. For example, assuming antimicrobial VMPs for dissemination in either bulk animal feed or drinking water are preferred for prophylaxis/metaphylaxis (e.g. premixes, oral powders/granules/solutions for drinking water) then European data (29 countries for 2014: overall sales = 9,009.5 tonnes of active ingredient of antimicrobials) reveals just over 90% of antimicrobial sales reported, in mg/PCU (Population correction unit, in 1,000 tonnes : The estimated weight at treatment of livestock and of slaughter animals.), were these VMP formulations (ESVAC 2016). Furthermore, injectable antimicrobials can also be used for prophylaxis/metaphylaxis in food animals.

Evidence-based recommendations for food animal antimicrobial mass medications are sparse but mostly embody the antithesis of prudent use. This is at odds with the pleas of the United Nations, WHO, FAO and OIE calling for rational antimicrobial use in food animals. The need for antimicrobial mass medications is based on beliefs that a group/s of animals (especially newly received, stressed) will contract a major bacterial disease (i.e. morbidity) and/or die (i.e. mortality),

resulting in economic and welfare consequences. Ancillary benefits are better average daily weight gains (i.e. growth promotion) and belief that less antimicrobial treatments are required later in the production cycle (i.e. reduced labour costs). Given the growing recognition of the one health agenda that animal and human systems are connected, it is relevant to better understand/question the original scientific evidence for antimicrobial prophylaxis/metaphylaxis in food animals to reduce morbidity and mortality from bacterial diseases. Beef production (feedlots or veal) is one of the world's largest food animal industries, and thus an appropriate choice for investigating antimicrobial prophylaxis/metaphylaxis.

The objectives were to perform a systematic review and meta-analysis of randomised controlled clinical trials (RCTs) investigating antimicrobial prophylaxis and/or metaphylaxis for preventing naturally occurring BRD. The primary objective was to assess RCTs investigating BRD antimicrobial prophylaxis/metaphylaxis for their impact on preventing morbidity. The secondary objective was to assess RCTs investigating BRD antimicrobial prophylaxis/metaphylaxis for their impact on preventing mortality. Other objectives were to assess the characteristics of antimicrobials (e.g. type, route of administration) on preventing BRD morbidity and mortality and compare prophylaxis to metaphylaxis.

MATERIALS AND METHODS

An open literature search involved online search engines, including Pub-Med, Google Scholar, Scopus, Web-of-Science, CAB abstracts and VetMed Resource, using the following search terms:

At least one of:	cattle, calf, calve, veal, bovine, cow, steer, bull,
AND at least one of:	antibiotic, antimicrobial, antibacterial, cillin, mycin, cycline, sulpha, floxacin, ceftiofur, tilmicosin, tildipirosin, florfenicol, trimethoprim, tylosin
AND at least one of:	respiratory, shipping, pneumonia,
AND at least one of:	prophylaxis, prophylactic, prevent, prevention, preventive, preventative, control, metaphylaxis, metaphylactic

Google searches were also performed to find other sources of potential publications. Prophylaxis and prevention were defined as the same type of mass medication.

Inclusion criteria for the publications were as follows:

I. Clinical trial involving visually healthy cattle comparing an antimicrobial prophylaxis/metaphylaxis group against a negative control group for naturally occurring BRD.
II. No antimicrobials administered to cattle immediately prior to transport or start of the trial.
III. Explanation of the establishment of the negative control group (e.g. group of cattle either not treated or given a placebo).
IV. No antimicrobials given to healthy individuals in the negative control group during the course of the clinical trial.
V. Criteria (definition) for either prophylactic or metaphylactic medications. Prophylaxis was defined as group medication of asymptomatic cattle upon 'arrival' at the test facility. Too few publications were identified as defining prophylaxis as group medication 'prior' to transport of cattle, and thus excluded from this investigation. Definitions for metaphylaxis varied between publications, including:
    a. group medication of asymptomatic cattle upon arrival at the test facility.
    b. group medication of cattle with pyrexia and no other symptoms.
    c. group medication of cattle in contact with clinical BRD cattle.
    d. group medication of cattle when the BRD morbidity within the group $\geq$10%.

Publications defining metaphylaxis as group medication of asymptomatic cattle upon arrival were re-defined as prophylaxis to be consistent with the other prophylaxis RCTs. All other definitions were accepted as metaphylaxis.

VI. Specification of randomisation in the study design. Randomisation was accepted if individuals were randomised to groups or pens of cattle were randomly chosen (i.e. random-block design). According to Perino and Apley (1998), every-other-calf or odd-and-even number schemes as cattle arrived and processed into pens were accepted as randomisation (i.e. systematic randomisation). The intent was not to bias cattle allocations but to serve as a practical method under field conditions. Random but unequal allocations were also acceptable if the allocations did not exceed a 2-to-1 ratio.
VII. Disclosure of all treatments given during the clinical trial (i.e. type of antimicrobial, dosing regimen, route of administration, other medications).
VIII. Disclosure of relevant results for the primary objective of the study (i.e. total number of cattle in each group, morbidity data, animals excluded).

Other potential publications were identified by examining the reference lists of obtained articles. These in turn were further examined using the criteria described above. English translations were solicited for articles published in languages other than English.

Publications were excluded:

I. If clinical trials were focused on the treatment of clinical BRD cattle and not prophylaxis and/or metaphylaxis of visually healthy cattle.
II. If there was no negative control group as part of the study design.
III. If antimicrobials were given to healthy cattle in the negative control group (e.g. premixes) during the course of the clinical trial.
IV. If the clinical trial involved artificial BRD infections instead of naturally occurring BRD.
V. If randomisation was not described as part of the study design.
VI. If data could not be extracted for the primary objective of the study.
VII. If other diseases occurred during the clinical trial and specific BRD morbidity could not be derived from the results.

Descriptive and quantitative data were extracted from each RCT described in publications meeting the inclusion criteria. Publications describing more than one RCT were specified with separate lines (rows) of data. Some publications described the RCTs performed at multiple geographically separate sites; if negative control and treatment groups were reported for each test

facility, then separate lines of data were specified. If accepted RCTs were published in both a peer-reviewed and other types of articles, then only the peer-reviewed article was used.

Data extracted from each publication included:

- Total number of cattle in control and treatment groups.
- BRD morbidity after the observation period for control and treatment groups.
- BRD mortality after the observation period for control and treatment groups.
- Type of production system (e.g. feedlot, veal calf facility, etc.).
- Type and definition of mass medication (prophylaxis versus metaphylaxis).
- Description of randomisation method, if provided.
- Specification if blinding or double blinding was part of the study design. Blinding could have included personnel giving cattle treatments and/or personnel checking pens during the observation period.
- Disease definition of BRD used for morbidity data.
- Antimicrobial/s given to the treatment group (type, route of administration, dose).
- Observation period (days) of RCTs.

Data analysis

Analysis of the morbidity data was performed with a random effects model (R package '*metafor*' 1.9–8) (Viechtbauer 2010) using restricted maximum likelihood as the method for estimation of τ^2 (the true between-study variance). Heterogeneity between studies was identified by the I^2 and τ^2 statistics. Due to the heterogeneity between studies, the summary effect measure (*in casu* relative risk-RR) was calculated using random effect meta-analysis with inverse-variance weights. Potential factors affecting heterogeneity were analysed with a random effects meta-regression. Separate analysis was performed for morbidity and mortality data, respectively.

Data distribution from the RCTs was assessed with funnel plots (Viechtbauer 2010). Also, a trim-and-fill analysis (Duval and Tweedie 2000) was performed on the residuals using the *trimfill* function in *metafor* to test for funnel plot asymmetry and identify missing studies. The analysis assumes funnel plot symmetry and attempts to remove (trimming) smaller studies associated with asymmetry while filling the distribution with missing studies to balance the distribution.

RCTs morbidity data were further assessed using the number needed to treat (NNT = 1/ARR) and absolute risk reduction (ARR). To calculate the expected relation between the NNT and attack rate (CER), the following expression was used (Fig. 4):

$$\mathrm{ARR} = \mathrm{CER} - \mathrm{EER} = \mathrm{CER} - \mathrm{RR} \times \mathrm{CER}$$

and, as

$$\mathrm{NNT} = 1/\mathrm{ARR}\colon\ \mathrm{NNT} = \frac{1}{\mathrm{ARR}} = \frac{1}{\mathrm{CER} - \mathrm{RR} * \mathrm{CER}} = \frac{1}{\mathrm{CER} * (1 - \mathrm{RR})}$$

where CER is the control group event rate, EER is the experimental group event rate and RR is the relative risk estimate.

Mortality data differed from morbidity data in that most studies showed very low mortality rates with several zero-event cells for mortality in the control and/or treatment groups. Therefore, mortality data were analysed with the Mantel-Haenszel method to calculate the summary RR and 95% confidence intervals (CI) (Higgins and Green 2011). For studies with zero-events, a value of 0.5 was added to all cells for zero-cell correction.

RESULTS

Each online search engines identified several publications, ranging from 62 to 706 titles/abstracts. A total of 58 publications (38 peer-reviewed + 5 international conferences + 15 other sources) met the criteria for the primary objective, summarizing 169 individual RCTs, and published between 1966 and 2016 (Scheel 1966; Perry *et al.* 1971, 1986; Janzen and McManus 1980; Breeze *et al.* 1982; Lofgreen 1983; Peters 1985; Albak, Bradstock and Cruise 1986; Gill *et al.* 1986; Schumann, Janzen and McKinnon 1990; Harland *et al.* 1991; Schumann, Janzen and McKinnon 1991; Van Koevering *et al.* 1992; Hill, Gill and Ball 1993; Morck *et al.* 1993; Lauridsen, Jorgensen and Olsen 1994; McCoy *et al.* 1994, 1995; Gallo and Berg 1995; Galyean, Gunter and Malcolm-Callis 1995; Hughes, Tice and O'Connor 1996; Kreikemeier, Stokka and Marston 1996; Brazle 1997; Klemesrud *et al.* 1997; McClary and Vogel 1999; Mechor and Vogel 1999; Frank and Duff 2000; Schmidt *et al.* 2001; Frank *et al.* 2002; Hibbard *et al.* 2002; Kato *et al.* 2003; Lechtenberg and Hanna 2003; Cusack 2004; Skogerboe *et al.* 2004; Anonymous 2005, 2013; Godinho *et al.* 2005; Kilgore *et al.* 2005; Encinias *et al.* 2006; Bremer *et al.* 2007; Martín *et al.* 2007; Benton *et al.* 2008; Catry *et al.* 2008; Coe *et al.* 2008; Johnson *et al.* 2008; Caluwaerts *et al.* 2009; Heinrichs *et al.* 2009; Checkley *et al.* 2010; Sgoifo Rossi *et al.* 2010; Baggott *et al.* 2011; González-Martín *et al.* 2011; Lechtenberg *et al.* 2011; Bechtol *et al.* 2012; Hendrick, Bateman and Rosengren 2013; Schlegel *et al.* 2014; Fazzio *et al.* 2015; Stanford *et al.* 2015; Dedonder *et al.* 2016). Other sources of publications included proprietary data described in two Freedom of Information Act summaries (3 RCTs), nine university research progress reports (18 RCTs) and four pharmaceutical companies technical bulletins (20 RCTs). Prophylaxis RCTs included 45 publications (27 peer-reviewed–77 RCTs + 3 international conferences–9 RCTs + 15 other sources–36 RCTs) (Fig. 1), and metaphylaxis RCTs included 14 publications (11 peer-reviewed-39 RCTs + 2 international conferences-6 RCTs + 1 other source-2 RCTs) (Fig. 2). Two publications assessed both prophylaxis and metaphylaxis.

RCTs in feedlots were described in 51 publications (149 RCTs), four concerning veal/dairy calves (10 RCTs), two cow-calf operations (6 RCTs) and one bull-testing station (5 RCTs). Observation periods for RCTs ranged from 10 to 365 days (<20 days—26 RCTs; 20–39 days—91 RCTs; 40–80 days—40 RCTs; >80 days—11 RCTs).

The majority of publications described a uniform processing of cattle/calves upon arrival to the test facility, including injections with a variety of vaccines, vitamin products, dewormers and occasionally other products (e.g. growth implants). Afterwards, cattle were separated into treatment and control groups. These were considered typical field conditions for introduction of calves into feedlots and veal calf operations.

Most clinical trials described antimicrobial use according to the label dose (prophylaxis— 99 RCTs; metaphylaxis—44 RCTs), with a minority over the label dose (prophylaxis—11 RCTs; metaphylaxis—2 RCTs), and under the label dose (prophylaxis—12 RCTs; metaphylaxis—1 RCT). Thirteen BRD publications described the initial treatment of the negative control with saline using the same route of administration as the treatment group (45 RCTs), one with a placebo oral bolus (1 RCT), one with same formulation as the treatment group minus the antimicrobial substance (6 RCTs) and 43 publications with no placebo

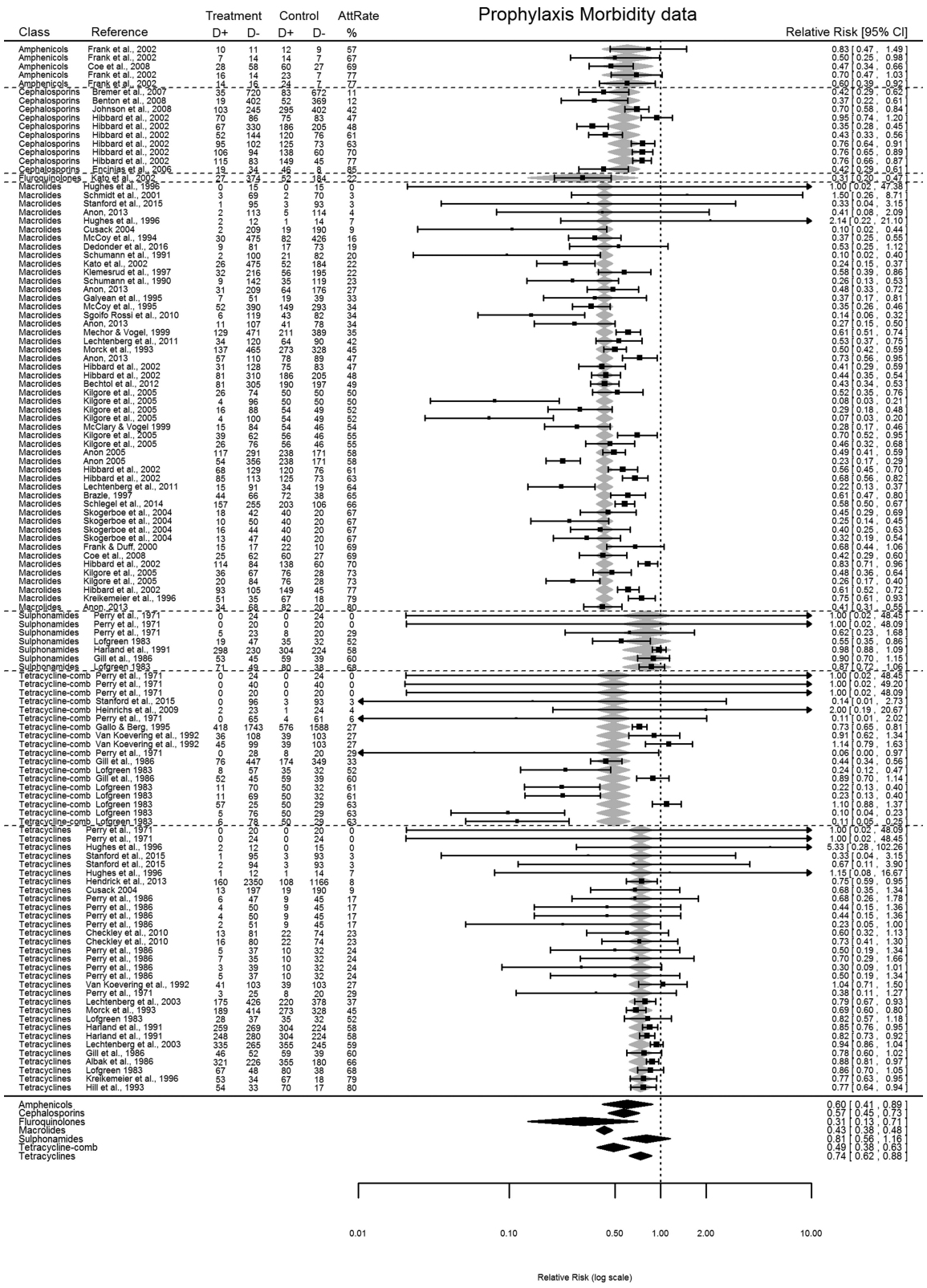

Figure 1. Forest plot of prophylaxis RCTs morbidity data sorted by antimicrobial class and control group attack rates. Random-effects meta-regression model RR predictions represented as shaded grey and black diamonds. AttRate—control group attack rate % (CER%); antimicrobials investigated included macrolides (tylosin, tilmicosin, tulathromycin, gamithromycin, tildipirosin), tetracyclines (oxytetracyline, chlortetracycline, doxycycline), amphenicols (florfenicol), cephalosporins (ceftiofur), sulfonamides (sulfadimethoxine, sulfamethazine, trimethoprim sulphonamide), and fluoroquinolones (enrofloxacin), tetracycline combinations (oxytetracyline and/or chlortetracycline + neomycin, or sulfadimethoxine and/or sulfamethazine).

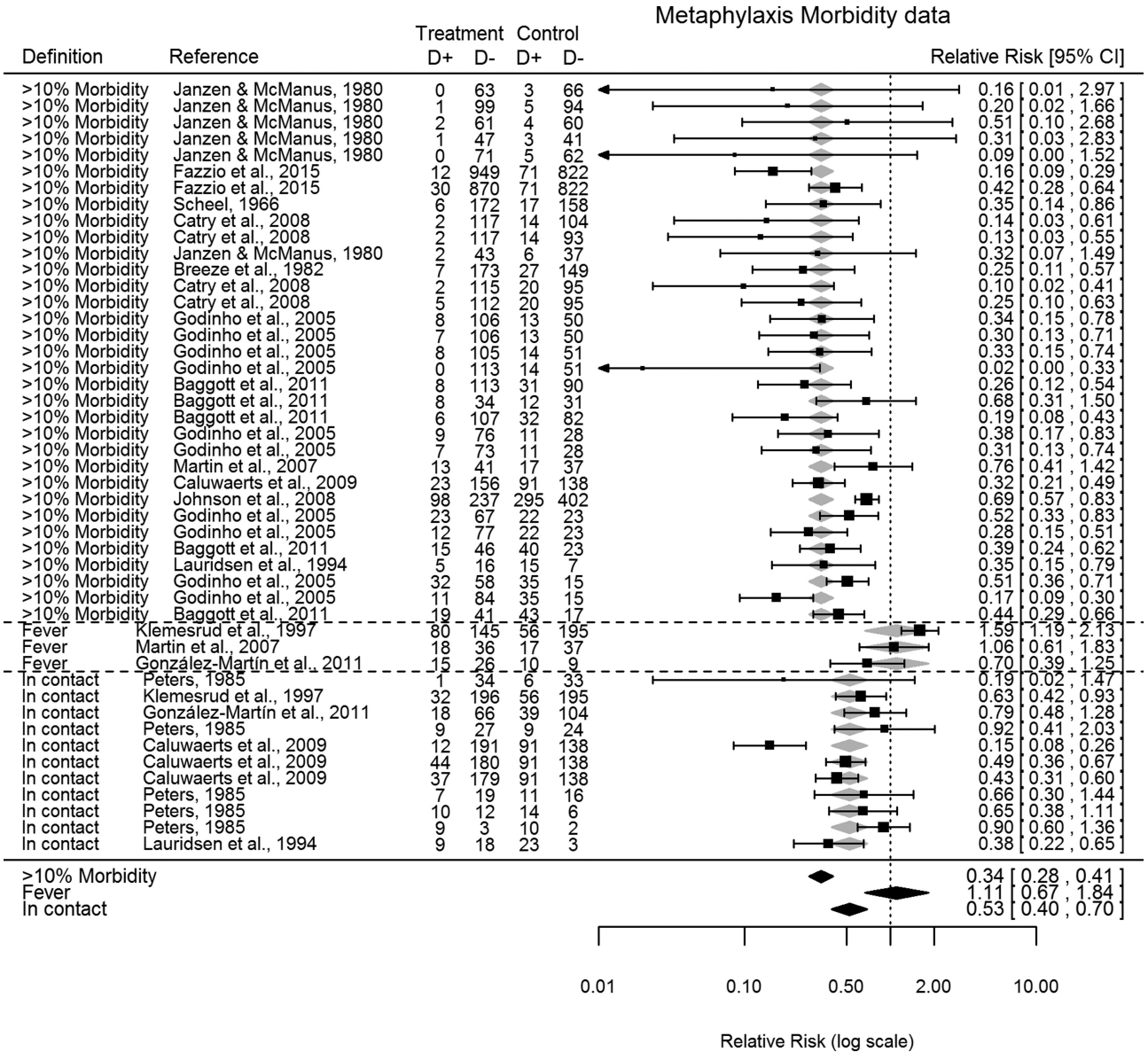

Figure 2. Forest plot of metaphylaxis RCTs morbidity data sorted by metaphylaxis definition. Random-effects meta-regression model RR predictions represented as shaded grey and black diamonds. '>10% Morbidity'—group medication of cattle when the BRD morbidity within the group ≥10%. 'Fever'—group medication of cattle with pyrexia and no other symptoms. 'In contact'—group medication of cattle in contact with clinical BRD cattle.

treatment of the control group (118 RCTs). The majority of RCTs (150) described two or more visual clinical signs in their BRD assessment (e.g. depression, poor body condition, anorexia, abnormal respiration, cough, oculo-nasal discharge). Of these, 118 RCTs also included the presence of fever in the assessment. No description was stated for 19 RCTs.

Methods of randomisation described included 20 publications (prophylaxis—60 RCTs; metaphylaxis—23 RCTs) with random-block design, 19 publications (prophylaxis—17 RCTs; metaphylaxis—20 RCTs) with systematic randomisation, 5 publications (prophylaxis—7 RCTs; metaphylaxis—2 RCTs) describing computer/statistical randomisation and 14 publications (40 RCTs) with no description. Also, 26 publications (prophylaxis—45 RCTs; metaphylaxis—34 RCTs) utilised blinding in the study design, with 4 publications (prophylaxis—2 RCTs; metaphylaxis—8 RCTs) describing the person/s giving the treatments as blinded and 22 publications (prophylaxis—43 RCTs; metaphylaxis—26 RCTs) describing the person/s checking cattle/pens for BRD as blinded.

Many RCTs demonstrated a benefit in RR for reducing morbidity, with either antimicrobial prophylaxis or metaphylaxis (Figs 1 and 2), although results varied considerably between studies. The combined RR estimate (prophylaxis + metaphylaxis) was 0.49 (95% CI = 0.45–0.53). Data asymmetry was identified with funnel plots (Fig. 3). Using the Duval and Tweedie *Trim and Fill* method, the adjusted combined RR estimate was 0.52 (0.48–0.57). Funnel plot asymmetry was more evident for RCTs describing metaphylaxis, particularly a lack of small studies reporting poor efficacy (Fig. 3). Initially, metaphylaxis RCTs (RR, 95% CI = 0.42, 0.35–0.49) performed significantly better ($P = 0.031$) in reducing BRD morbidity than prophylaxis (RR, 95% CI = 0.52, 0.47–0.57). However, adjusted RR estimates revealed the two types of mass medications performed equally (metaphylaxis RR, 95% CI = 0.53, 0.43–0.64; prophylaxis RR,

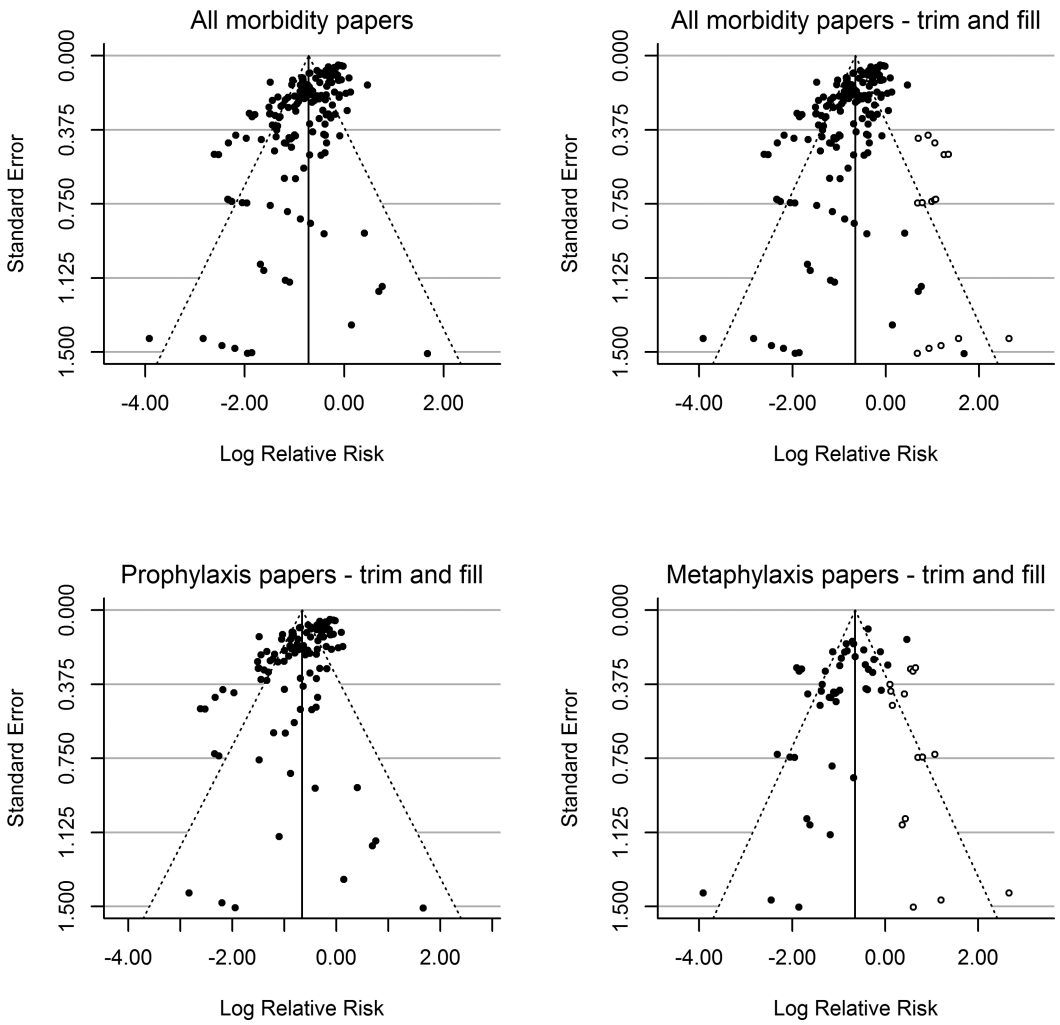

Figure 3. Funnel plots of the morbidity data from RCTs. The upper panels show all morbidity data without (left) and with (right) Duval and Tweedie *trim and fill* to correct for potential publication bias (test for heterogeneity: Q (df = 168) = 1061.977, *P*-value < 0.0001). Published studies are represented with filled circles, where the added (fill) studies are shown with open circles. The lower panels show separate plots for prophylaxis studies (left) (test for heterogeneity: Q (df = 121) = 824.153, *P*-value < 0.0001) and metaphylaxis studies (right) (test for heterogeneity: Q (df = 46) = 195.687, *P*-value < 0.0001).

95% CI = 0.52, 0.47–0.57). RCTs using parenteral antimicrobials (subcutaneous or intramuscular) alone or in combination with oral administrations performed significantly better at lowering morbidity compared to oral administration alone (i.e. RR, 95% CI = 0.47, 0.43–0.52 versus RR, 95% CI = 0.62, 0.49–0.79; *P* = 0.034). Blinded RCTs demonstrated significantly different results (*P* = 0.037) than non-blinded RCTs (blinded-RR, 95% CI = 0.45, 0.40–0.51; non-blinded-RR, 95% CI = 0.54, 0.48–0.61).

For prophylaxis RCTs, macrolides performed best in reducing BRD morbidity (RR, 95% CI = 0.43, 0.38–0.48; 28 pubs—50 RCTs), compared to tetracyclines (RR, 95% CI = 0.74, 0.62–0.88; 20 pubs—31 RCTs), tetracycline combinations (RR, 95% CI = 0.49, 0.38–0.63; 10 pubs—18 RCTs), amphenicols (RR, 95% CI = 0.60, 0.41–0.89; 2 pubs—5 RCTs), cephalosporins (RR, 95% CI = 0.57, 0.45–0.73; 7 pubs—10 RCTs), sulfonamides (RR, 95% CI = 0.81, 0.56–1.16; 7 pubs—7 RCTs) and fluoroquinolones (RR, 95% CI = 0.31, 0.13–0.71; 1 pub—1 RCT) (Fig. 1). For metaphylaxis RCTs, no significant differences were detected between antimicrobial classes (*P* = 0.86).

Metaphylaxis definitions included 11 publications (33 RCTs) defined as the BRD morbidity ≥10% within the group; 3 publications (3 RCTs) defined as pyrexia and no other symptoms; 5 publications (11 RCTs) as cattle in-contact within groups with visual BRD cattle. Metaphylaxis definitions demonstrated significantly different results. Best results on BRD morbidity were obtained with a '≥10%-morbidity' definition (RR, 95% CI = 0.34, 0.28–0.41), compared to an 'in-contact' definition (RR, 95% CI = 0.53, 0.40–0.70; *P* = 0.011) or 'fever' definition (RR, 95% CI = 1.11, 0.67–1.84; *P* < 0.001) (Fig. 2).

The majority of RCTs (prophylaxis+metaphylaxis) fitted a correlation of decreasing NNT with increasing control group attack rates (Fig. 4). NNT for RCTs dropped below the NNT median at attack rates >25%. Observation periods (duration) of RCTs affected morbidity outcomes with short RCTs (<20 days-RR, 95% CI = 0.35, 0.28–0.42) demonstrating significantly better (*P* = 0.011) outcomes compared to longer RCTs (20–39 days-RR, 95% CI = 0.50, 0.45–0.56; 40–80 days-RR, 95% CI = 0.58, 0.49–0.67; > 80 days-RR, 95% CI = 0.68, 0.51–0.91). Best ARR results on BRD morbidity were clustered to only short RCT durations (e.g. ≤30 days) (Fig. 5a). Also, best ARR results on BRD morbidity were a feature of small rather than larger RCTs.

Publications described uniformly that identified BRD cattle were 'pulled' from the pen and treated with a pre-specified treatment protocol for that study, and returned. Thus, mortality data

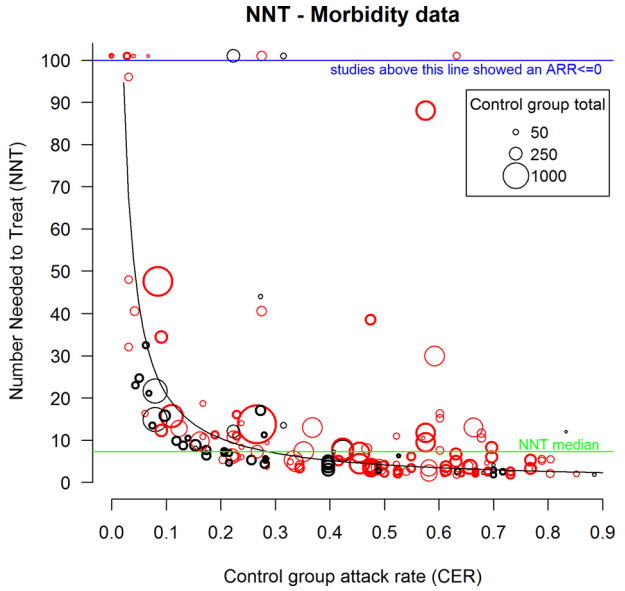

Figure 4. NNT plot of all morbidity data from RCTs involving either antimicrobial prophylaxis (red circles) or metaphylaxis (black circles). Size of the circles reflects the sample size of the RCT (see the legend). Bolded circles are blinded RCTs. Green line represents the overall NNT median value = 7.27. The curve represents the expected NNT as a function of CER assuming a uniform RR (=0.52) across all values of CER. NNT, number needed to treat; ARR, absolute risk reduction; RCT, randomised clinical trial.

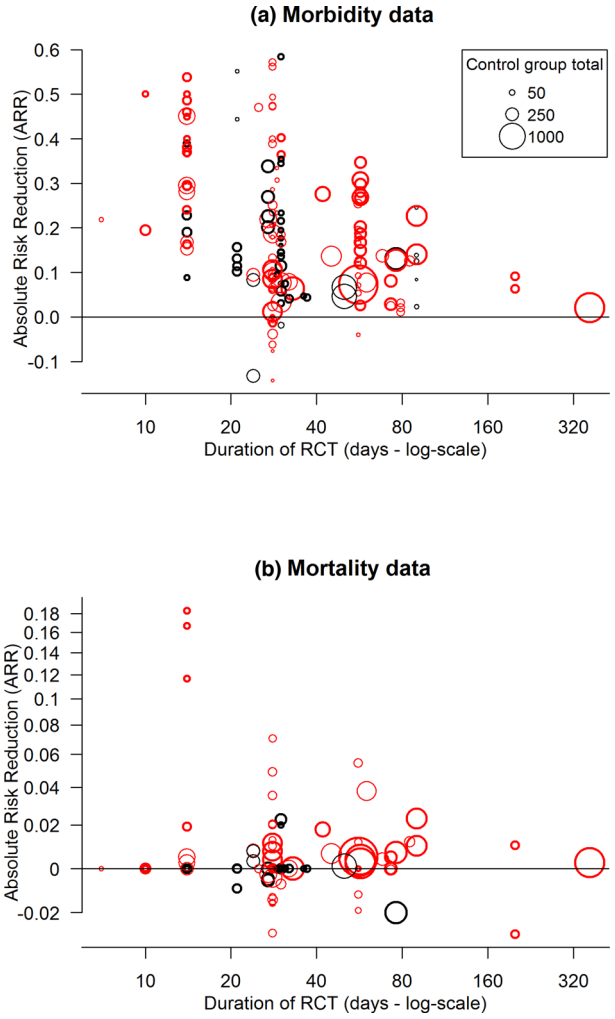

Figure 5. Plot of absolute risk reductions in (a) morbidity or (b) mortality for each RCT versus the duration of the RCT. For publications stating a range of duration days for RCTs, then the average value was calculated. RCTs involving either antimicrobial prophylaxis (red circles) or metaphylaxis (black circles). Size of the circles reflects the sample size of the RCT (see the legend). Bolded circles are blinded RCTs. For the purpose of visualisation of the wide range of ARR values for the mortality data, the y-values in (b) are shown on a modified log-scale ($\text{sign}(y)^{*}\log_{10}(10^{*}|y|+1)$). Labels at the tick marks are the original ARR values.

were confounded since all BRD cattle (i.e. treatment and control groups) were treated with antimicrobials, after recorded as morbidity data. Nevertheless, mortality data were analysed since it represented a treatment-only strategy, without prior mass medication (e.g. control group) compared to a treatment strategy, with prior mass medication (e.g. treatment group). From the original publications accepted for the morbidity data analysis, 47 publications (38 prophylaxis—89 RCTs, 11 metaphylaxis—39 RCTs) contained sufficient mortality data. BRD mortality rates were very low, with 37 of 89 (41.5%) prophylaxis RCTs and 32 of 39 (82%) metaphylaxis RCTs reported zero mortality in the control groups. The highest mortality rate was 18% (Fig. 5b).

Antimicrobial mass medications (prophylaxis + metaphylaxis) led to a relative reduction in mortality risk (RR, 95% CI = 0.62, 0.54–0.72). This was correlated with control group results, with RR declining with increasing mortality rates. A subgroup analysis revealed relative risk reductions with a control group mortality above 1.5% (RR, 95% CI = 0.55, 0.45–0.67) compared to below 1.5% (RR, 95% CI = 0.74, 0.57–0.96). However, the majority of RCTs demonstrated only minor effects in ARR (e.g. <5%) (Fig. 5b).

DISCUSSION

To the authors' knowledge, this is the first critical appraisal of evidence for antimicrobial prophylaxis and metaphylaxis to prevent disease morbidity and mortality in a major food animal species. A systematic review and meta-analysis of RCTs concerning antimicrobial mass medications for preventing BRD identified advantages and disadvantages. Prophylaxis and metaphylaxis demonstrated moderate, yet highly variable relative risk reductions in BRD morbidity (adjusted combined RR, ±95% = 0.52, 0.48–0.57). BRD morbidity reductions were dependent on the antimicrobial classes used (Fig. 1), metaphylaxis definition criteria (Fig. 2), BRD attack rates (Fig. 4) and duration of the RCTs (Fig 5a). Disadvantages include that best positive RR results were achieved with antimicrobial classes (e.g. macrolides) considered as broad-spectrum critically important antimicrobials (CIAs) to human and veterinary medicine, or combination antimicrobials (Fig. 1). Also, the NNT to prevent one BRD case was very high under circumstances of low attack rates and variable when the infection pressure was too high for medication to prevent BRD transmission (Fig. 4).

Aetiologies for BRD outbreaks are founded in physiological, management and environmental factors in conjunction with viral and bacterial infectious agents. Genetic selection has resulted in domesticated cattle with small lungs relative to their metabolic demands, contributing to decreased respiratory compensation, particularly during periods of exertion or disease (Weekly and Veit 1995). Generally, high-risk calves/cattle are typically lightweight, recently weaned, highly co-mingled, or of auction market origin, extended transport times and unknown health/vaccination history. Despite widespread use of vaccines

and antimicrobial mass medications, a sobering picture has suggested limited progress in North America to reduce the impact of BRD over the last 10–20 years (Hilton 2014). National Animal Health Monitoring System data show an increase in BRD feedlot mortality from 1.03% in 1994 to 1.6% in 2011, despite ~16% were treated for BRD and up to 31% received prophylactic antimicrobials on arrival. Dairy heifer rearing data showed that 18.1% of pre-weaned dairy heifers were treated for BRD, including a BRD mortality of 2.3% (Dargatz 2014). Other data reveal that feedlot mortality increased by 0.05% per year over the last 13 years (Engler 2014). The reaction has been an increasing reliance on antimicrobial prophylaxis and/or metaphylaxis to control BRD, but the need for mass medications is more driven by the antiquated structure of the feedlot and veal calf industries compared to the disease itself. A major obstacle to control BRD remains the segmented infrastructure of these industries, as relatively unchanged for several decades (Ives and Richeson 2015). Calves/cattle progress through the production phase, changing ownership at any and all points, resulting in transporting, co-mingling from various sources, minimal biosecurity and other stressors, providing ample opportunity for immunosuppression and pathogen colonisation of the lower respiratory tract. It has been estimated the average number of middle men between the cattle rancher and the consumer is 15 (Ives and Richeson 2015). Cattle can be transported between two to five times throughout their lifetime, resulting in degrees of dehydration, physiologic stress and environmental/nutritional changes. This persistent infrastructure also impedes alternatives to antimicrobial mass medications, since the major BRD predisposition factors are present at the time of arrival to the facilities.

A BRD field diagnosis has major limitations for accurately identifying all BRD cattle. Common clinical signs (e.g. depression, anorexia, fever) are not pathognomonic. A recently published study using a hierarchical Bayesian latent class meta-analysis comparing BRD clinical signs to slaughter lung lesions revealed an estimated predicted diagnostic sensitivity and specificity of 0.27 (95% CI = 0.01–0.96) and 0.92 (0.14–1.00), respectively (Timsit *et al.* 2016). There was much variability between studies due to different criteria for visual BRD diagnosis. This variability is further influenced by the number of cattle to be managed per employee, at large facilities. For example, the reported average number of cattle at high risk of developing BRD to be managed per employee at feedlots increased from 2739 to 3464 head between 2009 and 2014, in the USA and Canada (Lee *et al.* 2015). The relevance of the RCTs from this systematic review and meta-analysis also reflects the decision-making criteria of producers, since every identified BRD case was further treated with antimicrobials. Based on NNT (Fig 4), antimicrobial mass medications had a minor effect on either reducing BRD morbidity risk or affecting the decision-making process for using further treatment antimicrobials. For example, the NNT median was 7.27, or an approximate 14% reduction in ARR. Pharmaco-economic benefits only occurred at high attack rates (e.g. ≥50%) where benefits were also variable between RCTs.

Concerns have been expressed previously about the quality of RCTs for BRD, primarily for treatment trials (O'Connor *et al.* 2010b). Consensus statements exist for design specifications of clinical trials (e.g. CONSORT—Consolidated Standards of Reporting Trials), but the REFLECT statement for livestock clinical trials was not published until 2010 (O'Connor *et al.* 2010a). Generally, veterinary RCTs lag behind human RCTs in quantity and quality study design features (e.g. blinding, description of randomisation, saline-treated placebo). Other limitations found in this investigation included a lack of RCTs for certain antimicrobial classes and metaphylaxis definitions. Certain types of beef production systems were under-represented (e.g. veal calves). Also, not all types of non-CIAs were represented by RCTs. More long-term studies could have better confirmed the declining benefits of initial antimicrobial mass medications. Significant explanatory variables were identified, but heterogeneity remained high in the models, due to the diversity of issues explored. Also, this heterogeneity further reflects the lack of foresight of old fashion practices of antimicrobial mass medication, based on beliefs of non-standardised risks without knowledge of the type/s of pathogens involved or antimicrobial susceptibilities. Like other food animal diseases, BRD is a disease complex encompassing multiple pathogens, and combined with a lack of foresight, will thus attract broad-spectrum antimicrobials for its successful prevention.

The results could be viewed further as general observations about antimicrobial mass medications under field conditions, describing cohorts of food animals with similar circumstances (e.g. transport, co-mingling, minimal biosecurity, broad disease definitions). Aspects of these results could fit concepts expressed in mathematical models of infectious disease transmission. BRD demonstrated disease patterns of low to high morbidity but consistently low mortality. Eventually, saturation (the resulting decline in the number of susceptible individuals to infection) occurs over time (up to 90 days for BRD) with more stable population dynamics (Grassly and Fraser 2008). The broad range of attack rates from RCTs reflects field variations in infectiousness (characteristics of infected individuals that determines the rate of spread to the susceptible population that can be broken down into biological, behavioural and environmental components) and susceptibility (biological, behavioural and environmental) of cohorts of cattle. For example, at low attack rates (<15%), the basic reproduction number (R_o) (the expected number of secondary infections resulting from infected individual/s in a population. Mathematical models typically incorporate variables that describe the probability of transmission per animal contact, the number of contacts with the infectious animal per unit time and the duration animal/s are infectious.) is sufficiently low (<1) based on a small offspring distribution (the number of secondary infections as a function of infectiousness over time) that does not economically justify prior antimicrobial mass medications (based on NNT). Under these circumstances, the disease could die out ($R_o < 1$) or become endemic ($R_o = 1$), but unlikely to progress to an epidemic ($R_o > 1$). A morbidity threshold does exist where antimicrobial mass medications provided more consistent reductions in morbidity risk (Figs 2 and 3), but negligible effect on mortality (Fig. 5b). This is broadly consistent with general observations that a disproportionate amount of disease transmission results from a small fraction of infected individuals (Grassly and Fraser 2008). The random effects among individuals tend to cancel each other out as the number of infected individuals increases, resulting in a more predictable progression to epidemic dynamics. Antimicrobial mass medications represent the main intervention for BRD (i.e. $R_o - 1$) to prevent/control an epidemic. The results of this investigation revealed that the impact of this intervention was influenced by the duration of the RCTs. For example, the highest impact clustered with only short and small RCTs (≤30 days) (Fig. 5), with progressively less impact over longer and larger RCTs. Longer RCTs better reflect feedlot/veal facilities, since cattle are typically kept for months. Also, high variability from antimicrobial interventions reflects the complex BRD infectious disease dynamics, where the likelihood of each of three possible outcome population scenarios

(endemic, epidemic, disease die out) is dependent on factors, including:

I. Herd immunity—when a significant proportion of the population have immunity (e.g. vaccines, natural acquired or colostral immunity). Thus, more difficult for diseases to spread between individuals if a proportion are already immune, breaking the 'chain of infection'.
II. Animal stress factors that promote immunosuppression (e.g. weaning, castration, dehorning)
III. Animal husbandry practices that promote contagious diseases (e.g. stocking density, transport of animals, comingling animals from different sources, poor biosecurity).
IV. Characteristics of the bacterial clone involved in the disease (e.g. virulence factors, antigenicity, previous exposure to the population).

Although RCTs results for BRD mortality were confounded by previous treatment of BRD cattle, it does reveal an interesting aspect. The majority of RCTs reported zero mortality in control groups based on a 'treatment-only' strategy of visual BRD cases, with no prior mass medication, as just an effective method of preventing mortality.

CONCLUSIONS

Prudent use of antimicrobials is the judicious practice of medical principles, as 'the cost-effective use of antimicrobials which maximises clinical therapeutic effect while minimizing both drug-related toxicity and the development of antimicrobial resistance'. (WHO 2001). This includes an accurate diagnosis, short-term effective first antimicrobial professional prescriptions based on microbial sensitivity or proven efficacy (RCTs, safety, PK/PD, spectrum of activity) and low impact on selecting antimicrobial-resistant bacteria. BRD antimicrobial mass medications fails in aspects of prudent use in that the disease to prevent is poorly distinguishable from primary viral or cases with lung lesions, and without knowledge of inciting pathogen/s or microbial sensitivity. This systematic review and meta-analysis of RCTs revealed that antimicrobial mass medications lead to a mean overall relative reduction in disease burden but did not economically lower the absolute risk for either displaying visual BRD symptoms or being selected for further antimicrobial treatments. Best relative risk reductions were primarily with broad-spectrum critically important antimicrobial classes. Metaphylaxis has a similar impact as prophylaxis, but the potential for lower antimicrobial consumption with an appropriate morbidity threshold definition that eliminates the least efficient (highest NNT) possibilities and prevents an epidemic. Prophylaxis/metaphylaxis for BRD represents major antimicrobial consumption for highly variable short-term gains in ARR, whereas RCTs of longer duration (e.g. >30 days) show progressive dampened variable ARR. Antimicrobial mass medications can also be associated with negligible improvements or worsened BRD morbidity/mortality.

SUPPLEMENTARY DATA

Supplementary data are available at *FEMSPD* online.

Conflict of interest. None declared.

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