Evaluation of 4 predictive algorithms for intramammary infection status in late-lactation cows

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ABSTRACT

The objective of this observational study was to compare 4 cow-level algorithms to predict cow-level intramammary infection (IMI) status (culture and MALDI-TOF) in late-lactation US dairy cows using standard measures of test performance. Secondary objectives were to estimate the likely effect of each algorithm, if used to guide selective dry cow therapy (SDCT), on dry cow antibiotic use in US dairy herds, and to investigate the importance of including clinical mastitis criteria in algorithm-guided SDCT. Cows (n = 1,594) from 56 US dairy herds were recruited as part of a previously published cross-sectional study of bedding management and IMI in late-lactation cows. Each herd was visited twice for sampling. At each farm visit, aseptic quarter-milk samples were collected from 20 cows approaching dry-off (>180 d pregnant), which were cultured using standard bacteriological methods and MALDI-TOF for identification of isolates. Quarter-level culture results were used to establish cow-level IMI status, which was considered the reference test in this study. Clinical mastitis records and Dairy Herd Improvement Association test-day somatic cell count data were extracted from herd records and used to perform cow-level risk assessments (low vs. high risk) using 4 algorithms that have been proposed for SDCT in New Zealand, the Netherlands, United Kingdom, and the United States. Agreement between aerobic culture (reference test; IMI vs. no-IMI) and algorithm status (high vs. low risk) was described using Cohen’s kappa, test sensitivity, specificity, negative predictive value, and positive predictive value. The proportion of cows classified as high risk among the 4 algorithms ranged from 0.31 to 0.63, indicating that these approaches to SDCT could reduce antibiotic use at dry-off by 37 to 69% in the average US herd. All algorithms had poor agreement with IMI status, with kappa values ranging from 0.05 to 0.13. Sensitivity varied by pathogen, with higher values observed when detecting IMI caused by Streptococcus uberis, Streptococcus dysgalactiae, Staphylococcus aureus, and Lactococcus lactis. Negative predictive values were high for major pathogens among all algorithms (≥0.87), which may explain why algorithm-guided SDCT programs have been successfully implemented in field trials, despite poor agreement with overall IMI status. Removal of clinical mastitis criteria for each algorithm had little effect on the algorithm classification of cows, indicating that algorithms based on SCC alone may have similar performance to those based on SCC and clinical mastitis criteria. We recommend that producers implementing algorithm-guided SDCT use algorithm criteria that matches their relative aspirations for reducing antibiotic use (high specificity, positive predictive value) or minimizing untreated IMI at dry-off (high sensitivity, negative predictive value).

Key words: selective dry cow therapy, algorithm, antimicrobial, intramammary infection

INTRODUCTION

Selective dry cow therapy (SDCT) uses screening tests to guide antibiotic therapy toward cows that are likely to benefit from treatment and away from those unlikely to benefit. Implementation of SDCT in clinical trials has reduced antibiotic use at dry-off by 21 to 58%, without negatively affecting postcalving health and productivity (Cameron et al., 2014; Vasquez et al., 2018; Kabera et al., 2020; Rowe et al., 2020a,b). To be successful, SDCT programs should be conducted in herds with good milk quality, use a teat sealant to protect untreated quarters from new IMI during the dry period (Winder et al., 2019), and adopt a cost-effective
screening test that identifies cows or quarters in need of antibiotic treatment at dry-off and quarters not in need of antibiotic treatment. The screening tools currently available for application within SDCT programs include direct tests such as aerobic culture, PCR, as well as data-based algorithms which use test-day SCC and clinical mastitis records to enable risk profiling of individual cows on the day of dry-off, with high-risk cows being the exclusive recipients of antibiotic therapy.

Algorithm-guided SDCT is expected to become a common dry cow therapy (DCT) approach for US herds in the future because risk profiling can be easily automated using herd management software. Algorithm-guided SDCT is also likely to be more cost-effective than blanket DCT and culture-guided SDCT on the average US farm when routine SCC test results are available (Rowe et al., 2021b), while delivering equivalent postcalving health and productivity (Rowe et al., 2020a,b). In the United States, approximately three-quarters of large US dairies use DHIA services (NAHMS, 2016) and almost 100% of large farms have an on-farm computer record-keeping system, indicating that a computer-driven protocol can benefit many dairy farms.

Although the benefits of algorithm-guided SDCT are well recognized, a review of clinical trials and industry recommendations confirms that there is no consensus on algorithm design. To our knowledge, the most widely promoted and adopted algorithms have originated in the Netherlands (Vanhoudt et al., 2018), New Zealand (DairyNZ, 2012), the United Kingdom (Bradley et al., 2010, 2018), and the United States (Rowe et al., 2020a). All 4 algorithms are based on one or more cow-level SCC measurements during lactation, and in most cases, clinical mastitis history. However, each algorithm varies in the number of DHIA tests that are evaluated and employs different thresholds for SCC and clinical mastitis event histories, suggesting that the algorithms may vary in their ability to identify cows with IMI (sensitivity, Se) and cows without IMI (specificity, Sp). Describing the test characteristics of these commonly recommended algorithms would help US producers identify algorithms to suit their aspirations for reducing antibiotic use (i.e., high Sp) and their motivation to minimize the risk of IMI being untreated at dry-off (high Se). The objective of this observational study was to compare 4 cow-level algorithms to cow-level IMI status (culture and MALDI-TOF) in late-lactation US dairy cows using standard measures of test performance. Secondary objectives were to estimate the likely effect of each algorithm, if used to guide SDCT, on dry cow antibiotic use in US dairy herds and to investigate the importance of including clinical mastitis as a criterion in SDCT algorithms.

MATERIALS AND METHODS

The data set used in this study was derived from a cross-sectional study of bedding management and quarter-level IMI that was conducted between August 2017 and April 2018 (Rowe et al., 2019). Investigating SDCT algorithms was not part of the original design for the bedding study.

Herd Enrollment and Sample Collection in the Original Study

The original data set comprised a convenience sample of 80 herds from 10 states. Herd eligibility criteria included the following: milking herd size greater than 200 cows, have a working relationship with the University of Minnesota or a local Zoetis Quality Milk Specialist, and be using 1 of 4 bedding materials: manure solids, nonmanure organic, new sand, or reclaimed sand. In July 2017, a list of eligible herds (n = 152) was created and 80 were selected using a randomized, stratified sampling method in an attempt to enroll an equal number of herds using each bedding type and to maximize the representation of each bedding type within US dairy regions (Northeast, Midwest, Northwest, and Southwest). No bulk tank SCC criteria were used when recruiting herds. Each farm was visited once during summer (August to September 2017) and once during winter (December 2017 to April 2018). A detailed description of how cows were enrolled and sampled can be found in Rowe et al. (2019). At each visit, aseptic quarter-milk samples were collected from 20 lactating cows approaching dry-off. Cows had to be greater than 180 d pregnant (i.e., approximately 100 d before next calving), and not in the hospital pen on the day of visit to be eligible for enrollment. Cows were purposely selected into the study according to parity, such that within each herd, 40% of subjects were primiparous and 60% multiparous. Duplicate, aseptic milk samples were collected from each functional quarter of enrolled cows according to National Mastitis Council guidelines (NMC, 2017). Briefly, after milking staff performed their usual pre-milking teat preparation routine, investigators, wearing clean disposable gloves, scrubbed teat ends with 70% isopropyl alcohol-soaked gauze swabs, discarded 3 squirts of foremilk, and sampled approximately 20 to 30 mL of milk into sterile 60-mL vials. Samples were stored at −20°C at the study site before being freighted overnight on ice to the Laboratory for Udder Health at the Veterinary Diagnostic Laboratory, University of Minnesota (St. Paul). Samples were later cultured using standard bacteriological methods, which are outlined later in this report. Study investigators conducted questionnaires with the farm manager or
owner at farm visits to obtain information about herd demographics, case definitions for clinical mastitis, data recording practices, and dry period management. Herd electronic records were collected after the follow-up period to capture cow demographic information, lactation and reproductive events (e.g., dry-off and calving dates), and health and production outcomes, including DHIA data.

Screening of Herds and Cows for the Current Study

Of the 80 herds recruited for the original study (Rowe et al., 2019), 56 were determined to be eligible for the current study. Herds were excluded if they were not using DairyComp 305 (Valley Ag Software, n = 6), not conducting DHIA testing (n = 7), had an average of less than 5 DHIA tests per enrolled cow from the current lactation (n = 4), had unsuitable clinical mastitis records (n = 7), and had less than 10 eligible cows in the final data set (n = 2). Counts of exclusions for each criterion do not sum to 24, as some herds met multiple exclusion criteria. The threshold of 5 DHIA tests per enrolled cow was an arbitrary decision, based on what we felt was likely to represent the minimum allowable amount of SCC data for individual cows.

To determine suitability of clinical mastitis records, a herd questionnaire was used to identify case definitions and event codes. Herds that did not define clinical mastitis on the basis of visibly abnormal milk or inflammatory signs in the mammary gland (or both) were excluded. Monthly clinical mastitis frequencies were tabulated for each herd during the time period of the study to identify and exclude herds with intermittent recording of cases. Intermittent recording was defined as large fluctuations in monthly case counts and by months where no cases were recorded. No critical limits were used in this definition.

Individual cows were excluded from the current study if they had one or more quarters with a contaminated result (n = 397). Cows with only 3 functional quarters were still included in the final data set if each quarter had a valid culture result (n = 189 cows). Cows were excluded if they did not have at least 1 DHIA test within 42 d of enrollment (n = 193), to meet the requirements of the algorithm used in the Netherlands (Vanhoudt et al., 2018).

Explanatory Variables: Algorithm Status

Somatic cell count and clinical mastitis records from the lactation of enrollment were used to determine the algorithm status of cows (i.e., low vs. high risk of having an IMI). Algorithms recommended by researchers in the Netherlands [Dutch, Vanhoudt et al. (2018)], New Zealand [NZ, DairyNZ (2012)], the United Kingdom [UK, Bradley et al. (2010, 2018)], and the United States [US, Rowe et al. (2020a,b)] were evaluated for prediction of cow-level IMI status at enrollment. Criteria for each algorithm are outlined in Table 1. For the Dutch algorithm, cows were classified as low risk if the last test-day SCC (i.e., most recent SCC before enrollment) was <150,000 cells/mL for primiparous cows and <50,000 cells/mL for multiparous cows. For the NZ algorithm, cows were classified as low risk if all test-day SCC from the lactation of enrollment were below 120,000 cells/mL for primiparous cows and <150,000 cells/mL for multiparous cows. For the UK algorithm, cows were classified as low risk if test-day SCC from the last 3 tests were <200,000 and no clinical mastitis cases were recorded during the same time period. No consideration was made for the time interval between SCC tests for any algorithm, except that cows had to have at least 1 SCC test within 42 d of enrollment to be included in the study (required for the Dutch algorithm). For the US algorithm, cows were classified as low risk if all test-day SCC from the lactation of enrollment were <200,000 cells/mL and fewer than 2 cases of clinical mastitis were recorded during that lactation.

Table 1. Overview of algorithms used to guide selective dry cow therapy

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Criteria for low-risk status</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td>Parity = 1: SCC &lt;150,000 cells/mL at the last test. Parity ≥2: SCC &lt;50,000 cells/mL at the last test. Last test must be within 6 wk of dry-off.</td>
<td>Vanhoudt et al. (2018)</td>
</tr>
<tr>
<td>New Zealand</td>
<td>Parity = 1: SCC &lt;120,000 cells/mL at all tests. Parity ≥2: SCC &lt;150,000 cells/mL at all tests. No clinical mastitis during whole lactation.</td>
<td>DairyNZ (2012)</td>
</tr>
<tr>
<td>UK</td>
<td>SCC &lt;200,000 cells/mL for each of the last 3 tests. No clinical mastitis between the third last test and dry-off.</td>
<td>Bradley et al. (2010, 2018)</td>
</tr>
<tr>
<td>US</td>
<td>SCC &lt;200,000 cells/mL at all tests. &lt;2 cases of clinical mastitis during whole lactation.</td>
<td>Rowe et al. (2020a,b,d)</td>
</tr>
</tbody>
</table>
Outcome Variables—Analysis 1: Cow-Level IMI Status

Cow-level IMI status was determined from bacteriological testing of quarter-milk samples. Milk samples were thawed at room temperature, homogenized by gentle inversion, and plated onto Columbia CNA agar with 5% sheep blood and MacConkey agar. Agar plates were inoculated with one loop-full (approximately 10 μL) of sample, using disposable plastic loops and incubated in aerobic conditions at 37 ± 2°C for 42 to 48 h. Only one sample from each quarter was cultured unless this first sample was contaminated. Samples were classified as contaminated if more than 2 isolates were recovered.

Isolates were identified using a MALDI-TOF mass spectrometer (Microflex; Bruker Daltonics Inc.). Peaks produced by each isolate were analyzed by the MALDI-TOF Biotyper reference library. The confidence level for each diagnosis reported by the software was used in the following fashion: >2.0, species level diagnosis recorded; 1.8–2, genus level diagnosis recorded; <1.8, MALDI-TOF diagnosis not recorded and traditional identification methods used. Diagnoses obtained using MALDI-TOF were further evaluated by comparing peaks to a database of commonly isolated mastitis pathogens that have been internally validated at the Laboratory for Udder Health using 16S sequencing. Traditional identification methods included; differential growth on selective media, colony morphology, catalase reaction, Gram stain, and cytology. To improve the Sp of IMI classification (i.e., reduce false positives), NAS isolates with <2 colonies (<200 cfu/mL) and Bacillus spp. isolates with <5 colonies (<500 cfu/mL) were reclassified as no growth and the quarter was considered uninfected (Dohoo et al., 2011). Cows with one or more infected quarters were classified as positive for an IMI. Cows without a full set of culture results were reclassified uninfected (Dohoo et al., 2011). Cows with one or more infected quarters were classified as positive for an IMI. Cows without a full set of culture results were excluded from analysis to reduce the risk of misclassification bias. Pathogens considered as major pathogens included Staphylococcus aureus, Streptococcus, and Streptococcus-like organisms and coliforms, and minor pathogens included NAS, Corynebacterium spp., and Bacillus spp. (Gohary and McDougall, 2018; Lipkens et al., 2019; Rowe et al., 2020d).

Statistical Analysis

Sample Size Calculation. Sample size calculations were conducted for the larger study of bedding management and quarter-level IMI (Rowe et al., 2019). No formal power calculations were conducted before undertaking this study.

Variable Management. Herd demographic information and laboratory findings were recorded in spreadsheet sheets (Google Sheets and Microsoft Excel V16), which along with electronic herd records, were imported into the R Statistical Programming Environment (R Core Team, 2018) for analysis.

Analysis 1: Algorithm Prediction of Cow-Level IMI Status at Enrollment. The ability of algorithms to predict cow-level IMI was evaluated in a similar way to diagnostic test validation. Agreement between algorithm status and IMI status was calculated using Cohen’s kappa (κ). The κ values were interpreted in the following fashion: 0.01–0.20 (none to slight agreement), 0.21–0.40 (fair agreement), 0.41–0.60 (moderate agreement), 0.61–0.80 (substantial agreement), and 0.81–1.00 (almost perfect agreement). Estimation of test Se (#true positives/#infected), Sp (#true negatives/#uninfected), PPV (#true positives/#test-positives), and NPV (#true-negatives/#test-negatives) were conducted using univariable generalized estimating equations (GEE, binomial family, logit link) in the ‘geepack’ package (Halekoh et al., 2006) and estimated marginal means using the ‘emmeans’ package (Lenth et al., 2020). Generalized estimating equations were used to account for the clustering of cows within herds using an “independence” working covariance structure. Test characteristics were calculated for cow-level IMI caused by all pathogens and major pathogens. Furthermore, Se was also estimated for each algorithm for the detection of individual pathogens (e.g., Streptococcus uberis) and pathogen groups (e.g., Streptococcus spp. and Streptococcus-like organisms; SSLO).

Secondary Objectives. As a secondary analysis, we reported the proportion of cows classified as high risk (overall and stratified by herd), as a method to estimate the likely effect of implementing these SDCT algorithms on antibiotic use at dry-off. In addition, to determine the effect of including clinical mastitis events as an algorithm criterion, we compared each algorithm (n = 4) to an alternative version that was solely based on SCC measurements. For example, for the US algorithm, we determined the agreement using the proposed criteria for low-risk animals (SCC <200,000 cells/mL from the entire lactation and <2 cases of clinical mastitis) to the alternative algorithm (SCC <200,000 cells/mL from the entire lactation). This was repeated for the other algorithm groups. Given that the Dutch algorithm does not use clinical mastitis as a criterion, it was assumed that agreement would be perfect (κ = 1).

RESULTS

Descriptive Results

Herd Enrollment. A total of 1,594 cows from 56 herds were available in the final data set. Herds were
enrolled from the following states: California (n = 11), Idaho (n = 5), Indiana (n = 1), Michigan (n = 5), Minnesota (n = 8), New York (n = 6), Oregon (n = 1), Texas (n = 2), and Wisconsin (n = 17). The median number of milking cows per herd was 1,800 (235 to 9,660) and the average daily cow milk production per herd was 38 (23 to 47) kg. Enrolled cows were either Holstein (n = 1,388, 87.1%) or other (n = 206, 12.9%), which included Holstein-cross, Jersey, Brown-Swiss, and their crosses. Housing systems used for lactating cows included freestall (n = 55, 98.2%) and dry lot (n = 1, 1.8%). The majority of herds practiced blanket DCT (n = 49, 87.5%), with the remaining conducting selective- or intermittent-DCT (n = 6, 10.7%) and no DCT (n = 1, 1.8%). The majority of herds used either an internal (n = 41, 73.2%) or external teat sealant at dry-off (n = 6, 10.7%).

Prevalence of Cow-Level IMI. Cow-level IMI status from 1,594 cows at enrollment is summarized in Table 2. The number of cows with at least 1 infected quarter was 762 (47.8%). The number of cows infected with major and minor pathogens were 259 (16.2%) and 569 (35.7%), respectively. The number of cows with IMI caused by NAS and SSLO were 467 (29.3%) and 569 (35.7%), respectively. The most common bacterial species causing IMI was Staphylococcus chromogenes, which infected 19.3% of cows. Other common causes of cow-level IMI included Staphylococcus sp. (6.8%), Aerococcus spp. (6.0%), Lactococcus spp. (5.3%), Bacillus spp. (5.5%), and Corynebacterium spp. (3.6%). Only 3 cows (0.2%) had IMI caused by coliform bacteria. For a detailed description and discussion of the quarter-level prevalence of IMI observed for cows in this study, please refer to Rowe et al. (2019).

Algorithm Prediction of Cow-Level IMI at Enrollment

Test characteristics for the efficacy of each algorithm to predict culture-detected, cow-level IMI status at enrollment is summarized in Table 3. All algorithms had poor agreement with IMI status for all pathogens (κ range: 0.04–0.11) and for major pathogens only (κ range: 0.04–0.11). Furthermore, no algorithm had a high Se and Sp simultaneously. Sensitivity ranges for cow-level IMI were all pathogens (0.37–0.69) and major pathogens (0.44–0.70). Specificity ranges were all pathogens (0.44–0.75) and major pathogens (0.39–0.71). The ranges of PPV for cow-level IMI were all pathogens (0.50–0.57) and major pathogens (0.18–0.23). The ranges of NPV for cow-level IMI were all pathogens (0.54–0.58) and major pathogens (0.87–0.88).

Table 2. Cow-level prevalence of IMI in 1,594 cows from 56 US dairy herds

<table>
<thead>
<tr>
<th>Item</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cows at risk</td>
<td>1,594</td>
</tr>
<tr>
<td>No growth</td>
<td>832 (52.2)</td>
</tr>
<tr>
<td>Infected cows</td>
<td>762 (47.8)</td>
</tr>
<tr>
<td>Major pathogens</td>
<td>259 (16.2)</td>
</tr>
<tr>
<td>Minor pathogens</td>
<td>569 (35.7)</td>
</tr>
<tr>
<td>Gram-positive</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>20 (1.3)</td>
</tr>
<tr>
<td>NAS</td>
<td>467 (29.3)</td>
</tr>
<tr>
<td>Staphylococcus chromogenes</td>
<td>308 (19.3)</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>23 (1.4)</td>
</tr>
<tr>
<td>Staphylococcus haemolyticus</td>
<td>23 (1.4)</td>
</tr>
<tr>
<td>Staphylococcus sciuri</td>
<td>18 (1.1)</td>
</tr>
<tr>
<td>Staphylococcus simulans</td>
<td>27 (1.7)</td>
</tr>
<tr>
<td>Staphylococcus xylosus</td>
<td>24 (1.5)</td>
</tr>
<tr>
<td>Staphylococcus sp.</td>
<td>109 (6.8)</td>
</tr>
<tr>
<td>Streptococcus and Streptococcus-like organisms</td>
<td></td>
</tr>
<tr>
<td>Aerococcus spp.</td>
<td>96 (6.0)</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>22 (1.4)</td>
</tr>
<tr>
<td>Lactococcus spp.</td>
<td>85 (5.3)</td>
</tr>
<tr>
<td>Lactococcus garvieae</td>
<td>59 (3.7)</td>
</tr>
<tr>
<td>Lactococcus lactis</td>
<td>19 (1.2)</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>52 (3.3)</td>
</tr>
<tr>
<td>Streptococcus dysgalactiae</td>
<td>17 (1.1)</td>
</tr>
<tr>
<td>Streptococcus uberis</td>
<td>14 (0.9)</td>
</tr>
<tr>
<td>Streptococcus sp.</td>
<td>23 (1.4)</td>
</tr>
<tr>
<td>Other gram-positive</td>
<td></td>
</tr>
<tr>
<td>Bacillus spp.</td>
<td>87 (5.5)</td>
</tr>
<tr>
<td>Corynebacterium spp.</td>
<td>58 (3.6)</td>
</tr>
<tr>
<td>Miscellaneous gram-positive</td>
<td>33 (2.1)</td>
</tr>
<tr>
<td>Gram-negative</td>
<td></td>
</tr>
<tr>
<td>Coliform</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>Miscellaneous gram-negative</td>
<td>18 (1.1)</td>
</tr>
<tr>
<td>Other organisms</td>
<td></td>
</tr>
<tr>
<td>Yeast</td>
<td>8 (0.5)</td>
</tr>
</tbody>
</table>

1Staphylococcus aureus, Streptococcus, and Streptococcus-like organisms and coliforms.
2Non-aureus Staphylococcus spp., Corynebacterium spp., and Bacillus spp.
3Included Arthrobacter, Micrococcus, Listeria, Trueperella, and unidentified gram-positive bacteria.
4Included Pantoea, Raoultella, Stenotrophomonas, and unidentified gram-negative bacteria. See Rowe et al. (2019) for a full breakdown of pathogens identified from late-lactation cows.
Table 3. Comparison of test characteristics (95% CI) of 4 algorithms to detect cow-level IMI in late-lactation cows

<table>
<thead>
<tr>
<th>Item</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pathogens (prevalence = 47.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agreement (Cohen’s kappa)</td>
<td>0.62 (0.56–0.68)</td>
<td>0.70 (0.64–0.76)</td>
<td>0.44 (0.37–0.52)</td>
<td>0.59 (0.51–0.66)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.53 (0.47–0.58)</td>
<td>0.69 (0.63–0.74)</td>
<td>0.37 (0.32–0.43)</td>
<td>0.56 (0.50–0.63)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.52 (0.47–0.57)</td>
<td>0.44 (0.38–0.49)</td>
<td>0.75 (0.69–0.79)</td>
<td>0.56 (0.50–0.62)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>0.50 (0.45–0.55)</td>
<td>0.53 (0.49–0.57)</td>
<td>0.57 (0.52–0.62)</td>
<td>0.54 (0.50–0.58)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>0.54 (0.51–0.58)</td>
<td>0.61 (0.56–0.65)</td>
<td>0.56 (0.53–0.60)</td>
<td>0.58 (0.54–0.63)</td>
</tr>
<tr>
<td>Major pathogens(^1) (prevalence = 16.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agreement (Cohen’s kappa)</td>
<td>0.04 (0.01–0.07)</td>
<td>0.07 (0.04–0.11)</td>
<td>0.11 (0.07–0.16)</td>
<td>0.06 (0.02–0.09)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.62 (0.56–0.68)</td>
<td>0.70 (0.64–0.76)</td>
<td>0.44 (0.37–0.52)</td>
<td>0.59 (0.51–0.66)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.52 (0.47–0.57)</td>
<td>0.39 (0.33–0.45)</td>
<td>0.71 (0.66–0.76)</td>
<td>0.52 (0.46–0.58)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>0.20 (0.17–0.24)</td>
<td>0.18 (0.15–0.22)</td>
<td>0.23 (0.19–0.28)</td>
<td>0.19 (0.16–0.23)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>0.88 (0.84–0.90)</td>
<td>0.87 (0.83–0.90)</td>
<td>0.87 (0.84–0.89)</td>
<td>0.87 (0.83–0.90)</td>
</tr>
</tbody>
</table>

\(^1\)Staphylococcus aureus, Streptococcus, and Streptococcus-like organisms and coliforms.

Secondary Analyses

Estimating Antibiotic Use in Each Algorithm.
Algorithm status for cows (n = 1,594) and herds (n = 56) is summarized in Table 5. The proportion of cows classified as high risk provides an indication for likely antibiotic use when implemented in a SDCT program. Overall, the proportion of high-risk cows for each algorithm were Dutch (0.50), NZ (0.63), UK (0.31), and US (0.50). The average proportion of high-risk cows within herds (n = 56) for each algorithm were Dutch (0.51, SD = 0.17), NZ (0.62, SD = 0.19), UK (0.31, SD = 0.17), and US (0.50).

Table 4. Sensitivity of 4 algorithms to predict cow-level IMI status caused by various pathogens in late-lactation cows

<table>
<thead>
<tr>
<th>Item</th>
<th>Sensitivity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cows at risk</td>
<td>1,594 (100.0)</td>
</tr>
<tr>
<td>All IMI</td>
<td>0.53 (0.47–0.58)</td>
</tr>
<tr>
<td>Major pathogens(^1)</td>
<td>0.62 (0.56–0.68)</td>
</tr>
<tr>
<td>Minor pathogens(^2)</td>
<td>0.51 (0.44–0.57)</td>
</tr>
<tr>
<td>NAS</td>
<td>0.52 (0.45–0.58)</td>
</tr>
<tr>
<td>Staphylococcus chromogenes</td>
<td>0.50 (0.42–0.58)</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>0.78 (0.58–0.91)</td>
</tr>
<tr>
<td>Staphylococcus haemolyticus</td>
<td>0.70 (0.53–0.87)</td>
</tr>
<tr>
<td>Staphylococcus scroti</td>
<td>0.50 (0.30–0.70)</td>
</tr>
<tr>
<td>Staphylococcus simulans</td>
<td>0.67 (0.47–0.82)</td>
</tr>
<tr>
<td>Staphylococcus xylosus</td>
<td>0.46 (0.35–0.57)</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>0.53 (0.45–0.62)</td>
</tr>
<tr>
<td>SSLO(^3)</td>
<td>0.63 (0.57–0.69)</td>
</tr>
<tr>
<td>Aerococcus spp.</td>
<td>0.57 (0.49–0.66)</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>0.68 (0.46–0.84)</td>
</tr>
<tr>
<td>Lactococcus spp.</td>
<td>0.64 (0.56–0.70)</td>
</tr>
<tr>
<td>Lactococcus garvieae</td>
<td>0.59 (0.50–0.68)</td>
</tr>
<tr>
<td>Lactococcus lactis</td>
<td>0.79 (0.62–0.90)</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>0.69 (0.57–0.87)</td>
</tr>
<tr>
<td>Streptococcus dysgalactiae</td>
<td>0.76 (0.56–0.89)</td>
</tr>
<tr>
<td>Streptococcus uberis</td>
<td>0.76 (0.56–0.89)</td>
</tr>
<tr>
<td>Other gram-positive</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>0.60 (0.41–0.76)</td>
</tr>
<tr>
<td>Bacillus spp.</td>
<td>0.51 (0.39–0.62)</td>
</tr>
<tr>
<td>Corynebacterium spp.</td>
<td>0.48 (0.35–0.62)</td>
</tr>
</tbody>
</table>

\(^1\)Staphylococcus aureus, Streptococcus, and Streptococcus-like organisms and coliforms.
\(^2\)NAS, Corynebacterium spp., and Bacillus spp.
\(^3\)Streptococcus and Streptococcus-like organisms: Aerococcus spp., Enterococcus, Lactococcus spp., and Streptococcus spp.
and US (0.49, SD = 0.20). The distribution for the herd-level proportion of high-risk cows within 56 herds is summarized using a ridgeline plot (i.e., overlapping density plots) in Figure 1. For each algorithm, a wide range in the proportion of high-risk cows per herd was observed, including Dutch (0.00–0.84), NZ (0.09–1.00), UK (0.00–0.67), and US (0.00–0.92).

**Evaluating the Importance of Clinical Mastitis as a Criterion.** Removal of clinical mastitis criteria for each algorithm had little effect on the algorithm classification of cows, which is evidenced by substantial agreement between algorithm status with and without clinical mastitis as a criterion ($\kappa > 0.95$). For the NZ algorithm, removal of the clinical mastitis criterion resulted in 36/996 (3.6%) high-risk cows shifting to low risk. Of these 36 cows, 15 (41.7%) had an IMI. Removal of clinical mastitis criterion for the UK algorithm caused 14/495 (2.8%) of high-risk cows to shift to low risk, of which 6 (42.9%) had an IMI. Removal of the clinical mastitis criterion for the US algorithm caused 4/793 (0.5%) high-risk cows to shift to low risk, none of which had IMI.

**DISCUSSION**

As producers and veterinarians continue to rely on indirect testing to determine which quarters or cows have a high risk of having an IMI at the time of dry-off, it is imperative that we continue to investigate and optimize predictive algorithms to guide SDCT. Determining which algorithm is best for an individual farm is dependent on the producer’s attitude toward risk (i.e., how many IMI and what type is he or she willing to leave untreated) and their relative aspirations for antimicrobial reduction. If the goal is to minimize the risk of not treating a cow with an IMI (i.e., false-negatives), one should choose the test with the highest Se and NPV. If the intent is to maximize reductions in antimicrobial use, the test that provides the highest Sp and PPV might be chosen, thereby reducing the number of false-positive cows. Here, the abilities for each of 4 individual data-driven algorithms to predict an IMI with any pathogen or any major pathogen in late-lactation cows were explored.

**All Algorithms Had Poor Agreement with Cow-Level IMI Status**

We evaluated test characteristics by applying the respective criteria to one large data set containing historical and microbiological data for 1,594 cows from 56 US dairy herds. All algorithms had poor agreement with
cow-level IMI status, with κ values ranging from 0.05 to 0.13. Furthermore, test Se values were all ≤70%, and Sp values all ≤75%. The NZ algorithm achieved the highest Se by applying relatively low SCC thresholds (120,000 and 150,000 cells/mL for parity = 1 and parity >1 cows) over the entire lactation. Although this approach classified more infected cows as high risk than other algorithms (Se = 0.69), it also classified a greater proportion of uninfected cows as high risk (1 – Sp = 0.56) and classified more cows as high risk in general (63%, Table 5). In contrast, the UK algorithm had the highest Sp (0.75) and classified only 31% of cows as high risk, indicating that this approach could result in greater reductions in antibiotic use at dry-off than other approaches. However, this algorithm had the lowest Se (0.37), indicating that 63% of infected cows would not be treated if this approach had been implemented for the cows in this study. We hypothesize that this pattern of low Se and high Sp is due to the UK algorithm using relatively high SCC thresholds (200,000 cells/mL) and restricting to the final 3 SCC of the lactation. The Se and Sp estimates for US and Dutch algorithms appeared to be more balanced than NZ and UK algorithms, albeit at low values.

**Sensitivity of Algorithms Was Higher for IMI Caused by Traditionally Recognized Pathogens**

As previously documented in similar algorithm studies, Se increased when IMI definitions were restricted to only include major pathogens (McDougall and Compston, 2014; Rowe et al., 2020d). This is as expected, as major-pathogen IMI more commonly cause increases in SCC than IMI caused by non-major pathogens (Petzer et al., 2017). Algorithms with higher SCC thresholds (UK) or algorithms using only a single test date approaching dry-off (Dutch) appreciated more gains in Se for similar reasons, with the latter attributed to the transient nature of major infections (less false positives than the other algorithms) versus the timing of sampling for culture. One must also consider species-specific pathogenicity as related to non-major pathogens. Non-aureus *Staphylococcus* spp. and *Corynebacterium* spp. are known to produce a limited or absent inflammatory response and often do not result in clinical signs (De Vliegher et al., 2012; Vanderhaeghen et al., 2015; Schwarz et al., 2019). Previous research on the pathogenesis of specific NAS at dry-off is limited, but research at the group level outlines their transient nature and high spontaneous elimination rates (Wilson et al., 1999) and limited associations with postcalving clinical mastitis (Rowe et al., 2021a). Furthermore, NAS commonly colonize the teat canal of cows without causing an IMI, which can cause false-positive diagnoses when milk samples are tested using culture or PCR (Hiittö et al., 2016). It is for these reasons that some experts recommend only the treatment of cows with major pathogens at dry-off and why algorithm analysis is often restricted to these organisms (Österås and Solvørod, 2009; Lipkens et al., 2019). Therefore, we hypothesize that failing to treat cows infected with non-major pathogens would have limited effects on udder health. However, clinical trials are required to compare postcalving health in treated and untreated cows that are infected with non-major pathogens.

**Sensitivity Was Higher for IMI Caused by Traditionally Recognized Pathogens**

Aerobic culture results indicated a limited number of IMI characterized as major mastitis pathogens despite our large sample size of cows and farms. However, we were still able to highlight differences in test characteristics by pathogen. Our findings indicated that many of the strategies had relatively high Se for detection of *Streptococcus uberis, Streptococcus dysgalactiae, Staphylococcus aureus,* and *Lactococcus lactis* (Table 4), which are often associated with clinical mastitis in American herds (Lago et al., 2011; Scillieri Smith et al., 2020). This aligns with research that shows that IMI caused by these organisms during lactation are often associated with chronic subclinical infections marked by increases in SCC (Zadoks et al., 2003; Wyder et al., 2011; Scillieri Smith et al., 2020). Furthermore, IMI caused by these pathogens in late lactation has been associated with postcalving clinical and subclinical mastitis in the subsequent lactation (Green et al., 2002; Rowe et al., 2021a). It should be noted that for the Dutch algorithm, *Staphylococcus aureus* had the lowest Se (0.60); characteristics of this organism include large variations in SCC dependent upon inflammatory episodes or strain type (Sears et al., 1990; Dingwell et al., 2006), and often the summary effect of increasing SCC over time is a better indication of IMI (Djabri et al., 2002). It is therefore plausible that a single SCC test may not be sufficient to reliably detect quarters infected with *Staphylococcus aureus* at dry-off.

**Potential Reasons for Poor Test Characteristics for Algorithms**

Limitations in the ability of algorithms to detect IMI caused by all pathogens at dry-off has been identified in numerous studies (Torres et al., 2008; Gohary and McDougall, 2018; Rowe et al., 2020d). This may be partially attributed to the presence of IMI with limited pathogenicity, as outlined in the previous section. In addition, accuracy of algorithms may also be affected

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**Characteristics for Algorithms**

**Potential Reasons for Poor Test Characteristics for Algorithms**

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*Journal of Dairy Science* Vol. 104 No. 10, 2021
by their SCC thresholds and number of tests evaluated. For example, if SCC are measured on a monthly basis, there will be a lag between milk sampling for SCC and the dry-off event, during which time the infection status of the cow may change. Finally, factors other than IMI can influence SCC such as parity and genetics (Schepers et al., 1997; Petzer et al., 2017). Relationships among these factors as well as with mastitis pathogens, or the host-pathogen-environmental interactions, can alter immune response and manifest as changes in SCC.

Despite poor agreement of algorithm risk status assignment and IMI status, algorithm-guided SDCT has been successfully implemented in the field. For example, clinical trials have validated the use of the UK (Bradley et al., 2010), and US (Rowe et al., 2020a,b) algorithms. Furthermore, a simulation model (Scherpenzeel et al., 2016) using data from a field study (Scherpenzeel et al., 2014) demonstrated that the Dutch algorithm could reduce antibiotic use with only small increases in postcalving clinical (incidence rate ratio = 1.04) and subclinical mastitis (prevalence ratio = 1.1). Subsequent work by the same research group using census data of Dutch dairy herds recently concluded that a nation-wide ban on blanket DCT in 2013, and subsequent adoption of SDCT had limited effects on udder health (Santman-Berends et al., 2021). One potential explanation for ongoing success of these programs on well-managed dairies is that the NPV for major pathogen IMI are sufficiently high (≥0.87 for all algorithms in this study) to prevent the majority of IMI present at dry-off from persisting through the dry period to affect udder health in the subsequent lactation.

Inclusion of Clinical Mastitis into Algorithms Had a Limited Effect on Risk Profiling of Individual Cows

The addition of clinical mastitis criteria within each program had little effect on the algorithm classification of cows as evidenced by substantial agreement between risk status using algorithms with and without clinical mastitis as a criterion (κ > 0.95). Therefore, its inclusion is unlikely to result in large improvements in test characteristics. However, given that records of mastitis cases for individual cows are usually readily available within on-farm data systems, it may be prudent to include clinical mastitis criteria in SDCT algorithms used in the field, as the risk for lactational clinical mastitis in our study herds was relatively low (18.1%) and herds were regularly conducting DHIA testing. Therefore, it cannot be determined if, applied on a farm with higher incidences of clinical mastitis or infrequent DHIA testing, algorithm sensitivities would improve with inclusion of this measure.

Comparisons Between Our Findings and Previous Test Characteristic Studies

Our analysis provides side-by-side comparisons of 4 distinct algorithms, applying each to the same data set and using only one laboratory for the reference test. The US and UK algorithms have been evaluated in field studies for health effects and test characteristics (Bradley et al., 2010; Rowe et al., 2020a,b,d). Other publications have documented test characteristics for the same or similar criteria as proposed with the NZ (Gohary and McDougall, 2018) and Dutch algorithms (Lipkens et al., 2019). Results of these studies vary with definitions of IMI, inclusion criteria for herds (e.g., bulk milk SCC was not an inclusion criterion in the current study), timing of milk sampling for culture and SCC, and farm management type. Therefore, caution should be taken when comparing test characteristics between studies. Challenges aside, for the US algorithm, previous findings documented higher Se for all pathogens (0.66) and major pathogens (0.72) and lower Sp (0.47 and 0.44, respectively; Rowe et al., 2020d) as compared with the current findings of 0.56 (Se, all pathogens), 0.59 (Se, major pathogens), 0.56 (Sp, all pathogens), and 0.52 (Sp, major pathogens). It should be noted that IMI was coded at the cow-level in the current study, and at the quarter-level in the previous study. Test characteristics were not formally reported in the original UK algorithm study, but quarter-level Se and Sp were 0.58 and 0.57, respectively, according to the culture data reported. Lipkens et al. (2019) evaluated the same SCC threshold as the UK algorithm from the last 3 tests (sans mastitis cases) in Belgian cows and found Se and Sp values to be 0.58 and 0.67, respectively, for major pathogens.

For a modified version of the NZ algorithm (a threshold of 150,000 cell/mL over the entire lactation for all parities), Se and Sp of 0.48 and 0.73 for all pathogens (Gohary and McDougall, 2018), and 0.85 and 0.72 for major pathogens were found (McDougall et al., 2017), respectively. Using ROC curves, this threshold was also later chosen as optimal SCC for indirectly detecting major pathogens using both the last test (0.71 and 0.80 for Se and Sp, respectively) and all tests (0.86 and 0.65 for Se and Sp, respectively; Gohary and McDougall, 2018). Test Se was better for detection of all pathogens in the current study (0.69 vs. 0.48), but worse for major pathogens (0.70 vs. 0.85). This may be due to different pathogen profiles among cows managed on pasture (i.e., NZ) and in confinement (US). Furthermore, parity specific thresholds were used in the current study, as was the recommendation for New Zealand dairy farmers (DairyNZ, 2012). It should be noted that recommendations for New Zealand dairy farmers were recently
changed to be less prescriptive with regard to SCC thresholds (DairyNZ, 2020), which is consistent with our conclusion that no single algorithm is appropriate for all producers.

Using data from 15 Flemish herds, Lipkens et al. (2019) evaluated a 100,000 cells/mL threshold for multiparous cows and a 50,000 cells/mL threshold for primiparous cows (i.e., SCC cut-points used for the Dutch algorithm). Test Se and Sp for major pathogens were 0.73 and 0.40 for multiparous animals and 0.58 and 0.49 for primiparous animals, respectively, which equates to pooled estimates of 0.67 and 0.43, when standardizing for the prevalence of primiparous cows in this study (42%). This finding is similar to the Se (0.62) and Sp (0.52) identified in our study.

**Antibiotic Reductions from Implementing Algorithm-Guided SDCT Are Likely to Vary Between Herds**

Overall, the proportion of high-risk cows for each algorithm were 50%, 50%, 63%, and 31% for the Dutch, US, NZ, and UK, respectively, which highlights a major benefit to the use of these programs: a likely reduction in antibiotic use at dry-off of between 37% and 69%. Here, the NZ algorithm resulted in the smallest reductions, whereas UK experienced the largest reductions. It is important to emphasize that there was a large range in the proportion of cows classified as high risk among herds (Table 5 and Figure 1). For example, the Dutch algorithm classified 51% of cows as high risk in the average herd. However, the herd-prevalence of high-risk cows among study herds (n = 56) ranged from 0 to 84%, indicating that antibiotic reductions achieved using the Dutch algorithm for SDCT could range from 16 to 100%. Consequently, the expected cash impact of switching from BDCT to a SDCT program using this algorithm is likely to vary among US herds (Rowe et al., 2021b). Given this variation, we recommend that herds use their own data to estimate the effect of SDCT on antibiotic use at dry-off and likely cash impact (a SDCT partial budget calculator can be found at https://dairyknow.umn.edu/research/udder-health/selective-dry-cow-therapy-cost-calculator/). It is also expected that that prevalence of IMI at dry-off is likely to vary among herds, as was demonstrated for the herds in this data set (Rowe et al., 2019). Therefore, NPV and PPV should be estimated for individual herds as they will vary according to the prevalence of IMI (Rowe et al., 2020d).

**Strengths and Limitations of This Study**

**Internal Validity.** Apart from the performance of algorithm itself, another influence on estimates for algorithm Se and Sp is the reference test method, which involved aerobic culture of a single milk sample. Identifying an IMI using this method has an estimated Se and Sp of 0.65 and 0.95, respectively (Dohoo et al., 2011). It is therefore possible that the test characteristics for the algorithms reported in this study may be better than reported, which was demonstrated in a recent study by our group (Rowe et al., 2020d) using quantitative bias analysis (Lash et al., 2011). We chose to not conduct Bayesian latent class analysis (a statistical method that allows for imperfect reference tests) because our study objective was to compare our index tests (algorithms) to traditional bacteriology, which is the current test of choice for guiding antibiotic therapy in veterinary medicine. The reliability of herd-level estimates of algorithm risk status (outlined in Table 5 and Figure 1) are likely to vary among herds because the sample size for each herd was not adjusted to account for the number of cows in each herd.

**External Validity.** The collection of data from multiple herds and states increases the generalizability of our findings. However, readers should consider that herds were originally recruited using the following inclusion criteria: relationship with the University of Minnesota or Zoetis, milking size of greater than 200 cows, and the use of specific bedding types in lactating cows. Furthermore, additional herds were excluded due to poor quality data or failure to use DairyComp 305 software. These selection criteria could have favored selection of larger, well-managed herds, thus reducing the generalizability of our findings. We used IMI status in late lactation as a proxy for IMI status at dry-off, which may limit generalizability. However, pathogen profiles observed in this study were similar to recent surveys of US cows at dry-off (Rowe et al., 2020a,c). Furthermore, the cow-level IMI prevalence for all pathogens (47.8%) and major pathogens (16.2%) is comparable to herds in
Belgium (Lipkens et al., 2019) and New Zealand (Gohary and McDougall, 2018). However, major pathogen prevalence was slightly higher in Lipkens et al. (2019; 24.4%) and appreciably lower in Gohary and McDougall (2018; 4.6%).

CONCLUSIONS

We found that 4 algorithms had poor agreement with milk culture in late-lactation cows. No algorithm was able to simultaneously maximize Se and Sp for the detection of all IMI, with some algorithms having favorable Se and others having a more favorable Sp. We recommend that producers use algorithms that match their relative aspirations for reducing antibiotic use (high Sp, PPV) and minimizing untreated IMI at dry-off (high Se, NPV). Discussion of these considerations with the farm’s milk quality expert or veterinarian is recommended. We also found that the performance of algorithms varied among target pathogens, with higher test Se observed for cows infected with Strepococcus uberis and Staphylococcus aureus. Further studies are needed to describe the effect of IMI at dry-off so that algorithms can be refined to selectively target specific pathogens. Finally, we found that inclusion of clinical mastitis as an algorithm criterion had little effect on risk classification of cows, indicating that algorithms based on SCC alone may be equally effective when implemented in the field.

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