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Bovine Respiratory Disease Diagnosis

What Progress Has Been Made in Clinical Diagnosis?

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KEYWORDS

- Bronchopneumonia • Diagnosis • Gold standard • Accuracy

KEY POINTS

- Using the definition bovine respiratory disease complex may be a limitation for the progress of knowledge on infectious bronchopneumonia.
- The absence of an affordable gold standard for the definition of bovine infectious bronchopneumonia needs to be accounted for.
- Clinical and paraclinical diagnostic tests used in practice should be thoroughly validated in terms of repeatability/agreement as well as for their accuracy.

INTRODUCTION

Accurate diagnosis of bovine respiratory disease (BRD) is an ongoing challenge that impairs the ability to optimally treat and prevent BRD. This article focuses on the clinical diagnosis of infectious bronchopneumonia. The limitations of different diagnostic procedures are highlighted to indicate current strengths, potential pitfalls, and knowledge gaps. A companion article in this issue addresses causal diagnosis of infectious bronchopneumonia.[1]

IS BOVINE RESPIRATORY DISEASE TERMINOLOGY AN OBSTACLE FOR PROGRESS TOWARD A BETTER CASE DEFINITION?

The terminology BRD, and bovine respiratory disease complex, was initiated more than 5 decades ago[2] and mainly attempted to summarize the complexity of the

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Vet Clin Food Anim 36 (2020) 399–423
https://doi.org/10.1016/j.cvfa.2020.03.004

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interaction of respiratory tract infections with environmental and host-related risk factors in cattle. In those days, this definition meant progress in comprehension of respiratory diseases of cattle, but the individual case definition to initiate therapy has always remained poorly defined. Different scoring systems have been used in studies worldwide, which often did not distinguish between upper and lower respiratory tract disease, or between viral and bacterial infections, or, more clearly stated, between infections requiring antimicrobial treatment or not. Taking into account the worldwide pressure to reduce and rationalize antimicrobial use, the general or syndromic BRD concept may no longer cover the practical and scientific needs. It is surprising that only in food animal species such broad definitions of respiratory tract diseases, summarizing both infectious and noninfectious diseases into a single entity, are in use. In humans and companion animal species (small animals and horses), no such terminology is applied, for the obvious reason that respiratory tract infections are more clearly distinguished from dysregulated airway inflammation processes resulting in asthma or chronic obstructive pulmonary disease in these species. With the current pressure on antimicrobial use, food animal veterinarians must admit that they often treat a simple runny nose or noninfectious pneumonia as requiring antimicrobial therapy as much as life-threatening bacterial pneumonia, and recognize that they can no longer count on support for these practices.

In humans and companion animals, strictly viral pneumonias (eg, respiratory syncytial virus in humans or equine influenza virus) are diagnosed and primarily not treated with antimicrobials. Antimicrobials are used only if levels of a biomarker, such as C-reactive protein (commonly used in humans) are increased, indicating that bacterial superinfection is likely. In contrast, in food animals, clinicians often behave as if bacterial infection always follows viral pneumonia, indicating the need for antimicrobials in every case. On the one hand, this thinking has some merit. Ruminants are frequently exposed to adverse climatic conditions and accumulation of air pollutants that can breach innate immunity and aggravate the consequences of infection.[3] On the other hand, risk averseness in food animal species for economic and ethical reasons, together with pressure from the owners, might tempt clinicians to prioritize security more than risk and initiate antimicrobial therapy. The fact remains that the use of a single vague terminology to summarize the complexity of respiratory disease is oversimplified and dangerous, especially if the definition is linked to the initiation of antimicrobial use, which is currently still the main reason for any BRD case definition. This situation places us 180° in opposition between the current practices of bovine veterinarians and their clients, and societal demands, further challenging a market already under pressure for climate and animal welfare reasons. As recently shown in a review of antimicrobial trials for BRD using negative controls, there is a wide variation of relapse rates in nontreated cases, questioning the necessity of systematic use of antimicrobials and/or indicating case definition limitations.[4] It is stimulating to observe that practitioners are experimenting with strictly antiinflammatory options in early suspected pneumonia cases.[5] Especially in dairy cattle, this approach could also avoid unnecessary milk loss, although efficacy of such treatment must be confirmed to prevent negative welfare impacts of untreated pneumonia.

The evidence that the currently preferred metaphylactic antimicrobial therapeutic approaches in BRD are most efficient in terms of economics, animal welfare, and limiting antimicrobial resistance selection is, according to a recent meta-analysis, very weak.[6] The effects of metaphylaxis in reducing morbidity and mortality are not questioned, but the expense at which they are efficient is likely too great. For example, at an attack rate of 10%, the number needed to treat (an index allowing quantification of the treatment effect as the inverse of the absolute risk reduction) was 20, signifying that medicating 20 animals with antimicrobials was necessary to prevent/treat 1 new case of disease. This number becomes 7 from an attack rate of 20% onwards. Clearly, for human infants, these numbers to save individuals at the expense of the group would be generally accepted. In contrast, for calves or cattle, given the currently incompletely clarified but likely risk to human health, no such treatment to save a limited number of animals is likely to be supported by the general public. Although it is acknowledged that animal welfare and economics must be considered, these are the issues future bovine practitioners face, implying the need for a robust definition of antimicrobial treatment indication.

TOWARD NEW DEFINITIONS: DOES THE TERM BOVINE RESPIRATORY DISEASE STILL REFLECT THE NEEDS OF PRACTICE AND RESEARCH?

What definitions and terminology would better fit the current societal and scientific needs with regard to BRD? Some options are available from human and small animal medicine. One option is to distinguish upper respiratory tract infection (URTI) and lower respiratory tract infection (LRTI). This designation coincides with anatomic localization, differentiating rhinitis and pharyngitis from bronchitis and pneumonia. The advantage of this distinction is that it could provide clearer guidance regarding the need for antimicrobial treatment if it could be confirmed that URTIs generally do not require antimicrobials, whereas LRTIs often do. However, clinicians need tools to differentiate URTI from LRTI. This differentiation can partially be fulfilled by thoracic ultrasonography, as elaborated later, but the question of whether the infection is viral or bacterial remains. A critical issue is the turnaround time between sampling and availability of results. Understandably, practitioners and animal owners are not willing to postpone any treatment too long. Substantial progress has been made in the area of rapid diagnostics, described elsewhere in this issue.[1] However, any rapid test must be able to distinguish between bacterial contamination, colonization, and infection of the lower respiratory tract; these might be distinguished by concurrent identification of relevant bacteria and evidence of inflammation. Bovine medicine is currently constrained by these limits, and clinicians urgently need an exploration of better diagnostic tools for both causal identification and markers of inflammation to direct antimicrobial decision making. The strongest counterargument for the general use of this terminology is that URTI or LRTI does not inform clinicians of the clinical status of the animal, which is a prerequisite to initiating therapy. The clinical status, and whether the status results in economic losses or compromised animal welfare, needs to be taken into account when considering treatment.

In addition, airway inflammation with noninfectious causes has become a leading subject in human and horse respiratory health.[7] Many air pollutants, such as particulate matter, endotoxins, and ammonia, induce airway inflammation and hamper innate respiratory defense.[7] This process is characterized by influx of inflammatory cells; mucus accumulation; bronchoconstriction; and, chronically, airway remodeling.[7] This noninfectious inflammation facilitates secondary infection by opportunistic flora.[7] The relevance of such processes for the bovine lung has barely been explored. Altogether, definition of respiratory tract infection, respiratory tract disease, and in particular identifying animals requiring antimicrobial therapy is a major challenge currently seriously hampered by a lack of knowledge in the bovine species. Bovine infectious bronchopneumonia is nowadays the major reason for using antimicrobials in respiratory disease conditions.

CHALLENGES FOR THE DETERMINATION OF THE ACCURACY OF A NEW TEST

At present, the available information on diagnosis of respiratory tract infection mainly targets feedlot, dairy, and veal calves. The production context is important because the individual animal value may limit the cost of diagnostic test technology that can be used. In feedlot calves, an economic study on the impact of diagnostic test strategies for BRD has shown that the specificity of the diagnostic method was the most important driver in terms of costs.[8] The specificity is also important for avoiding unnecessary antimicrobial treatment. From a welfare perspective, sensitivity is important because delay in detection can be associated with animal suffering and increased risks of treatment failure. Recently, a review of the diagnostic tests used in feedlot diagnosis of BRD complex was also performed summarizing the key findings of practical diagnostic tests that can be used calf-side.[9]

Because of the complexity of infectious respiratory disease in cattle, a perfectly accurate and practical definition will never exist. The challenge for the determination of an accurate new diagnostic test (index test) must be fully understood in the light of this premise. Studies of diagnostic test accuracy have specific risks of bias that may falsely overestimate diagnostic test accuracy. The choice of the reference standard test to compare the index test results is also critically important because it will ultimately serve as a comparator to determine the index test sensitivity (ability of the new test to find affected animals) and specificity (ability of the new test to find nonaffected animals).

RISKS OF BIAS AND APPLICABILITY IN STUDIES OF DIAGNOSTIC TEST ACCURACY

Diagnostic test accuracy studies are particularly challenging because of their bivariate nature. Such studies include a mix between 2 different populations (affected vs nonaffected), in which test accuracy parameters (sensitivity and specificity) are derived. One of the most important risks of bias in diagnostic test accuracy study is the so-called 2-gate versus 1-gate design.[10] The difference between these types of design has been described for studies of thoracic ultrasonography for the diagnosis of respiratory disease in cattle.[11] Briefly, the 2-gate design is present when the inclusion criteria to define affected versus nonaffected animals are different (**Fig. 1**); in the 1-gate design, animals are identified by 1 mutually exclusive criterion. The 2-gate situation presents increased risk of overestimating test accuracy because the difference between affected and nonaffected cases is overestimated because of the study design. This study design is generally affected by the so-called spectrum bias, which means that the definition of affected animals tends to select more severely affected cases, for which the index test has higher chances of good performance (inflated test sensitivity). Because animals with unclear status tend to be rejected in selection of nonaffected cases, the specificity of the index test in this setting is also inflated. Other risks of bias that need to be known have been described extensively elsewhere[11,12] and are summarized in **Table 1**.

THE CHALLENGE OF THE ABSENCE OF AN AFFORDABLE AND PRACTICAL GOLD STANDARD

Classification bias is a common concern when assessing a new test for bovine infectious bronchopneumonia. If the reference standard test is not 100% accurate, there is a risk of underestimating index test accuracy if not accounting for this imperfect comparator. Necropsy could be considered a reasonable gold standard; however, using only this standard would make research on diagnostic test accuracy difficult,

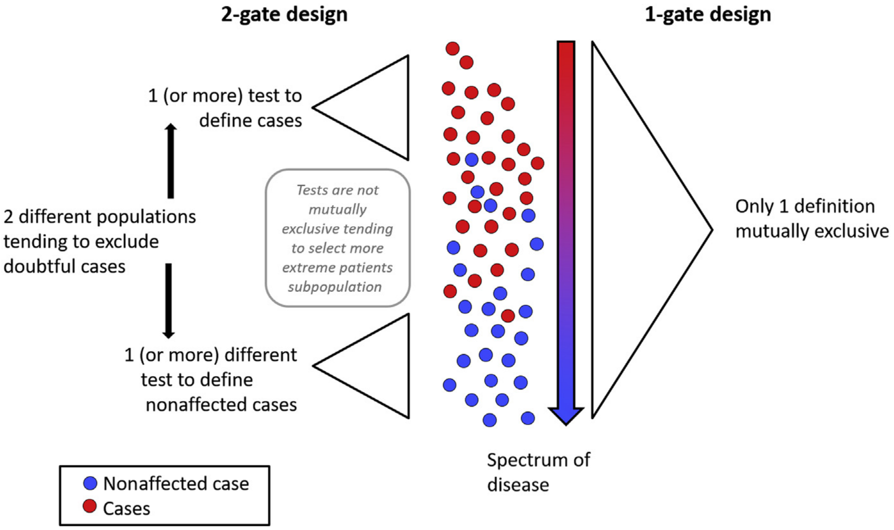

Fig. 1. Two-gate versus 1-gate designs in diagnostic test accuracy studies. The 2-gate design is similar to a case/control design. The case definitions of cases/noncases are not mutually exclusive, generally resulting in the exclusion of the doubtful animals and often resulting in overestimation of test accuracy because sensitivity and specificity are evaluated in artificially distinct populations. In the 1-gate design, there is only 1 mutually exclusive case/noncase definition, thus including doubtful cases. The accuracy obtained from these studies is generally closer to the expected accuracy that practitioners should expect in a practical setting.

because of the invasiveness of the gold standard and associated costs. Also, the necropsy needs to be performed as quickly as possible after use of the diagnostic test being investigated. This requirement highlights a weakness of the use of abattoir lung findings assessed long after testing, because lesions may have occurred or resolved since testing.

Experimental models of infection are an interestingly used alternative to obtain a gold-standard status for infected versus noninfected cattle, but they are generally limited to specific viral and bacterial challenge combinations. These challenges may not mirror naturally occurring infectious bronchopneumonia because they do not incorporate different stressors associated with natural disease. For this reason, the external validity of experimental models is limited.

In most natural infectious respiratory disease studies, imperfect case definition is the default for comparing a new diagnostic test. Using a composite reference standard test is an alternative. This approach uses a combination of different tests to define a positive or negative case.[13] Various case definitions can be developed using the “or” (at least 1 positive test to define an affected patient), “and” (all positive tests to define a patient), and “K” rules (at least K positive of tests out of a specific number of tests performed). However, concerns have been raised against this practice because (1) the risk of error increases if the index test (new test to assess) and tests included in case definition are correlated (ie, making the same types of errors), and (2) the accuracy of this case definition may vary depending on the true prevalence of the disease.[13]

The absence of a gold-standard diagnostic test is a problem in almost every medical field.[14] Recently, bayesian latent class methods have been applied for the

Table 1
Risk of bias and applicability concerns potentially affecting diagnostic test accuracy studies on bovine infectious bronchopneumonia

Risk of Bias	Explanation	Potential Impact
Spectrum bias	There are concerns that selection of affected animals or nonaffected animals is not representative of the full spectrum of the disease Eg, selecting affected animals if depressed increased respiratory score and abnormal auscultation vs nonaffected (not depressed, normal respiratory score and normal auscultation); this design would exclude animals with 1 or 2 abnormal inclusion criteria, therefore artificially inflating the difference between affected and nonaffected animals	Overestimation of test accuracy (eg, cases where the diagnosis is more difficult are excluded from this type of study)
Classification bias	The reference standard that serves as comparator for establishing index test accuracy is not 100% accurate Eg, determining thoracic ultrasonography accuracy in calves using an increased clinical score without accounting for imperfect accuracy of clinical score	Potential underestimation of index test accuracy because the reference standard is treated as a gold standard test
Diagnostic review and incorporation bias	Situations where the index test and reference standard test are not independent Eg, performing the reference standard test knowing the index test result. Eg, determination of ultrasonography accuracy for lung lesions detection (index test) using CT as a reference standard and concomitant knowledge of ultrasonography findings	In this case, the apparent accuracy of the index test could be affected in the way the radiologist would interpret the CT knowing the results of thoracic ultrasonography (potentially overinterpreting CT lesions in ultrasonography-positive animals, and underdetection of lesions in ultrasonography-negative animals)
Clinical review bias	This type of bias occurs when clinical information for the animals receiving the tests, as it would be in practice, is missing Eg, in a study assessing clinical signs associated with LRTI, not specifying, for example, the age and type of production (dairy, beef, veal) and minimal management practices could affect the accuracy of the test when further applied in practice	In this case, the interpretation of test results need a specific context. Eg, gut filling of the calves would not have the same meaning in a farm feeding dairy calves 2 L of milk per meal twice daily vs a farm feeding calves 3–4 L 3 times daily

Partial verification bias	The index test result has an impact on the probability of performing the reference standard test Eg, bias that can be found in a retrospective study where a test was more prescribed than another depending on a first test result. Eg, a study where thoracic radiographs were more commonly performed in animals where abnormal findings were suspected based on auscultation or ultrasonography	In this case, because most animals with normal index test results are not investigated further, the absence of reference standard test in that population could include bias in the apparent index test accuracy
Differential verification bias	This type of bias occurs when different reference standard tests are applied to the animals Eg, necropsy would be considered as a reference standard test for animals that have severe clinical signs of respiratory tract infection, but animals with no severe clinical signs are only followed with a clinical follow-up as a reference standard test	The accuracy of the 2 reference standard tests may differ and should be accounted for in the analyses of index test accuracy
Inconclusive results/ withdrawal bias	Some animals are withdrawn from the study because of either impossibility to perform or interpret the index test or the reference standard test Eg, animals that were not tractable enough to perform the index test safely (eg, BAL was excluded or some BAL samples were excluded from the analyses because of blood contamination)	This type of bias tends to inflate the apparent test accuracy, discarding animals or results where the index test could not be performed or interpreted

Abbreviations: BAL, bronchoalveolar lavage; CT, computed tomography.

determination of diagnostic test accuracy in bovine respiratory tract infection.[15–18] These flexible methods account for possible misclassification because of reference standard test imperfection and have been shown to give unbiased estimates of test accuracy. As with any bayesian methods, they are flexible and can account for prior information if reasonable knowledge is available. Specific guidelines for reporting these studies are also available.[19] Using these methods may be helpful for any study using an imperfect diagnostic test.[20] One of the criticisms of these techniques is that an objective definition of the latent status clinical meaning may be lacking, in the sense that they capture by essence some shared test characteristics on that specific disease (**Fig. 2**).

VALIDATION OF THE DIAGNOSTIC TEST, AND DISTINCTION BETWEEN SCREENING VERSUS CONFIRMATORY TEST

When using any new diagnostic test, it is critically important to know whether its conduct or results depend on the person performing the test (interoperator agreement/reliability) as well as whether that specific test conducted repeatedly by the same operator or laboratory would give an identical result (test-retest results). There are some discrepancies in the literature on the interpretation and calculation of agreement and reliability parameters. Reproducibility is a general term that addresses these 2 concepts.[21] As an example, the authors reported the agreement between 6 different raters scoring the same 50 video loops of thoracic ultrasonography images,[22] or agreement between raters scoring specific clinical signs in calves.[23] The reliability of a test is intended to determine how well patients' tests results can be distinguished from each other, accounting for test measurement error. In the previous study assessing thoracic ultrasonography, reliability indices (eg, intraclass correlation) were

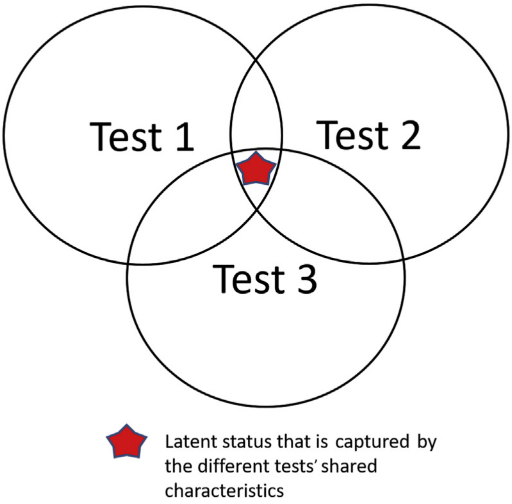

Fig. 2. The latent class when using 3 different tests with imperfect accuracy. The concept of latent class may be challenging to represent using different tests for assessing the disease status. The latent class can be considered conceptually as the shared characteristics between the tests used. In a study focusing on clinical scoring, thoracic ultrasonography, and inflammatory blood markers, this latent class (*star*) can be represented as the shared characteristics between abnormal clinical score, lung lesions, and active inflammation, and could be a definition of infectious bronchopneumonia.

determined to report how reliable measurement of lung consolidation was when conducted by the different raters. Benchmarks have been recommended for determination of clinically relevant agreement and reliability indices.[24–26] However, it is important to recognize that there is no consensus on the best strategy for use of these different parameters in practice.[27] Using different types of complementary indices is useful to judge test agreement and reliability.[24]

Screening Tests

The application of diagnostic testing depends on the way tests are used in diagnosis. There are 2 different testing applications for investigation of infectious lower respiratory tract disease: screening and confirmatory testing. This terminology indicates the use of serial testing, with an easily accessible, performable, and preferably cheap screening test followed by a confirmation test only in animals positive in the screening test. Although debatable, screening tests generally are used rapidly and visually, such as clinical signs scoring or automatic detection of clinical signs/activity. Confirmation tests generally require deeper manipulation of the animal and/or a more expensive or time-consuming investigation. In epidemiology, a good screening test requires high sensitivity, to rule out the disease in negative cases, whereas the confirmation test should be highly specific to rule in positive cases. This process, inherently serial, results in higher specificity; this means clinicians are more confident of a positive test result. The outcome of such a strategy may be good for limiting unnecessary antimicrobial use but, given imperfect test sensitivity of the screening test, sick cattle may be missed. An alternative is to opt for parallel testing, with multiple tests on the same animal, and the animal considered positive when one of the tests is positive. Given imperfect test specificity, this approach increases the possibility of unnecessary treatment.

In addition, the clinical application of any diagnostic test also requires a good idea of the reason why it is performed. This context is particularly helpful to estimate the pretest probability of the disease, which can potentially be used to transform the test result to the probability that the patient has or does not have the disease.[28] An overview is given next on what tests are currently available, with their diagnostic accuracy, advantages, and limitations further summarized in **Table 2**.

Clinical sign assessment

Abnormal clinical signs or behavior have been historically used for day-to-day diagnosis of infectious bronchopneumonia. The infectious agents cause nonspecific clinical signs such as fever, anorexia, and depression, which are the response to cytokine release and downstream activations.[44] Clinical respiratory signs are then observed, such as abnormal or rapid breathing patterns, nasal discharge, or coughing.

Fever is a nonspecific sign of infectious bronchopneumonia that is observed secondary to experimental challenges for all major respiratory pathogens.[44] However, the duration of increased body temperature is variable depending on the settings and challenges. For example, following tracheal *Mannheimia haemolytica* challenge, fever is generally observed the day following challenge, then rapidly decreases despite evidence of ongoing infection.[44,45] This rapid change limits the ability to detect sick calves with fever if body temperature is not assessed at the correct time. In contrast, nonrespiratory or noninfectious (eg, heat stress) processes can be associated with increased body temperature. The accuracy of rectal temperature measurement depends on the thermometer used as well as on the technique used by the operator.[46] Continuous or automated monitoring of body temperature has been

Table 2
Summary findings of clinicoanatomic tests used for the diagnosis of infectious bronchopneumonia in cattle

Study	Study Summary	Test Under Investigation	Reference Standard Test	Were Possible Misclassifications of the Reference Standard Test Accounted For?	Sensitivity: 95% CI or BCI (%)	Specificity: 95% CI or BCI (%)	Comments
Clinical Scores							
Buczinski et al,[38] 2014	106 preweaned dairy calves in 13 dairy farms with thoracic auscultation, ultrasonography and clinical scoring	WRSC	Bilateral thoracic ultrasonography: positive if at least 1 site had consolidation depth ≥1 cm	No	55.4 (42–68)	58 (44–71)	Used ≥5 as a positivity threshold
Love et al,[33] 2014	2030 preweaned dairy calves with deep nasopharyngeal swab and WRSC	CRSC BRD3	Positive if: nasopharyngeal swab PCR positive for BRSV, IBR, or BVDV, or aerobic bacterial pathogen (or *Mycoplasma* spp) positive and WRSC ≥ 5)	No	89.4	90.3	Used BRD3 scoring system (score ≥ 5) further referenced as the CRSC (BRD1 and BRD2 score accuracy are also detailed)
Buczinski et al,[18] 2015	106 and 86 preweaned dairy calves in 2 different populations with thoracic ultrasonography and clinical scoring	WRSC	Bilateral thoracic ultrasonography: positive if at least 1 site had consolidation depth ≥1 cm	Reference standard uncertainty was accounted for using a bayesian latent class model	62.4 (47.9–75.8)	74.1 (64.9–82.8)	Used ≥5 as a positivity threshold vs negative if <5

Love et al,[34] 2016	536 calves from 5 premises in California, mixed enrollment criteria: animals suspected as sick (n = 135) by initial observation screening (depression, sunken eye, coughing, abnormal respiration) and a random selection of calves (n = 401)	CRSC BRD3	Bilateral auscultation and ultrasonography: positive if either abnormal auscultation or ultrasonographic evidence of multiple comet tails, consolidation of abscesses	No	SSe 46.8, DSe 72.6	87.4	Used ≥5 as a positivity threshold vs negative if <5, SSe estimated Se on randomly selected calves, DSe estimated Se on the suspected cases, specificity determined in all negative cases as classified by the reference standard test
Buczinski et al,[36] 2018	608 preweaned dairy calves in 39 dairy farms; clustering was accounted for using a random farm effect	Same clinical signs as in the WRSC and CRSC but updated weights for the clinical signs	Thoracic ultrasonography: positive if at least 1 site had consolidation ≥1 cm	Reference standard uncertainty was accounted for using a bayesian latent class model	81.6 (68.2–97.6)	71 (65.7–77.5)	Used ≥10 as a cutoff, various other cutoffs points with Se and Sp were also reported
Maier et al,[35] 2019	689 weaned dairy calves (89 with apparent signs of sickness, 600 randomly chosen)	6 different scores derived from Love et al,[33] 2014; adapted for postweaned calves (including body condition and diurnal temperature fluctuation)	Abnormal lung sounds or consolidation/abscesses ≥2 by 2 cm or any amount of pleural effusion	No	SSe 64.8–84.2, DSe from 76.9–100	45.7–76.7	Results from 4 different models obtained in a training sample (n = 515) tested in a new subgroup of 174 calves SSe: estimated Se on randomly selected calves, DSe estimated Se on the suspected cases, specificity determined in all negative cases as classified by the reference standard test

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Table 2
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Study	Study Summary	Test Under Investigation	Reference Standard Test	Were Possible Misclassifications of the Reference Standard Test Accounted For?	Sensitivity: 95% CI or BCI (%)	Specificity: 95% CI or BCI (%)	Comments
Remote Early Disease Identification							
White et al,[37] 2016	Two feedlot population of 168 and 311 beef calves	REDI algorithm	Visual observation by the pen riders	Reference standard uncertainty was accounted for using a bayesian latent class model	81.3 (55.5, 95.8)	92.3 (88.2, 96.9)	1-gate study using 2 populations of feedlot calves followed during 30–37 d after arrival in the feedlots
Infrared Thermography							
Schaefer et al,[30] 2007	133 weaned beef calves	Absolute IRT value is equal to the orbital (eye) maximum value (best cutoff 38.1°C)	≥2 of the following symptoms: a core temperature of ≥40°C, a white blood cell count of <7 or >111,000/µL, a clinical score of ≥3, and neutrophil/lymphocyte ratio of <0.1 or >0.8. A true-negative animal had ≤1 of these signs or symptoms	No	67.6	86.8	2-gate study

Schaefer et al,[31] 2012	65 beef Hereford Angus calves 220 kg BW	Infrared thermal value (FLIR-S60 camera) of the true-positive animals at peak temperature and true animals at their average maximum infrared thermal value (best cutoff 35.29°C)	≥3 of the following signs: a core temperature of >40 C, a white blood cell count of <7 or >111,000/μL, a clinical score of >3, or a neutrophil/lymphocyte ratio of 0.8 (neutrophilia). A true-negative had a score of 0 or 1	No	100	97.4	2-gate study design The IRT value was based on serial measurements (typically >20 by day), the prevalence of truly affected calves was low (n = 9)
Thoracic Auscultation							
Buczinski et al,[38] 2014	106 preweaned dairy calves, thorax divided into 4 different areas	Thoracic auscultation positive if crackles, wheezes, or no sounds; otherwise negative	Bilateral thoracic ultrasonography: positive if at least 1 site had consolidation depth ≥1 cm	No	5.9 (from 0 to 16.7)	98.9 (from 97.3 to 100)	1-gate study design Accuracy ranges based on the lung field examined
Buczinski et al,[39] 2016	209 dairy calves raised as veal calves, whole thorax auscultated	Thoracic auscultation	Bilateral thoracic ultrasonography: positive if at least 1 site had consolidation depth ≥1 cm	Reference standard uncertainty was accounted for using a bayesian latent class model	72.9 (50.1–96.4)	53.3 (43.3–64.0)	1-gate study design Operator performing auscultation was blind to thoracic ultrasonography results
Pardon et al,[40] 2019	8–10 veal calves scored by 49 veterinary practitioners	Thoracic auscultation (normal vs abnormal based on veterinarian experience)	Bilateral thoracic ultrasonography: positive if at least 1 site had consolidation depth ≥1 cm	No	63 (20–100)	46 (0–100)	1-gate study design (range representing the spread of the results obtained by the 49 veterinarians, not CI)

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Table 2
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Study	Study Summary	Test Under Investigation	Reference Standard Test	Were Possible Misclassifications of the Reference Standard Test Accounted For?	Sensitivity: 95% CI or BCI (%)	Specificity: 95% CI or BCI (%)	Comments
Computer-aided Auscultation							
Mang et al,[41] 2015	35 beef feedlot steers visually determined as sick, 35 steers not apparently sick	Whisper stethoscope (abnormal if score ≥2)	Pen-rider examination	Reference standard uncertainty was accounted for using a bayesian latent class model	92.9 (71–99)	89.6 (64–99)	2-gate design
Zeineldin et al,[42] 2016	24 feedlot steers with clinical signs of respiratory tract infection pen matched with 24 apparently healthy steers	Whisper stethoscope (abnormal if score ≥2)	Pen-rider examination	No	87.50	75	2-gate design
Thoracic Ultrasonography							
Rabeling et al,[29] 1998	18 calves up to 5 mo of age referred in a veterinary hospital with chronic lesions or arthritis	TUS (unit of interest is part of the lung field; 8 sites per calf)	Necropsy	No	85	98	Small case series of chronic cases, accuracy level at the site level not the calf, lung normal if well ventilated and not any lesion (vs abnormal)

Ollivett et al,[43] 2015	25 dairy calves (1–12 wk old) with normal WRSC <5	TUS positive if any nonaerated lung visible	Necropsy	No	94 (69–100)	100 (64–100)	2-gate design calves were selected if normal WRSC and stratified by ultrasonography findings to be compared with necropsy
Zeineldin et al,[42] 2016	Feedlot calves 6–8 mo old, 24 cases and 24 matched control calves	TUS (7th-11th ICS) positive if heterogenous hyperechoic or echoic area	Pen-rider examination	No	70.8	87.5	2-gate design
Berman et al,[16] 2019	209 veal calves and 301 preweaned dairy calves	TUS positive if consolidation depth $\geq$3 cm not considering site cranial to the heart	WRSC and serum haptoglobin	Reference standards uncertainty was accounted for using a bayesian latent class model	89 (55–100)	95 (92–98)	1-gate design Other ultrasonographic thresholds including or not cranial sites accuracy are also mentioned

The sensitivity is the ability of the test to diagnose sick animals whereas the specificity is the ability of the test to diagnose nonsick animals.

Abbreviations: BCI, bayesian credible interval; BW, body weight; CI, confidence interval; CRSC, Californian respiratory scoring chart; CRSC BRD3, third model of the Californian respiratory scoring chart; DSe, diagnostic sensitivity; ICS, intercostal space; IRT, infrared thermography; PCR, polymerase chain reaction; REDI, remote early disease identification; Se, sensitivity; Sp, specificity; SSe, screening sensitivity; TUS, thoracic ultrasonography; WRSC, Wisconsin respiratory scoring chart.

Data from Refs.[16,18,29,31–42]

studied for the detection of BRD. For example, reticuloruminal boluses detected abnormal rumen temperature from 0.5 to 5.7 days before other respiratory signs were detected in 24 bulls.[47] Many episodes of increased ruminal temperature were not associated with any clinical sign, although they still negatively correlated with average daily gain.[47] As reviewed by Wolfger and colleagues,[9] infrared thermography (IRT) of the nasal planum surface is another way to monitor bovine body temperature. It can be helpful to detect fever when diagnosis of respiratory disease infection is made.[31,47] The technique has a good test-retest repeatability and a limited interoperator variability.[32,48] Standardization of the method is required for distance and weather, which can affect readings.[48] More recently, the use of nasal planum IRT has been used to detect respiratory rate,[49] which could be useful in the distance assessment of calves.

Several combinations of clinical signs have been used in past attempts to standardize BRD case definition at the farmer/producer level. Because diagnosis and treatment (at least in North America and in some European countries) is often not performed by a veterinarian but by animal caretakers based on veterinary-supervised protocols, standardized clinical assessment has also been used as a first-line diagnostic test. The Wisconsin scoring chart for dairy calves, initially intended to standardize treatment decisions among laypeople, resulted in international awareness of the importance of case definitions and standardization.[50] Other dairy calf scores have been reported, such as the Californian[33,34] scoring chart with a specific chart for postweaned calves[35] and a modified chart accounting for imperfect reference standard definition.[36] Despite its widespread use, the Wisconsin scoring chart was not initially created to accurately diagnose infectious bronchopneumonia but to standardize BRD treatment. Its accuracy was very different from other scoring approaches developed thereafter (sensitivity and specificity within the range of 60% to 80%; see **Table 2**). The 3 main limitations of the Wisconsin scoring system are (1) the 4-scale score per clinical sign, which can lead to limited inter-rater agreement, versus dichotomous (normal vs abnormal sign) notation[23]; (2) linear score increases, which assume that each 1-unit increase has the same effect on disease risk; and (3) the absence of specific weighting between clinical signs, which assumes that any clinical sign has the same strength of effect. Studies in California[33,35] and Quebec[36] have addressed these limitations. In feedlot calves, the diagnosis of respiratory tract infection by the pen rider generally uses a step-by-step approach (such as the DART [assessment for presence of depression, decreased appetite, respiratory signs, and increased temperature at the chute] approach[9,51]) or can use a less structured approach.[15,17] The detection of sick feedlot calves had been described as an art rather than a science,[52] which may explain why some pen riders are better than others, as well as the lack of specific consensus on case definition. In a systematic review using slaughterhouse lung lesions to determine the accuracy of clinical detection, the authors found wide heterogeneity between studies, which was at least partly attributed to various clinical definitions.[17]

The results concerning the accuracy of common combinations of clinical signs are reported in **Table 2**. However, little information is available concerning inter-rater agreement of these systems. The authors recently observed that, even after some teaching period, the agreement between 3 different scorers was slight to fair (using Cohen and Fleiss kappa statistics) when using 4-scale scoring per clinical sign included in the Wisconsin respiratory scoring chart.[23] These pitfalls of clinical scoring show the necessity of a structured teaching approach to achieve a level of agreement within and between different farms. This teaching opportunity would help standardize cases definitions even if imperfect.

Continuous monitoring of behavior and feeding

Visual monitoring of cattle is generally limited to short periods of observation. Although serial point measurements are hampered by the prey-animal nature of cattle, hiding clinical signs when observed by predators, continuous measurements by technology can overcome this. Several studies have shown that the progress of respiratory infection is accompanied by behavioral or feeding changes, such as increased lying time[45,53] or decreased standing time[54]; decreased feeding period, dry matter, or milk intake[53,55–60]; bunk feeding frequency[60,61]; and increased time to approach the feedbunk after feed delivery.[56] For sick preweaned calves, decreased drinking speed[58] and decreased suckling time for nonnutritive visits[53,58] were observed. It is beyond the scope of this article to review all parameters and algorithms used for disease diagnosis in cattle. In the field setting, one of the main advantages of these systems is the possibility to detect early changes before the human eye.[56,58,60] However, this comes with the limitation of false-positive risk with possible false alarms. Limited information is available to date on the usefulness of these observations as practical daily monitoring tools. For example, the use of daily feeding behavior in group-housed dairy calves fed with an automatic milk feeder was not accurate enough to predict sick animals.[58]

The major limitation of automatic systems is that all so far have been validated against a clinical definition, judged to be state of the art at the time of the particular study. However, it is now realized that there are limitations to many of the definitions. Therefore, an uncomfortable fact is that, in almost all field studies on automatic detection, the reference standard test was human clinical diagnosis. This situation could have biased the research finding toward the null, because any discrepancy between the test of interest and case definition would be interpreted as a test error. One exception is the remote early disease identification (REDI) system, which was evaluated through a bayesian latent class model (see **Table 2**).

In feedlot calves, the REDI system was based on real-time animal positional information.[37,62] The accuracy of REDI is higher than that of pen-rider visual observation when accounting for the absence of a gold standard to detect a clinical case (see **Table 2**).[37] Using this method for the detection of respiratory tract infection resulted in higher first-treatment success and lower average number of antimicrobial doses per animal without negative production impacts.[63] The future for incorporating these types of behavior monitoring systems is to be able to refine algorithms for sensitivity to detect early cases with an acceptable false-positive fraction. The specificity has been determined as the most important characteristic of a diagnostic test from a feedlot economic perspective.[8] This characteristic should also be developed in relation to welfare, production, and economic outcomes. Development of big-data and machine learning technology will potentially rapidly change the application of these tests because they can integrate many different dimensions of calf characteristics that the human eye cannot manage and thus filter animals that need to be monitored by a caretaker or veterinarian.

Confirmatory Tests

Confirmation diagnostic tests are generally used after an initial suspicion is raised by a screening test. Most of the confirmatory tests described here are more commonly used by veterinarians (except for computer-aided lung auscultation).

Thoracic auscultation

Historically, thoracic auscultation is the most frequently used confirmation test, as a way to assess for the presence of increased bronchial sounds or abnormal sounds (eg crackles, wheezes, or absence of sound). However, the data concerning use of auscultation for disease assessment are surprisingly limited in veterinary and human medicine.[38–40] When using only abnormal respiratory sounds, the sensitivity to detect lung consolidation (diagnosed by ultrasonography) is low but very specific (see **Table 2**).[38] Adding increased bronchial sounds to the definition increased sensitivity and decreased specificity.[39] It should be remembered that auscultation as in human medicine is highly operator dependent. Recently the authors found a poor inter-rater reliability (Kripendorff alpha, 0.18; 95% confidence interval [CI], −0.01–0.38) between 49 Dutch practitioners.[40] The average sensitivity for lung auscultation to detect ultrasonographically defined lung lesions was 0.63 (from 0.2 to 1) and specificity was 0.46 (from 0 to 1). The variable accuracy has also been found in human medicine.[64] Using objective measurement of lung sounds to avoid inter-rater variability is therefore of interest and, recently, a computer-aided lung auscultation algorithm has been commercialized for feedlot calves, giving results after 8-second auscultation on a 1 to 5 step scale, with an abnormal score considered as greater than or equal to 2.[65] Currently available data concerning the accuracy of this stethoscope for the diagnosis of naturally occurring LRTI are limited to a case-control study[41,42] in which 35 steers with visual signs of disease were pulled with the same number of apparently healthy animals; assessment of the stethoscope found sensitivity and specificity of 92.9% (95% bayesian credible intervals [BCI] 71%–99%) and 89.6% (95% BCI, 64%–99%) respectively.[41] No information is available concerning its test-retest validation or use on cattle other than postweaned beef cattle (eg, calves around 250–300 kg).

Medical imaging of lung lesions

Medical imaging is another interesting way to confirm the presence of lung lesions associated with LRTI. Several imaging techniques have been used, including radiographs,[66–72] computed tomography,[66,73,74] and ultrasonography.[16,39,42,43,75–77] Ultrasonography especially has recently been studied more in depth because of its ease for use in field settings. The main findings on the accuracy of these imaging modalities are reported in **Table 2**.

Thoracic ultrasonography

The practical use of thoracic ultrasonography has recently been reviewed.[75] Available studies of the inter-rater agreement have shown that the presence of lung consolidation is a reliable parameter to monitor even if the operator does not have a strong expertise on medical ultrasonography use.[22,78] Diagnostic limitations associated with thoracic ultrasonography include the influence of the size of the animal and muscle development, which preclude the visualization of lung parenchyma cranial to the heart in large beef calves.[77] Also, it is not currently possible to distinguish active lung infection lesions that would benefit from treatment from lesions that are a sequela of previous disease for which treatment would not be beneficial. There is limited evidence that ultrasonography can be used for confirming infectious causes. Information obtained from thoracic ultrasonography assessment is therefore used to quantify lesions, which is associated with negative production outcomes.[79–82] Different recording systems exist to define normal versus abnormal findings.[75] Most available studies on lung lesion imaging are observational, and limited information is available concerning the added value of performing this test in terms of mitigating welfare or production outcomes. One of the main values of thoracic ultrasonography is to provide an imperfect but objective measurement to assess the effect of different interventions for infectious bronchopneumonia. Studies reporting ultrasonography accuracy results are described in **Table 2**.

Other imaging techniques

In the late 1980s, thoracic radiographs were mentioned as an interesting diagnostic technique to identify lung lesions in clinically healthy calves.[83] Specific findings associated with infectious bronchopneumonia have been further detailed in calves and cows.[66,67,69] Infectious pneumonia is characterized by tissue opacity (alveolar pattern) with or without air bronchogram.[66] Presence of cavitary lesions is generally associated with lung abscesses or emphysematous bulla.[67] Other patterns, such as bronchial pattern with thickened bronchial walls or interstitial patterns, can also be observed. One of the limitations of thoracic radiographs is the summation effect caused by superposition of three-dimensional structures in a two-dimensional image.[66] Moreover, the risk of exposure to radiation, and limited availability for practicing veterinarians working in purely food animal practice, have limited its field usefulness. Recently the authors compared thoracic radiographs with thoracic ultrasonography in 50 calves weighing less than 100 kg referred to a hospital, finding the tests to have similar accuracy compared with computed tomography.[84] Computed tomography has a strong potential to accurately detect slight to moderate lung changes and is used as a quasi–gold standard in human pneumonia studies.[85,86] However, because of the associated costs and necessity for sedation, it is of limited use in practice, but it can be used in referral or research imaging.

Blood markers for diagnosis of infectious bronchopneumonia

The systemic changes associated with infectious bronchopneumonia can be measured in different body fluids, but, from a practical standpoint, blood is predominantly used. White blood cell (WBC) changes have been well described in response to respiratory infection, but their discriminatory capacity is limited.[87] The basophil count, which was the most accurate white blood cell marker in the referenced study, had an area under the receiver operating characteristic curve (AUC) of 0.599, which indicates a low-accuracy test.[88] Comparable AUC ranges (0.5–0.6) were obtained from white blood cells and red blood cells analysis in feedlot calves with naturally occurring respiratory disease.[89] This finding confirms those of Wolfger and colleagues[9] that WBC findings are of limited practical use for infectious bronchopneumonia diagnosis.

Acute phase proteins (APPs) such as haptoglobin, fibrinogen, serum amyloid A, or C-reactive proteins have received attention for diagnosis of bovine respiratory tract infection and inflammation. The authors recently reviewed the diagnostic accuracy of these markers for naturally occurring respiratory infection.[90] The conclusion of this systematic review was that there was a high heterogeneity in reported test accuracy as well as sensitivity and specificity. Most of the studies reviewed were 2-gate (case-control) studies with patients at the end of the spectrum of disease, which, as discussed earlier, potentially biased the results toward inflated accuracy estimate of the APP tested. It was impossible to complete the meta-analysis because of the different study designs, settings, and case definitions. Thus, it is currently difficult to give a specific accuracy estimate of those markers for diagnosing infectious bronchopneumonia. Haptoglobin, which was the most commonly reported APP in this review, had sensitivity varying from 61% to 100% and a specificity from 80% to 100%. This finding contrasts with the recently reported sensitivity of 46% and specificity of 82% in a dairy calf study that also reported WBC accuracy.[87] Based on the ranges of reported accuracy and study limitations, it is difficult to give a practical recommendation on using only haptoglobin for a diagnosis in practice. Many other markers have been assessed but are not discussed further in this article because of limited field studies. Other tests, such as blood gas analysis, exhaled biomarkers, or analysis of respiratory secretion, are also not further detailed.

Necropsy

Necropsy is important in the investigation of respiratory tract problems. Necropsy not only serves to evaluate the lesions and identify specific pathogens but is also useful to monitor caretaker detection accuracy. Necropsy-based recording of the cause of death and percentage of calves that die of undiagnosed respiratory disease is a practical way to improve respiratory disease detection protocols. In a recent study of dairy calf mortality before 90 days of age, the agreement between the suspected cause of death based on treatments given versus gross necropsy or necropsy performed in a laboratory was slight to fair (Cohen kappa, 0.22 and 0.13, respectively).[91] In feedlot calves with lung lesions at slaughter, from 3% to 56% of these calves were detected as sick by the pen rider in 7 different studies included in a meta-analysis.[17]

SUMMARY

This article emphasizes different challenges inherent to BRD complex definitions, as well as limitations of clinical tests used for diagnosis. An important step to improve the case definition is to develop robust tests with high inter-rater and intrarater agreement and reliability, as well as to account for imperfection of case definition when determining diagnostic test accuracy. Maintaining health and welfare with decreased antimicrobial use would be a major benchmark allowing the veterinary profession to maintain its reputation and credibility in the One Health approach.

DISCLOSURE

S. Buczinski has received honoraria for acting as speaker or consultant as well as research grants for pharmaceutical companies (Zoetis, MSD, Hipra, and Ceva) and companies involved in commercialization of ancillary tests used in respiratory diseases (EI Medical Imaging, Geissler Corp). B. Pardon has received honoraria for acting as speaker or consultant for pharmaceutical (Zoetis, MSD, Vetoquinol, Dopharma, Boehringer Ingelheim, Dechra, Hipra, Ceva, Merial, and Elanco), agricultural (Algoet nutrition) and chemical (Proviron) companies, and nonprofit organizations (Boerenbond, AMCRA, DGZ-Vlaanderen).

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