**SUPPLEMENTAL MATERIAL 2**

**Risk of bias related to definition of disease.** Tables below show the signaling questions, the guideline to answer each one, and the criteria to judge the risk of bias for this domain.

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| **Signaling questions**  | **Elaboration** | **Response options**  |
| **5.1. Was there a disease definition reported by the manuscript?** | This question aims to identify whether there is a definition of the disease reported by the manuscript. It does not focus on how the disease was defined.   Answer ‘No’ if the trial manuscript reported that the researchers did not use any disease definition.Answer ‘Probably no’ if the trial manuscript was unclear about disease definition reporting which is considered when:1. the manuscript reports that some disease (e.g., diarrhea) was evaluated in the population, without providing detail; or
2. the manuscript only uses the word "diarrhea" in its methodology and/or results without defining or explaining its definition.

Answer ‘Yes’ if the following two conditions exist:1. there is a definition of the disease which is clearly reported by the author of the manuscript (e.g., diarrhea was considered when calves had a fecal score >3 and rectal temperature >39.5°C); and
2. the methods of measuring the clinical outcome(s) used to define the disease were clearly outlined. For instance, if the diarrhea definition was based on fecal consistency, dehydration, and attitude, the manuscript must report the methods of assessing all these outcomes (e.g., fecal consistency was evaluated with a fecal score that ranged from 0 to 5, explaining what each category was).

Answer ‘Probably yes’ if the first condition exists, but the second one is incomplete (i.e., methods of assessing the outcomes are reported incompletely) or unclear.Answer ‘No information’ only if the manuscript did not inform about disease definition. | **N / PN / PY / Y / NI**  |
| **5.2. If PY / Y to 5.1: Was the disease definition used in the trial a well-defined definition?** | This question aims to assess the case definition (synonym: disease definition), considering the clinical outcomes included in the definition. If a trial regarding antimicrobial efficacy in calf diarrhea does not have a well-defined definition of illness or if the case definition is only based on fecal consistency (without considering other possible systemic signs of illness), the trial results might be biased because some of the calves which were given antimicrobial treatment might not benefit from antimicrobial therapy.Answer ‘No’ if the disease definition (i.e., diarrhea definition) was based on fecal consistency only, even if the method of measuring the fecal consistency was clearly outlined.Answer ‘Probably no’ if the disease definition (i.e., diarrhea definition) was based on fecal consistency and another clinical outcome (e.g., rectal temperature, dehydration), but at least one of these outcomes was unclear or incompletely outlined.Answer ‘Probably yes’ if the disease definition (i.e., diarrhea definition) was based on two well-defined clinical outcomes: fecal consistency and another clinical outcome (e.g., rectal temperature, dehydration); or if the disease definition (i.e., diarrhea definition) was based on fecal consistency and two or more additional clinical outcomes (e.g., rectal temperature, dehydration, appetite), and at least one of these outcomes was unclear or incompletely outlined.Answer ‘Yes’ only when the disease definition (i.e., diarrhea definition) was based on three or more well-defined clinical outcomes, including fecal consistency and other clinical outcomes (e.g., rectal temperature, dehydration, appetite, attitude). | **NA / N / PN / PY / Y** |
| **5.3. If PY / Y to 5.1: Did the disease definition, consider possible variations of the clinical disease related to fecal features?** | The question aims to assess the case definition, considering the possible variations in the clinical disease (e.g., fecal features variations). Antimicrobials should be administered to diarrheic calves that exhibit systemic signs of illness (see question 5.2) or have blood or mucosal shreds in their stool; the latter indicates a breakdown of the blood–gut barrier and an increased risk of bacteremia.If a trial regarding antimicrobial efficacy in calf diarrhea does not have a disease definition which considers the possible variations in fecal features (e.g., blood or mucosal shreds in their stool), the trial results might be biased because some of the calves which were given antimicrobial treatment could have feces without blood or mucosal shreds, making unnecessary the antimicrobial therapy likely. Answer ‘No’ if the disease definition (i.e., diarrhea definition) was based on fecal consistency as the only fecal feature, without considering other fecal characteristics (e.g., blood or mucosal shreds), even if the method of measuring the fecal consistency was clearly outlined.Answer ‘Probably no’ if the disease definition (i.e., diarrhea definition) was based on fecal consistency and other fecal characteristics (e.g., blood or mucosal shreds), but all fecal variables (including fecal consistency) were unclear or incompletely outlined.Answer ‘Probably yes’ if the disease definition (i.e., diarrhea definition) was based on a well-defined fecal consistency and other fecal outcomes (e.g., blood or mucosal shreds), but at least one of these latter outcomes was unclear or incompletely outlined.Answer ‘Yes’ only when the disease definition (i.e., diarrhea definition) was based on two or more well-defined clinical outcomes, including fecal consistency and other fecal features (e.g., blood or mucosal shreds). | **NA / N / PN / PY / Y** |
| **5.4. If N / PN to 5.2 or 5.3: Did the disease definition include the evaluation of laboratory outcomes?** | The question aims to assess the case definition, considering if the definition included the assessment of laboratory outcomes.The question aims to detect if the trial used a disease definition (e.g., diarrhea definition) based on fecal consistency plus laboratory outcomes (e.g., fecal pathogen shedding). The combination of fecal consistency and fecal pathogen shedding could generate a well-described case definition. However, the methods should be clearly described (e.g., how results of fecal pathogen shedding were categorized).Answer ‘No’ if the disease definition (i.e., diarrhea definition) was only based on fecal consistency without any laboratory outcome (e.g., fecal pathogen shedding), even if the method of measuring the fecal consistency was clearly outlined.Answer ‘Probably no’ if the disease definition (i.e., diarrhea definition) was based on fecal consistency and a laboratory outcome (e.g., fecal pathogen shedding), but both outcomes were unclear or incompletely outlined.Answer ‘Probably yes’ if the disease definition (i.e., diarrhea definition) was based on fecal consistency and a laboratory outcome (e.g., fecal pathogen shedding), but one of these outcomes was unclear or incompletely outlined.Answer ‘Yes’ only when the disease definition (i.e., diarrhea definition) was based on both a well-defined method for fecal consistency and fecal pathogen shedding. | **NA / N / PN / PY / Y** |
| **5.5 If PY / Y to 5.1: Did the trial use classified diarrhea severity?** | This question aims to identify if the trial used diarrhea severity to evaluate the efficacy of the given intervention. Mild diarrhea calves (liquid feces but with normal appetite and hydration status) may require a rehydration therapy with no additional antimicrobial treatment, but severe diarrhea (liquid feces, depression, and evident dehydration) may require antimicrobials plus a supportive therapy.If a trial regarding antimicrobial efficacy in calf diarrhea does not consider disease severity, results might be biased because some of the calves may have mild diarrhea and do not require antimicrobials.Answer ‘No’ if the trial manuscript reported that the researchers did not use any classification of diarrhea severity.Answer ‘Probably no’ for manuscripts with unclear reporting of disease classification which is considered when:1. the manuscript evaluated diarrhea severity (e.g., mild to severe diarrhea; complicated and uncomplicated diarrhea), but it does not explain the categories of the classification detailly; or
2. the manuscript only mentions different levels of diarrhea (e.g., mild to severe diarrhea) in its methodology and/or results without defining or explaining what they are.

Answer ‘Yes’ if the following two conditions exist:1. there is a classification of the disease which is clearly reported by the manuscript (e.g., uncomplicated diarrhea as any calves with liquid feces but with normal appetite, attitude, and hydration status; and complicated diarrhea as any calves with liquid feces, depression, anorexia, and evident dehydration); and
2. the methods of measuring the clinical outcome(s) used to define the disease classification were clearly outlined. For instance, if the diarrhea classification included fecal consistency, dehydration, and attitude, the manuscript must report the methods of assessing all these outcomes (e.g., fecal consistency was evaluated with a fecal score that ranged from 0 to 5, explaining what each category was).

\**For trials which answered ‘Yes’ or ‘Probably yes’ to question 5.4, the disease classification might be based on the level of fecal pathogen shedding, or a combination between clinical signs and that laboratory outcome.*Answer ‘Probably yes’ if the first condition exists, but the second one is incomplete (i.e., methods of assessing the outcomes are reported incompletely) or unclear.Answer ‘No information’ only if the manuscript did not inform any data about disease classification, considering all the possibilities mentioned above. | **NA / N / PN / PY / Y / NI** |
| **Risk-of-bias judgement**  | See the table below. | Low / High / Some concerns  |

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| **Signaling questions** | **Domain-level judgement** |
| **5.1****Was there a disease definition?** | **5.2****Was the disease definition a well-defined one?** | **5.3****Possible variations of the clinical disease?** | **5.4****Evaluation of laboratory outcomes?** | **5.5****Classification of the disease?** | **Default risk of bias** |
| N/PN | NA | NA | NA | NA | High |
| NI | NA | NA | NA | NA | Some concerns |
| Y/PY | Y/PY | Y/PY | NA | Y/PY | Low |
| Y/PY | Y/PY | Y/PY | NA | N/PN/NI | Some concerns |
| Y/PY | N/PN | Y/PY | Y/PY | Y/PY | Low |
| Y/PY | Y/PY | N/PN | Y/PY | Y/PY | Low |
| Y/PY | N/PN | N/PN | Y/PY | Y/PY | Some concerns |
| Y/PY | N/PN | Any response | Y/PY | N/PN/NI | Some concerns |
| Y/PY | Any response | N/PN | Y/PY | N/PN/NI | Some concerns |
| Y/PY | N/PN | Any response | N/PN | Any response | High |
| Y/PY | Any response | N/PN | N/PN | Any response | High |

**Y/PY** **=** ‘Yes’ or ‘Probably yes’; **N/PN =** ‘No’ or ‘Probably no’; **NI =** ‘No information’