AASV Foundation – Final Report

Title: Does knowledge of testing procedures or the format of culture and susceptibility reports from veterinary diagnostic laboratories (VDLs) influence antimicrobial selection decisions?

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Statement of the problem

Antimicrobials are one of the greatest discoveries of humankind, providing life-saving interventions for infectious diseases in both humans and animals. Antimicrobials remain important for modern animal agriculture in order to prevent, control and treat animal diseases. The utility of antimicrobials as a tool is rapidly diminishing due to the drastic increase in antimicrobial resistance (AMR). This increase, threatens both human and animal health, in addition to the multibillion-dollar losses that occur each year due to medical costs and economic losses. In fact, a 2016 review on AMR used historical data to estimate that "by 2050, 10 million lives a year and a cumulative 100 trillion USD of economic output are at risk due to the rise of drug-resistant infections if we do not find proactive solutions now to slow down the rise of drug resistance.⁷" AMR is an ecosystem problem, affecting human, animal and environmental health.

In order to combat antimicrobial resistance, the judicious use of antibiotics is required across all species. In veterinary medicine, this approach relies on the use of diagnostic resources to correctly identify therapeutic opportunities, along with effective communication between case veterinarians and laboratory diagnosticians. Veterinary diagnostic laboratory (VDL) test results require useful context for accurate practitioner interpretation. Whether this context is included in the lab report or expected as common knowledge will vary by test and laboratory. Anecdotally, there are significant differences in the context and form of susceptibility reports between animal species and humans. Laboratories that utilize broth microdilution antimicrobial susceptibility testing (AST) will report a minimum inhibitory concentration (MIC) and interpretation breakpoints (susceptible (S), intermediate (I), resistant (R), or no interpretation (NI)) for each antimicrobial present in a microtiter plate. Standardization of AST, MIC breakpoints and interpretations are all established by the Clinical and Laboratory Standards Institute (CLSI) Veterinary Antimicrobial Susceptibility Testing (VAST) subcommittee in the U.S. Breakpoint values for each interpretation are meant to be species, disease, pathogen, drug and regimen specific. Today, AST reports are commonly software generated for efficiency, through legacy formatting and may cover a wide array of species. VDLs continue to make significant improvement efforts focused on data sharing between laboratories, creating clinic or laboratory specific antibiograms, managing data in real-time and utilizing electronic platforms to access and aggregate case diagnostic results. It is the responsibility of the practitioner to understand the context of AST, reporting and species-specific breakpoints in order to select the most appropriate antimicrobial therapy.

To address overall AMR, multidisciplinary teamwork and research design is required and includes training in veterinary medicine. High priority needs and recommended approaches have been defined by the National Action Plan for Combating Antibiotic-Resistant Bacteria and the Addressing Antibiotic Resistance report from the Joint APLU | AAVMC Task Force on Antibiotic Resistance in Production Agriculture^{5,1}. Task force recommendations, were to "(1) design and implement a model curriculum to improve awareness, understanding, and help in the implementation of effective actions to combat antibiotic resistance and (2) develop and

implement educational and informational strategies, tools and programs that focus on different groups extending across our education spectrum.¹" The AMR Core Competencies Working Group was then formed to further these education and outreach recommendations.² This working group includes AMR and academia experts that created learning outcomes for 3 educational levels. The advanced level includes 60 learning outcomes specific to veterinary students. Collectively, these efforts ultimately seek to change or improve the behavior of veterinarians towards more judicious use of antimicrobials.

A literature review revealed no systematic evaluations to determine whether knowledge of testing procedure or format of culture and susceptibility reports from VDLs influences antimicrobial selection decisions. To date, most veterinary-based behavioral research has been focused on perceptions of AMR, stewardship and prescribing. Objectives of this study were to determine if training on VDL AST processes, reporting and interpretation would change antimicrobial selection and if the format and context of antimicrobial susceptibility reports would influence selection of antimicrobials by swine-interested veterinary students and veterinarians. To this end, the current study provided a detailed training on the VDL processes on susceptibility testing and reporting as well as on CLSI interpretive context for swine cases in an attempt to alter participant behavior.

Objectives

- Determine if training how laboratory susceptibility results are generated changes antimicrobial selection.
- Determine if the format and context of antimicrobial susceptibility reports changes antimicrobial selection.

Materials and methods

No live animals or author-collected samples were utilized for this study. All cases and antimicrobial susceptibility reports were extrapolated from common swine presentations and previous VDL submissions with identifiers removed. An Institutional Review Board (IRB) application was completed and the study was declared exempt by the Iowa State University (ISU) Office for Responsible Research based on federal requirements. The training included the use of multiple forms of education materials, including the creation of 3 swine case scenarios, 3 susceptibility report types and 2 educational videos. To house these materials and provide participants with a free, online and authenticated training opportunity, the Moodle learning management system was utilized in collaboration with the Center for Food Security and Public Health (CFSPH) at ISU. Within the Moodle platform, 3 separate modules or participant enrollment groups were created for the study.

To create the training materials, the authors began by reviewing the Clinical and Laboratory Standards Institute (CLSI) VET08 performance standards document³. Next, a storyboard was created to organize video recording of the bacteria identification and susceptibility testing process. The entire process from sample arrival to the reporting of antimicrobial susceptibility testing (AST) results was then observed and recorded at the most proximal VDL. Four VDLs in the United States (U.S.) with extensive swine caseloads were then contacted to review the draft AST process video in order to identify potential differences between laboratories. Feedback and suggestions from 3 cooperating VDLs were gathered in a live review of the draft video via video conference and incorporated during subsequent video editing. To provide additional training on result interpretation and swine application, the CLSI VET09 document was incorporated into a second training video⁴.

Three cases, named A, B and C, were created as practicing veterinarian scenarios with a thorough history, gross necropsy description and associated images provided by the American Association of Swine Veterinarians (AASV) digital library. Culture results for all cases were presented in 3 different susceptibility report types. Bacteria with CLSI porcine-specific respiratory tract breakpoints were utilized to include *Actinobacillus pleuropneumoniae*, *Streptococcus suis, Pasteurella multocida* and *Bordetella bronchiseptica*⁴. The order of cases varied by participant group. The level of information provided in each susceptibility report, named report type 1, 2 and 3, increased with each presented case. Report type 1 was presented first and utilized a current VDL report format (Figure 1). Next, report type 2 was presented with the addition of the 2019 ISU VDL porcine antimicrobial susceptibility profiles (Figure 2)⁶. Lastly, report type 3 was presented to include the previous 2 formats, along with CLSI established porcine-specific respiratory tract breakpoint formulations (Figure 3)⁴.

The participant enrollment groups were named, Duroc, Hampshire and Landrace. Cases, report types, videos and questions were held constant across all groups, but presented order and combination of case and report type differed between groups. This 3-way crossover design gave each participant the opportunity to see all 3 cases and all 3 report types in order to increase study power without introducing bias from previous case exposure. Figure 4 provides the movement of participants through each enrollment group of the Moodle platform. If assigned to the Duroc group, participants would complete the following path. Upon module entry, participants completed 2 demographic questions related to individual veterinarian or student status and year(s) in school or practice. Next, participants entered the initial case review. Duroc participants were presented with case A and report type 1 (A1) first, followed by antimicrobial and administration route options for selection. Options included a primary and potential secondary antimicrobial for treatment, along with the route(s) of administration. Next, case B and report type 2 (B2) were presented with the same antimicrobial options for selection. Followed by case C and report type 3 (C3). After initial case treatments were selected, participants entered the video training portion of the module to complete both videos. Next, Duroc participants entered the post-video case review. Here, the same case and report type combinations (A1, B2 and C3) were repeated, in the same order. Participants were again directed to select a primary and potential secondary antimicrobial for treatment, along with administration route(s). The last section entered as the final questionnaire that contained 3 open-ended and 3 multiple-choice questions for participants.

Pilot testing of the Moodle platform was completed by graduate students outside of the study. Each student was enrolled into 1 of the 3 participant enrollment groups and recorded the time to complete each section and reported any issues with the assigned module. Overall, no operational or technical issues were reported with any of the modules and each student completed the assigned module, including the 2 videos in about 1 hour. The enrollment objective for this study was 120 voluntary participants, preferably 60 veterinarians and 60 veterinary students. Volunteer participants were swine-interested veterinarians or veterinary students that were recruited via weekly AASV electronic letter, e-mail invitation or by veterinary school instructors from March to May of 2020. The authors elected to extend the study period to 2 months to account for curriculum and marketing challenges surrounding the COVID-19 pandemic. Each volunteer contacted the primary or corresponding author to express interest in study participation. Participant names, e-mail addresses and status (veterinarian or student) were

then accumulated and provided to CFSPH personnel for sequential allocation into 1 of the 3 enrollment groups. CFSPH then provided Moodle access to each participant via a pre-established username and password combination. The remaining authors were blinded to participant enrollment, login information and response completions. All interested participants were enrolled into the study to account for possible incompletions. Overall, 117 veterinarians from 6 countries and 75 veterinary students from 15 U.S. colleges were provided Moodle login credentials by CFSPH.

The flow of each participant enrollment group through the Moodle platform is further detailed in Figure 4. After logging into the platform, participants began by answering 2 demographic questions, regarding status as either veterinarian or student and year in practice or school. Response options for years in practice were 0-7, 8-14, 15-21 or greater than 21. Options for years in veterinary school were 1, 2, 3 or 4. Next, participants entered the initial case review and were presented the 3 swine bacteriology cases (A, B and C); with 3 different levels of antimicrobial susceptibility reports (1, 2 and 3), order and combination differed between enrollment groups. Participants were directed to assume that the client had adequate funds, staffing and supplies for each treatment option and route. After reviewing each case, participants were prompted to select a single or combination treatment route. Next, participants were asked to select the best antimicrobial for each case and to specify the route of administration. Antimicrobial options were held constant to reflect current AST report formats, to include ampicillin (AMP), ceftiofur (XNL), clindamycin (CLI), danofloxacin (DANO), enrofloxacin (ENRO), florfenicol (FFN), gamithromycin (GAM), gentamicin (GEN), neomycin (NEO), penicillin (PEN), sulfadimethoxine (SDM), spectinomycin (SPE), tetracycline (TET), tiamulin (TIA), tildipirosin (TIP), tilmicosin (TIL), trimethoprim/sulphamethoxazole (SXT), tulathromycin (TUL), tylosin tartrate/base (TYLT) and no drug selection (NDS). Options for administration route included feed-delivered, water-delivered, injectable or an open answer option. If interested, a text box was provided for participants to justify the antimicrobial selections.

After completion of the initial case review, participants entered the video training portion of the platform. Participants were directed to watch the 2 pre-recorded videos, describing the bacteriology process and porcine-specific AST interpretations. At the end of each video, a color was presented and participants were required to select the correct color option prior to proceeding as a mechanism to ensure that both videos were completed. Upon exiting the video training, participants entered the post-video case review. Here, participants were presented with the same case and report type combinations as the initial case review. Participants were asked the same questions regarding antimicrobial selection and route(s) to allow participants to change original responses based on concepts discussed in the training videos. The same assumptions were in place, along with the opportunity to justify each answer. The last section of the platform was the final questionnaire, in which participants were asked 3 open ended questions and 3 multiple-choice questions. Questions focused on susceptibility report preference, usefulness of training and if the training influenced future antimicrobial selection decisions. At study end, CFSPH transferred all participant responses to the blinded authors via pre-established usernames. Ultimately, 75 veterinarians and 53 veterinary students completed the training module and were utilized for descriptive analysis, accounting for a response rate of 66% and 71%, respectively. The Duroc group was composed of 24 veterinarians and 22 students. The Hampshire group included 25 veterinarians and 18 veterinary students. While, the Landrace group included 28 veterinarians and 13 veterinary students.

Results

To evaluate the study objective, participant antibiotic selections were compared before and after the training module. Tables 1 through 3 display the total antimicrobial selection counts by enrollment group. Participants who did not elect to utilize a secondary antibiotic were instructed to select the NDS option. Therefore, only the 2nd rows have NDS responses. Given that the authors elected to utilize twenty antimicrobial response options in an effort to remain aligned with current VDL susceptibility reports, results are reported by percentage of participants that did or did not change selections and are visually displayed by case.

The columns in Figure 5, represent the percentage of participants that did and did not change antimicrobial selections based on report type for the 1st and potentially 2nd antimicrobial selection. On the horizontal axis, the report types are listed with the number and amount of susceptibility report information increasing from left to right. Listed below each report type is the comparison of either PRE/POS 1st or PRE/POS 2nd. Selections made prior to training are represented by PRE and selections made after training are represented by POS. The first antimicrobial selection is labeled as 1st and the second selection as 2nd. Therefore, the count of antimicrobial selection changes and no changes between each participant's 1st and 2nd antimicrobial selection were totaled for each report type and divided by the total number of participants. Overall, the percentage of participants that changed or did not change antimicrobial selection was consistent across report types, 32-42% of participants changed selections, while 58-68% of participants did not change selections. The same approach was repeated for Figures 6 and 7, but instead of report type, enrollment group and case were utilized, respectively. Comparing PRE and POS, the percentage of participants that changed or did not change antimicrobial selection remained nearly the same. For enrollment group, 30-42% of participants changed selections, leaving 58-70% of participants that did not change selections. For case, 28-48% of participants changed selections, thus 59-72% of participants did not change.

Looking at individual responses, a total of 23 participants did not change any antimicrobial selections, represented by 17 veterinarians or 22% of the vet study population and 6 veterinary students or 11% of the student study population. Fisher's exact test was used to determine if there was an association between changing responses and participant status as a vet or student, the number of years in veterinary practice, or the number of years in veterinary school. There were no statistical differences associated with the number of years a participant was in practice or school. There were 2 instances, where change in antimicrobial selection was statistically significant when comparing vets and students. Significance was set a priori at the level of P < .05. Within the Landrace group, when evaluating case A and using report type 2, enrolled vets were less likely to change their 1st antimicrobial choice after training completion than near equally distributed veterinary students (P = .023). The Hampshire group, when evaluating case C and using report type 2 was similar, in that veterinarians were less likely to change their 1st antimicrobial choice compared to veterinary students, who were more likely to change their 1st antimicrobial choice (P = .001). Contingency tables (4 and 5) display the participant response counts. Overall, veterinarians accounted for 79% and 78% of the responses that did not change antimicrobial selection, respectively for each instance.

The remaining Figures, 8 through 13, display the change in compiled antimicrobial selection counts by case. The count of each antimicrobial selection PRE and POS video training is displayed as a column for comparison. Columns were removed if an antimicrobial option was not selected PRE or POS training by all participants. The following antimicrobials were never

selected by participants and will therefore not be discussed in the below results, CLI, SPE and TYLT. Case A changes are displayed in Figures 8 and 9. Figure 8 includes compiled counts from all participants for case A PRE1st and case A POS1st. The most profound changes after training video completion included an increase in the selection of AMP and TIA, along with a decrease in selection of ENRO and TIL. In addition, no participants selected DANO, GAM, GEN, NEO, TET or NDS as the first treatment choice. Figure 9 includes compiled counts from case A PRE2nd and case A POS2nd. For the second antimicrobial selection, the greatest changes included an increase in FFN and NDS selections, and a decrease in AMP and XNL. The following were not selected as a second treatment choice, GAM, GEN, NEO or TET. Case B changes are shown in Figures 10 and 11. Figure 10 includes compiled counts for case B PRE1st and case B POS1st. The largest changes included an increase in the selection of AMP and a decrease in the selection of XNL and SXT. No participants selected DANO, GAM, SDM, TUL or NDS. Figure 11 displays counts for case B PRE2nd and case B POS2nd. The greatest selection increase was for TIA and NDS, and the greatest decrease was AMP and GEN. No selections were made for DANO, GAM, SDM, TIP or TUL. Case C changes are in Figures 12 and 13. Figure 12 includes count selections for case C PRE1st and case C POS1st. The largest changes after training included an increase in the selection of FFN and a decrease in selection of ENRO. No participants selected DANO, GAM, SDM, SXT or NDS. Figure 13 displays counts for case C PRE2nd and case C POS2nd. The greatest selection increase was for FFN and NDS, and the greatest decrease was TET. No selections were made for XNL, DANO or SDM.

The final questionnaire of the study included 3 multiple-choice and 3 open-ended questions regarding the training. Two participants did not answer any open-ended questions. The multiple-choice response options were strongly agree, agree, neither agree nor disagree, disagree and strongly disagree. When participants were asked if "the training was a useful adjunct to my veterinary pharmacology training," 93% agreed or strongly agreed. When asked if the "participant would recommend this training to a colleague," 90% agreed or strongly agreed. When asked if "this training has influenced my future antimicrobial selection decisions," 74% agreed or strongly agreed. For the open-ended questions, when asked which report style was preferred, 4% of participants chose the current VDL report format (report type 1), with repeat comments that "the less info the better" and "it is what I am used to." For the next level, 18% of participants chose report type 2, which included the ISU VDL historical susceptibility information, comments included that this was "the least confusing option" and participants "liked having the VDL data readily available." Report type 3, the most complex option, included the CLSI breakpoint information and was selected by 76% of participants. Comments included "the more information the better" and participants "liked having VDL and breakpoint data to make the best decision."

The remaining open-ended questions asked participants what they learned from the 2 training videos and what the positive and negative aspects of the training were. Summarized comments regarding knowledge gained from the training videos included a better understanding of: today's laboratory process (57%), CLSI breakpoint information (40%), antimicrobial characteristics (32%), susceptibility charts (18%), and the importance of animal selection and sample handling (5%). Regarding the positive and negative aspects of the training, participants made the following comments: it was a quality review (32%), enjoyed the real cases (18%), enjoyed reviewing the laboratory process (18%), wanted the best answer at the end (15%), enjoyed the videos (14%), wanted a summary review or reference document (13%), wanted to learn how to pick the best antibiotic and apply the CLSI information (12%), and had issues

navigating the website or loading the content (10%). Overall, individual participant comments were thankful for the training and frequently mentioned the need for similar and more in-depth opportunities in the future.

Discussion

The goal in development of this training was to provide an open-access, no cost, time conscious training for swine-interested veterinary participants. Given the response rate and openended comments, all collected during a global pandemic, veterinarians and veterinary students are clearly eager for such opportunities. The study was designed to utilize 3 participant enrollment groups to rule-out potential selection differences based on case order, and the combination of case and report type. To identify selection differences based on report type, the information reported increased with each case. Report type 1 represented the current VDL format, and always preceded type 2 and type 3, respectively. Given that practitioners are currently expected to interpret and implement antimicrobial selections from report type 1, the authors elected to utilize the 19 antimicrobial options on this report for participant response options. This approach allowed the results to remain consistent, while minimizing the risk of selection bias by the authors, which could have potentially influenced participant selections. This outweighed impact on statistical analysis.

No correct answer was selected or provided to participants after case completion. This was discussed extensively by the authors and elected since several antimicrobial options could be considered appropriate and justified for each case. The authors wished to re-emphasize the importance of case or individual-based antimicrobial selection versus the utilization of a blanketed approach. Inclusion criteria for participants was generalized to swine-interested veterinarians or veterinary students. For this initial study, participants were not screened for completion of basic pharmacology coursework or practicing country. This was justified, given the training and 19 broad antimicrobial options. The authors recognize that answers for these participants would cause more response variation due to the lack of structured pharmacology training, along with differences in antimicrobial approvals, availability and regulatory guidelines for each country. Overall, the focus of this study was if participants would change answers based on provided training or report types, not if the participant selected the potentially correct antimicrobial option. However, this is an important consideration for future studies.

The percentage of participants that changed or did not change antimicrobial selections PRE and POS training remained consistent between not only report type, but also enrollment group and case. Ultimately, 28-48% of participants changed selections, while 58-72% did not change selections. Overall and for 2 case and report combinations, veterinarians were the least likely to change answers after training. This finding could explain the wider variation of change seen with the Landrace group, which included 28 veterinarians and 13 veterinary students. Ideally, participants would be more evenly distributed by status in the future, but for this study, less veterinary students in the Landrace group completed the voluntary training. There are several potential behavioral explanations for the consistent response ranges. It is well-known that anecdotal treatment outcomes drive current antimicrobial selections. This is a component of practice experience, if a treatment works well in a patient or population, it is likely to be repeated in another patient or population; if the treatment does not work well, it will not be repeated. Based on participant comments, experience with similar cases drove many of the antimicrobial selections; an appropriate response with proper foundation in laboratory testing and AST report interpretation. The higher percentage of participants who did not change selections, may have this foundation and the training just reemphasized key points, thus no change. Whereas the participants that changed selections may be lacking in this foundation and the training either improved understanding or made report interpretation even more complex with additional context. To assess these findings, additional studies with more specific participant inclusion and exclusion criteria are needed, perhaps the use of more novel case presentations to reduce anecdotal selections, along with specific antimicrobial treatment regimens as selections versus broad categories. With this approach, a correct answer could be selected by the authors, along with potential to provide feedback as to why it was correct compared to other options.

The final questionnaire responses were encouraging that greater than or equal to 90% of participants found the training useful and were likely to recommend it to a colleague. However, the responses on the training impact and report type were the most interesting. First, 74% of participants felt that the training influenced future antimicrobial selection decisions, yet only 28-48% of participants changed selections after the training. This provides additional evidence that the training likely reemphasized key points for at least a subset of the 58-72% of participants that did not change answers. Next, only 4% of participants preferred the current reporting format, while 76% preferred the most complex version with historical VDL and CLSI breakpoint information. This drives home the point that veterinarians and students are not only eager to learn more, but want more evidence available to assist in antimicrobial selection decisions. Per CLSI standards, all aspects of report type 1 should be provided in AST reports as a mechanism of standardization. Therefore, the addition of report types 2 and 3 will likely not be provided on AST reports, but they could be provided as open-access resources for practitioners as done by ISU VDL.⁶ It is also becoming more common for production systems and veterinary clinics to make personalized antibiograms based on historical AST results.

The open-ended responses were also enlightening as participants frequently mentioned a better understanding of the bacteriology process, CLSI breakpoints, antimicrobial characteristics and susceptibility charts. All of this information is essential for appropriate sample collection and submission, along with AST report interpretation and antimicrobial selection. Therefore, this and similar training has the potential to influence future prescribing, quality of VDL submissions, accuracy of diagnoses and patient treatment responses. Given the open-responses, it is clear that the study participants wanted more, including a third video to apply report type 3. Thereafter, ranked antimicrobial selections with justification could be provided, along with a reference document for future use. Considerations should be made to prioritize this type of training into student seminars or veterinary meetings with continuing education. This approach would reach a broader audience, who may not normally volunteer for such an opportunity. It would also allow for more discussion on the ambiguous topic of antimicrobial selection in veterinary medicine.

Figures and tables

Table 1: Duroc group (order A1B2C3) total antimicrobial selection counts. Acronyms for the antimicrobial options are listed by column. Each row is a combination of case, report type, selection prior to or after training video completion and first or second antimicrobial treatment option. Paired PRE and POS responses are shaded the same color. The numbers represent the compiled response count for each antimicrobial selection by question and antimicrobial.

	*AMP	XNL	CLI	DANO	ENRO	FFN	GAM	GEN	NEO	PEN	SDM	SPE	TET	TIA	TIP	TIL	SXT	TUL	TYLT	NDS
[†] A1PRE1st	13	0	0	0	9	5	0	0	0	2	1	0	0	4	0	4	0	8	0	0
A1POS1st	22	1	0	0	5	4	0	0	0	0	0	0	0	5	0	2	1	6	0	0
A1PRE2nd	4	2	0	1	1	3	0	0	0	1	0	0	0	7	1	7	2	4	0	13
A1POS2nd	0	1	0	0	0	6	0	0	0	0	0	0	0	10	0	6	1	2	0	20
B2PRE1st	18	4	0	0	2	12	0	3	1	2	0	0	0	2	0	0	2	0	0	0
B2POS1st	25	3	0	0	3	9	0	0	0	2	0	0	0	3	0	0	1	0	0	0
B2PRE2nd	5	0	0	0	2	6	0	1	0	4	0	0	0	7	0	0	1	0	0	20
B2POS2nd	2	0	0	0	2	8	0	0	0	4	0	0	1	11	0	0	1	0	0	17
C3PRE1st	1	1	0	0	23	4	0	4	0	0	0	0	3	0	5	2	0	3	0	0
C3POS1st	2	2	0	0	23	10	0	2	0	1	0	0	0	0	4	0	0	2	0	0
C3PRE2nd	0	0	0	0	2	9	0	2	1	0	0	0	5	0	1	1	0	0	0	25
C3POS2nd	0	0	0	0	1	12	0	0	0	0	0	0	1	0	1	2	0	1	0	28

*Antimicrobial options: ampicillin (AMP), ceftiofur (XNL), clindamycin (CLI), danofloxacin (DANO), enrofloxacin (ENRO), florfenicol (FFN), gamithromycin (GAM), gentamicin (GEN), neomycin (NEO), penicillin (PEN), sulfadimethoxine (SDM), spectinomycin (SPE), tetracycline (TET), tiamulin (TIA), tildipirosin (TIP), tilmicosin (TIL), trimethoprim/sulphamethoxazole (SXT), tulathromycin (TUL), tylosin tartrate/base (TYLT) and no drug selection (NDS)

[†]Combination of case (A, B or C), report type (1, 2 or 3), selections prior (PRE) or after (POS) training and first (1st) or second (2nd) antimicrobial option

Table 2: Hampshire group (order B1C2A3) total antimicrobial selection counts. Acronyms for the antimicrobial options are listed by column. Each row is a combination of case, report type, selection prior to or after training video completion and first or second antimicrobial treatment option. Paired PRE and POS responses are shaded the same color. The numbers represent the compiled response count for each antimicrobial selection by question and antimicrobial.

	*AMP	XNL	CLI	DANO	ENRO	FFN	GAM	GEN	NEO	PEN	SDM	SPE	TET	TIA	TIP	TIL	SXT	TUL	TYLT	NDS
[†] A3PRE1st	3	9	0	0	9	5	0	0	0	0	0	0	0	11	3	1	0	2	0	0
A3POS1st	7	7	0	0	6	6	0	0	0	0	0	0	0	12	3	0	0	2	0	0
A3PRE2nd	3	4	0	0	3	3	0	0	0	0	1	0	0	16	0	1	1	1	0	10
A3POS2nd	2	0	0	0	3	3	0	0	0	0	1	0	0	15	1	2	0	1	0	15
B1PRE1st	21	2	0	0	0	2	0	3	2	0	0	0	0	6	1	1	5	0	0	0
B1POS1st	27	1	0	0	2	5	0	3	0	2	0	0	0	3	0	0	0	0	0	0
B1PRE2nd	9	3	0	0	4	2	0	4	0	2	0	0	0	5	0	1	1	0	0	12
B1POS2nd	1	2	0	0	1	3	0	0	1	1	0	0	0	11	0	2	2	0	0	19
C2PRE1st	2	2	0	0	32	1	0	3	1	0	0	0	1	1	0	0	0	0	0	0
C2POS1st	2	0	0	0	30	3	0	5	0	0	0	0	0	0	3	0	0	0	0	0
C2PRE2nd	0	0	0	0	6	4	0	1	1	0	0	0	1	1	0	1	1	0	0	27
C2POS2nd	0	0	0	0	2	5	0	3	0	0	0	0	0	0	0	1	0	0	0	32

*Antimicrobial options: ampicillin (AMP), ceftiofur (XNL), clindamycin (CLI), danofloxacin (DANO), enrofloxacin (ENRO), florfenicol (FFN), gamithromycin (GAM), gentamicin (GEN), neomycin (NEO), penicillin (PEN), sulfadimethoxine (SDM), spectinomycin (SPE), tetracycline (TET), tiamulin (TIA), tildipirosin (TIP), tilmicosin (TIL), trimethoprim/sulphamethoxazole (SXT), tulathromycin (TUL), tylosin tartrate/base (TYLT) and no drug selection (NDS)

[†]Combination of case (A, B or C), report type (1, 2 or 3), selections prior (PRE) or after (POS) training and first (1st) or second (2nd) antimicrobial option

Table 3: Landrace group (order C1A2B3) total antimicrobial selection counts. Acronyms for the antimicrobial options are listed by column. Each row is a combination of case, report type, selection prior to or after training video completion and first or second antimicrobial treatment option. Paired PRE and POS responses are shaded the same color. The numbers represent the compiled response count for each antimicrobial selection by question and antimicrobial.

	*AMP	XNL	CLI	DANO	ENRO	FFN	GAM	GEN	NEO	PEN	SDM	SPE	TET	TIA	TIP	TIL	SXT	TUL	TYLT	NDS
[†] A2PRE1st	9	8	0	0	6	6	0	0	0	0	0	0	0	3	2	4	1	2	0	0
A2POS1st	11	7	0	0	5	5	0	0	0	0	0	0	0	6	0	2	2	3	0	0
A2PRE2nd	6	0	0	0	2	4	0	0	0	0	0	0	0	10	0	2	1	2	0	14
A2POS2nd	5	0	0	0	0	7	0	0	0	0	0	0	0	11	1	3	1	1	0	12
B3PRE1st	19	6	0	0	1	8	0	0	0	1	0	0	1	4	0	0	1	0	0	0
B3POS1st	22	1	0	0	2	10	0	0	0	2	0	0	0	3	0	0	1	0	0	0
B3PRE2nd	6	1	0	0	0	6	0	1	0	1	0	0	1	9	0	0	1	0	0	15
B3POS2nd	5	2	0	0	1	7	0	0	0	0	0	0	1	8	0	0	1	0	0	16
C1PRE1st	0	1	0	0	29	3	0	1	2	0	0	0	0	0	4	0	0	1	0	0
C1POS1st	2	1	0	0	23	8	0	1	1	1	0	0	0	0	2	0	0	2	0	0
C1PRE2nd	2	0	0	0	0	5	0	2	2	1	0	0	3	0	1	1	1	0	0	23
C1POS2nd	1	0	0	0	1	8	1	0	0	1	0	0	2	0	1	2	1	0	0	23

^{*}Antimicrobial options: ampicillin (AMP), ceftiofur (XNL), clindamycin (CLI), danofloxacin (DANO), enrofloxacin (ENRO), florfenicol (FFN), gamithromycin (GAM), gentamicin (GEN), neomycin (NEO), penicillin (PEN), sulfadimethoxine (SDM), spectinomycin (SPE), tetracycline (TET), tiamulin (TIA), tildipirosin (TIP), tilmicosin (TIL), trimethoprim/sulphamethoxazole (SXT), tulathromycin (TUL), tylosin tartrate/base (TYLT) and no drug selection (NDS)

[†]Combination of case (A, B or C), report type (1, 2 or 3), selections prior (PRE) or after (POS) and first (1st) or second (2nd) option

Table 4: Landrace enrollment group veterinarian and veterinary student response and total counts for whether antimicrobial selection was changed or not between the training videos for the 1st antimicrobial selection (PRE/POS1st) when presented case A and report type 2.

	Veterinarian responses	Veterinary student responses	Total counts
Changed antimicrobial selection	5	7	12
Did not change antimicrobial selection	23	6	29
Total counts	28	13	41

*Change in antimicrobial selection between vet and student was statistically significant (P = .023)

Table 5: Hampshire enrollment group veterinarian and veterinary student response and total counts for whether antimicrobial selection was changed or not between the training videos for the 1st antimicrobial selection (PRE/POS1st) when presented case C and report type 2.

	Veterinarian responses	Veterinary student responses	Total counts
Changed antimicrobial selection	4	12	16
Did not change antimicrobial selection	21	6	27
Total counts	25	18	43

*Change in antimicrobial selection between vet and student was statistically significant (P = .001)

	Actinobacillus pleuropneumoniae	Actinobacillus pleuropneumoniae				
Antimicrobial	– Pig 1	– Pig 2				
	*Int/MIC	*Int/MIC				
Ampicillin	S / <=0.2500	S / <=0.2500				
Ceftiofur	I / 4.0000	S / <=0.2500				
Clindamycin	R / 8.0000	R / 8.0000				
Danofloxacin	NI / <=0.1200	NI / <=0.1200				
Enrofloxacin	S / <=0.1200	I / 0.5000				
Florfenicol	S / 0.5000	S / 0.5000				
Gamithromycin	NI / 2.0000	NI / 2.0000				
Gentamicin	R / 8.0000	R / 8.0000				
Neomycin	R / 16.0000	R / 16.0000				
Penicillin	I / 0.5000	I / 0.5000				
Sulfadimethoxine	S / <=256.0000	S / <=256.0000				
Spectinomycin	NI / 64.0000	NI / 64.0000				
Tetracycline	R / >8.0000	R / >8.0000				
Tiamulin	S / 8.0000	S / 8.0000				
Tildipirosin	S / 4.0000	S / 4.0000				
Tilmicosin	S / 8.0000	S / 8.0000				
Trimethoprim/ Sulphamethoxazole	S / <=2.0000	S / <=2.0000				
Tulathromycin	S / 16.0000	S / 16.0000				
Tylosin (Tartrate/Base)	R / 32.0000	R / >32.0000				
	**Int/MIC = Interpretation/Minimum Inhibitory Concentration; S = Susceptible, I = Intermediate, R = Resistant, NI = no interpretation available based on antimicrobial, organism, species, and tissue combination; MIC levels are given in mcg/ml. In vitro antimicrobial test results do not represent therapeutic recommendations from the VDL or personnel therein. Extra/Off label usage of an antimicrobial, which is limited/prohibited for certain species may result in legal action by FDA-CVM.					

Figure 1: An example of the case antimicrobial susceptibility testing results presented and defined to study participants as report type 1. This report reflected current VDL report formats.

Antimicrobial	Actinobacillus pleuropneumoniae – Pig 1	Actinobacillus pleuropneumoniae – Pig 2	ISU VDL's Antimicrobial Susceptibility Profile for Actinobacillus pleuropneumoniae in 2018
	*Int/MIC	*Int/MIC	% susceptible (number tested)
Ampicillin	S / <=0.2500	S / <=0.2500	93% (67)
Ceftiofur	I / 4.0000	S / <=0.2500	100% (67)
Clindamycin	R / 8.0000	R / 8.0000	0% (67)
Danofloxacin	NI / <=0.1200	NI / <=0.1200	NI
Enrofloxacin	S / <=0.1200	I / 0.5000	100% (67)
Florfenicol	S / 0.5000	S / 0.5000	99% (67)
Gamithromycin	NI / 2.0000	NI / 2.0000	NI
Gentamicin	R / 8.0000	R / 8.0000	0% (67)
Neomycin	R / 16.0000	R / 16.0000	19% (67)
Penicillin	I / 0.5000	I / 0.5000	1% (67)
Sulfadimethoxine	S / <=256.0000	S / <=256.0000	81% (67)
Spectinomycin	NI / 64.0000	NI / 64.0000	3% (67)
Tetracycline	R / >8.0000	R / >8.0000	0% (31)
Tiamulin	S / 8.0000	S / 8.0000	99% (67)
Tildipirosin	S / 4.0000	S / 4.0000	100% (31)
Tilmicosin	S / 8.0000	S / 8.0000	84% (67)
Trimethoprim/ Sulphamethoxazole	S / <=2.0000	S / <=2.0000	99% (67)
Tulathromycin	S / 16.0000	S / 16.0000	52% (67)
Tylosin (Tartrate/Base)	R / 32.0000	R / >32.0000	0% (67)
	**Int/MIC = Interpretation Concentration; $S = SuscentR = Resistant, NI = no intro-based on antimicrobial, ontissue combination; MIC ofmcg/ml. In vitro antimicrorepresent therapeutic recoVDL or personnel thereinan antimicrobial, which iscertain species may result$	 Data reported as: % susceptible (# isolates tested). In Aug of 2018 a new test was added including: Tetracycline, Tildipirosin, and Gamithromycin. Oxytetracycline and Chlortetracycline were removed at this time. 	

Figure 2: An example of the case antimicrobial susceptibility testing results presented and defined to study participants as report type 2. This report contained the current VDL report format with the addition of the ISU VDL porcine antimicrobial susceptibility profiles.⁶

Antimicrobial	Actinobacillus pleuropneumoniae – Pig 1	Actinobacillus pleuropneumoniae – Pig 2	ISU VDL's Antimicrobial Susceptibility Profile for Actinobacillus pleuropneumoniae in 2018	CLSI Established Porcine-Specific Respiratory Tract Breakpoints
	*Int/MIC	*Int/MIC	% susceptible (number tested)	Actinobacillus pleuropneumoniae
Ampicillin	S / <=0.2500	S / <=0.2500	93% (67)	Injectable
Ceftiofur	I / 4.0000	S / <=0.2500	100% (67)	Injectable
Clindamycin	R / 8.0000	R / 8.0000	0% (67)	
Danofloxacin	NI / <=0.1200	NI / <=0.1200	NI	
Enrofloxacin	S / <=0.1200	I / 0.5000	100% (67)	Injectable
Florfenicol	S / 0.5000	S / 0.5000	99% (67)	Feed
Gamithromycin	NI / 2.0000	NI / 2.0000	NI	
Gentamicin	R / 8.0000	R / 8.0000	0% (67)	
Neomycin	R / 16.0000	R / 16.0000	19% (67)	
Penicillin	I / 0.5000	I / 0.5000	1% (67)	
Sulfadimethoxine	S / <=256.0000	S / <=256.0000	81% (67)	
Spectinomycin	NI / 64.0000	NI / 64.0000	3% (67)	
Tetracycline	R / >8.0000	R / >8.0000	0% (31)	Injectable
Tiamulin	S / 8.0000	S / 8.0000	99% (67)	Water
Tildipirosin	S / 4.0000	S / 4.0000	100% (31)	Injectable
Tilmicosin	S / 8.0000	S / 8.0000	84% (67)	Feed
Trimethoprim/ Sulphamethoxazole	S / <=2.0000	S / <=2.0000	99% (67)	
Tulathromycin	S / 16.0000	S / 16.0000	52% (67)	Injectable
Tylosin (Tartrate/Base)	R / 32.0000	R / >32.0000	0% (67)	
	**Int/MIC = Interpreta Inhibitory Concentratio Intermediate, R = Resis interpretation available antimicrobial, organism combination; MIC leve In vitro antimicrobial to represent therapeutic re the VDL or personnel to usage of an antimicrob limited/prohibited for co result in legal action by	m; S = Susceptible, I = stant, NI = no e based on n, species, and tissue ls are given in mcg/ml. est results do not ecommendations from herein. Extra/Off label ial, which is ertain species may	 Data reported as: % susceptible (# isolates tested). In Aug of 2018 a new test was added including: Tetracycline, Tildipirosin, and Gamithromycin. Oxytetracycline and Chlortetracycline were removed at this time. 	- The listed route(s) are the administration route(s) that were utilized to create the CLSI breakpoint for the corresponding pathogen. Each route and pathogen combination follows a specific antimicrobial regimen.

Figure 3: An example of the case antimicrobial susceptibility testing results presented and defined to study participants as report type 3. This report reflected the current VDL report format, ISU VDL porcine antimicrobial susceptibility profiles and CLSI established porcine-specific respiratory tract breakpoint formulations.^{6,4}

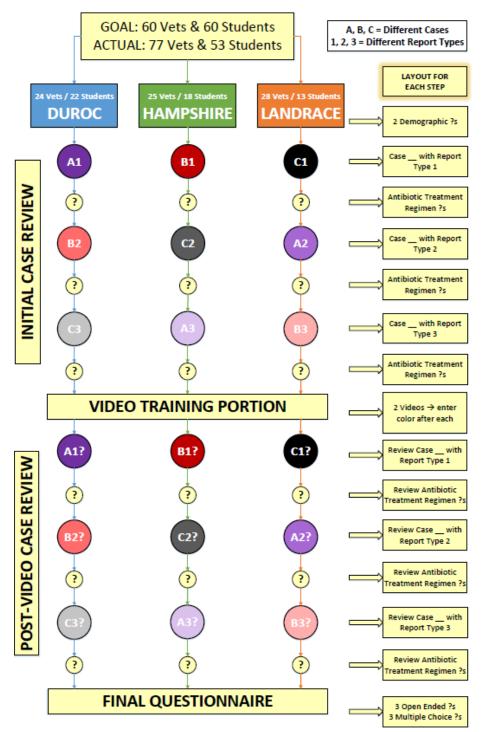


Figure 4: Diagram of the participant movements in Moodle training platform. The number of veterinarians and veterinary student participants are listed at the top, with the case (A, B and C) and report type (1, 2 and 3) listed to the upper right. The left side of the diagram shows the path of each participant enrollment group (Duroc, Hampshire and Landrace) through the initial case review, video training portion, post-video case review and final questionnaire. The items presented and collected from participants for each step are displayed on the right side of the diagram.

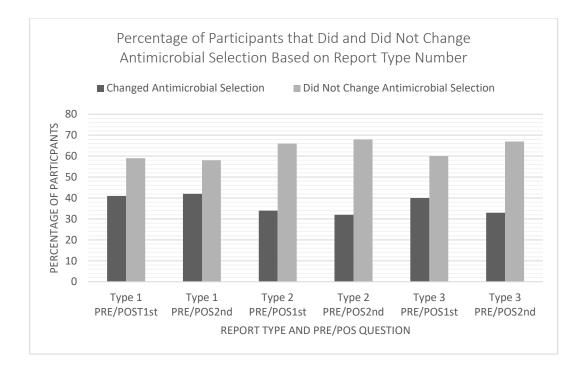


Figure 5: Bar graph comparison of the percentage of participants that changed and did not change antimicrobial selection after video training based on report type number (1, 2 and 3). Percentage of participants are located on the vertical axis and the report type number and 1st antimicrobial selection comparison (PRE/POS1st) or 2nd antimicrobial selection comparison (PRE/POS2nd) is on the horizontal axis. Dark grey bars on the left represent the percentage of participants that changed antimicrobial selection. Light grey bars on the right represent the percentage of participants that did not change antimicrobial selection.

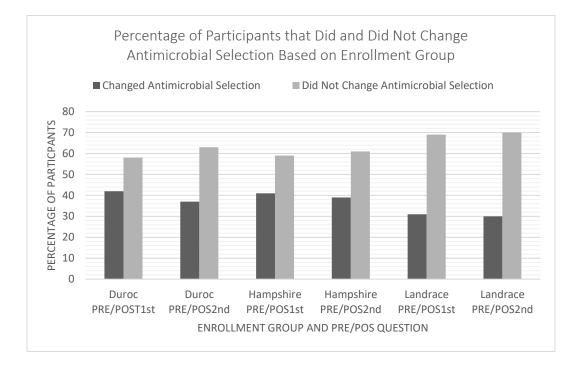


Figure 6: Bar graph comparison of the percentage of participants that changed and did not change antimicrobial selection after video training based on assigned enrollment group (Duroc, Hampshire and Landrace). Percentage of participants are located on the vertical axis and the report type number and 1st antimicrobial selection comparison (PRE/POS1st) or 2nd antimicrobial selection comparison (PRE/POS2nd) is on the horizontal axis. Dark grey bars on the left represent the percentage of participants that changed antimicrobial selection. Light grey bars on the right represent the percentage of participants that did not change antimicrobial selection.

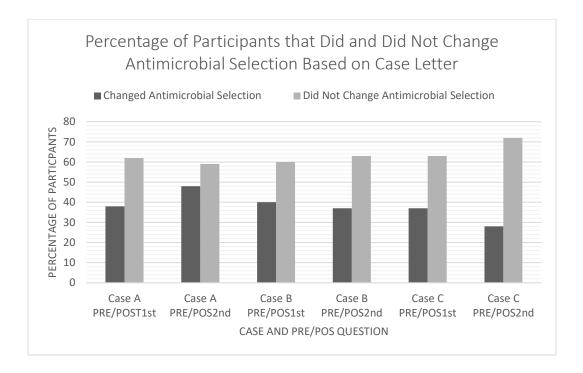


Figure 7: Bar graph comparison of the percentage of participants that changed and did not change antimicrobial selection after video training based on case letter (A, B and C). Percentage of participants are located on the vertical axis and the report type number and 1st antimicrobial selection comparison (PRE/POS1st) or 2nd antimicrobial selection comparison (PRE/POS2nd) is on the horizontal axis. Dark grey bars on the left represent the percentage of participants that changed antimicrobial selection. Light grey bars on the right represent the percentage of participants that did not change antimicrobial selection.

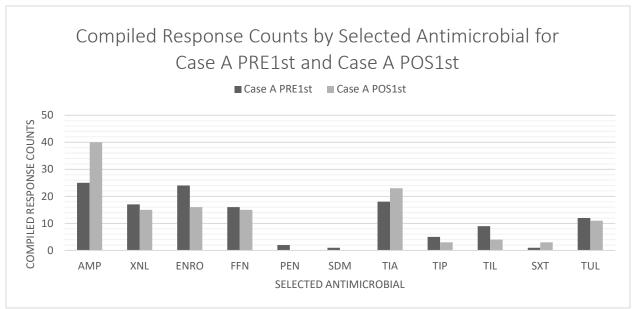


Figure 8: Bar graph comparison of the compiled participant response counts pre-training and post-training by selected antimicrobial. Compiled response counts are located on the vertical axis and selected antimicrobial options are abbreviated on the horizontal axis. Dark grey bars on the left represent counts for Case A PRE1st. Light grey bars on the right represent counts for Case A POS1st

*Antimicrobial options: ampicillin (AMP), ceftiofur (XNL), clindamycin (CLI), danofloxacin (DANO), enrofloxacin (ENRO), florfenicol (FFN), gamithromycin (GAM), gentamicin (GEN), neomycin (NEO), penicillin (PEN), sulfadimethoxine (SDM), spectinomycin (SPE), tetracycline (TET), tiamulin (TIA), tildipirosin (TIP), tilmicosin (TIL), trimethoprim/sulphamethoxazole (SXT), tulathromycin (TUL), tylosin tartrate/base (TYLT) and no drug selection (NDS) *No counts reported for CLI, DANO, GAM, GEN, NEO, SPE, TET, TYLT & NDS

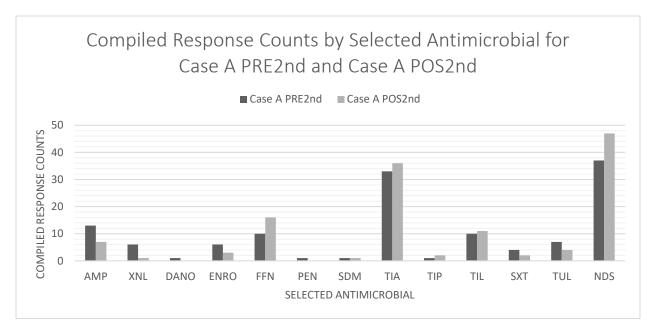


Figure 9: Bar graph comparison of the compiled participant response counts pre-training and post-training by selected antimicrobial. Compiled response counts are located on the vertical axis and selected antimicrobial options are abbreviated on the horizontal axis. Dark grey bars on the left represent counts for Case A PRE2nd. Light grey bars on the right represent counts for Case A POS2nd.

*Antimicrobial options: ampicillin (AMP), ceftiofur (XNL), clindamycin (CLI), danofloxacin (DANO), enrofloxacin (ENRO), florfenicol (FFN), gamithromycin (GAM), gentamicin (GEN), neomycin (NEO), penicillin (PEN), sulfadimethoxine (SDM), spectinomycin (SPE), tetracycline (TET), tiamulin (TIA), tildipirosin (TIP), tilmicosin (TIL), trimethoprim/sulphamethoxazole (SXT), tulathromycin (TUL), tylosin tartrate/base (TYLT) and no drug selection (NDS) *No counts reported for CLI, GAM, GEN, NEO, SPE, TET & TYLT

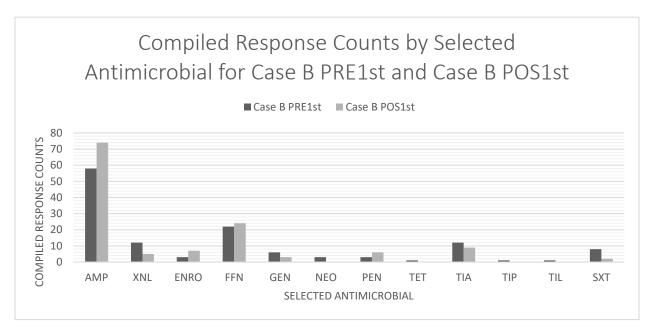


Figure 10: Bar graph comparison of the compiled participant response counts pre-training and post-training by selected antimicrobial. Compiled response counts are located on the vertical axis and selected antimicrobial options are abbreviated on the horizontal axis. Dark grey bars on the left represent counts for Case B PRE1st. Light grey bars on the right represent counts for Case B POS1st.

*Antimicrobial options: ampicillin (AMP), ceftiofur (XNL), clindamycin (CLI), danofloxacin (DANO), enrofloxacin (ENRO), florfenicol (FFN), gamithromycin (GAM), gentamicin (GEN), neomycin (NEO), penicillin (PEN), sulfadimethoxine (SDM), spectinomycin (SPE), tetracycline (TET), tiamulin (TIA), tildipirosin (TIP), tilmicosin (TIL), trimethoprim/sulphamethoxazole (SXT), tulathromycin (TUL), tylosin tartrate/base (TYLT) and no drug selection (NDS) *No counts reported for CLI, DANO, GAM, SDM, SPE, TUL, TYLT & NDS

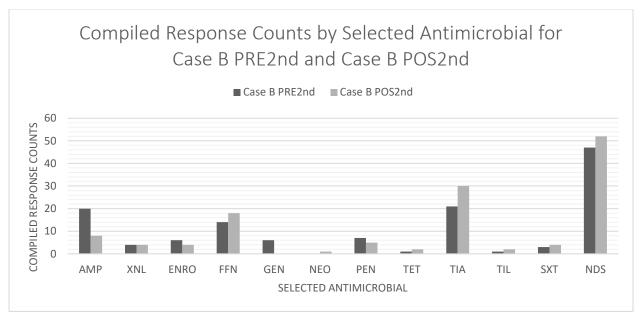


Figure 11: Bar graph comparison of the compiled participant response counts pre-training and post-training by selected antimicrobial. Compiled response counts are located on the vertical axis and selected antimicrobial options are abbreviated on the horizontal axis. Dark grey bars on the left represent counts for Case B PRE2nd. Light grey bars on the right represent counts for Case B POS2nd.

*Antimicrobial options: ampicillin (AMP), ceftiofur (XNL), clindamycin (CLI), danofloxacin (DANO), enrofloxacin (ENRO), florfenicol (FFN), gamithromycin (GAM), gentamicin (GEN), neomycin (NEO), penicillin (PEN), sulfadimethoxine (SDM), spectinomycin (SPE), tetracycline (TET), tiamulin (TIA), tildipirosin (TIP), tilmicosin (TIL), trimethoprim/sulphamethoxazole (SXT), tulathromycin (TUL), tylosin tartrate/base (TYLT) and no drug selection (NDS) *No counts reported for CLI, DANO, GAM, SDM, SPE, TIP, TUL & TYLT

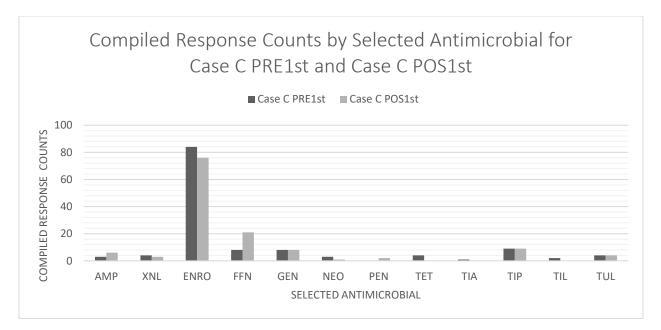


Figure 12: Bar graph comparison of the compiled participant response counts pre-training and post-training by selected antimicrobial. Compiled response counts are located on the vertical axis and selected antimicrobial options are abbreviated on the horizontal axis. Dark grey bars on the left represent counts for Case C PRE1st. Light grey bars on the right represent counts for Case C POS1st.

*Antimicrobial options: ampicillin (AMP), ceftiofur (XNL), clindamycin (CLI), danofloxacin (DANO), enrofloxacin (ENRO), florfenicol (FFN), gamithromycin (GAM), gentamicin (GEN), neomycin (NEO), penicillin (PEN), sulfadimethoxine (SDM), spectinomycin (SPE), tetracycline (TET), tiamulin (TIA), tildipirosin (TIP), tilmicosin (TIL), trimethoprim/sulphamethoxazole (SXT), tulathromycin (TUL), tylosin tartrate/base (TYLT) and no drug selection (NDS) [†]No counts reported for CLI, DANO, GAM, SDM, SPE, SXT, TYLT & NDS

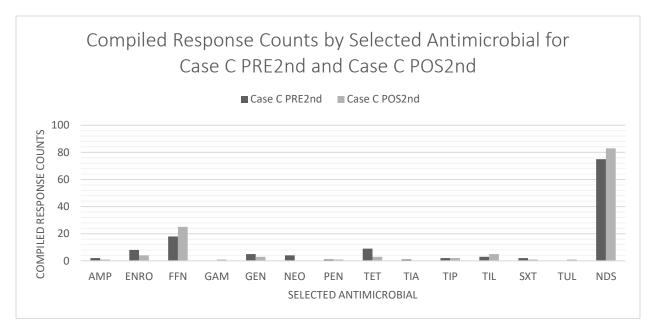


Figure 13: Bar graph comparison of the compiled participant response counts pre-training and post-training by selected antimicrobial. Compiled response counts are located on the vertical axis and selected antimicrobial options are abbreviated on the horizontal axis. Dark grey bars on the left represent counts for Case C PRE2nd. Light grey bars on the right represent counts for Case C POS2nd.

*Antimicrobial options: ampicillin (AMP), ceftiofur (XNL), clindamycin (CLI), danofloxacin (DANO), enrofloxacin (ENRO), florfenicol (FFN), gamithromycin (GAM), gentamicin (GEN), neomycin (NEO), penicillin (PEN), sulfadimethoxine (SDM), spectinomycin (SPE), tetracycline (TET), tiamulin (TIA), tildipirosin (TIP), tilmicosin (TIL), trimethoprim/sulphamethoxazole (SXT), tulathromycin (TUL), tylosin tartrate/base (TYLT) and no drug selection (NDS) *No counts reported for XNL, CLI, DANO, SDM, SPE & TYLT

References

- 1. Association of American Veterinary Medical Colleges and Association of Public & Land-Grant Universities (AAVMC, APLU). Addressing antibiotic resistance a report from the joint APLU | AAVMC task force on antibiotic resistance in production agriculture. 2015 October. <u>https://www.aplu.org/projects-and-initiatives/agriculture-human-sciences-andnatural-resources/antibiotics-and-agriculture/final-report-october-2015.pdf</u>
- 2. Association of American Veterinary Medical Colleges and Association of Public & Land-Grant Universities (AAVMC, APLU). Antimicrobial resistance core competencies working group, AMR learning outcomes. 2017. <u>https://www.aplu.org/library/aavmc-aplu-national-action-plan-to-address-antibiotic-resistance/file#:~:text=The%20Antimicrobial%20Resistance%20Core%20Competencies%20Working%20Group%20was%20formed%20to,teaching%20and%20in%20antibiotic%20resistance.&text=Antimicrobial%20Stewardship%20learning%20outcomes%20lead, of%20antibiotics%20can%20be%20preserved</u>

- Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolates from Animals; approved guideline. 4th ed. CLSI, June 2018. CLSI document VET08.
- Clinical and Laboratory Standards Institute (CLSI). Understanding Susceptibility Test Data as a Component of Antimicrobial Stewardship in Veterinary Settings; approved guideline. 1st ed. CLSI, July 2019. CLSI document VET09.
- 5. Federal Task Force on Combating Antibiotic-Resistant Bacteria. National action plan for combating antibiotic-resistant bacteria 2020-2025. 2020 October. <u>https://aspe.hhs.gov/sites/default/files/migrated_legacy_files//196436/CARB-National-Action-Plan-2020-2025.pdf</u>
- 6. Iowa State University Veterinary Diagnostic Laboratory (ISU VDL). Porcine antimicrobial susceptibility profiles. 2019. <u>https://vetmed.iastate.edu/sites/default/files/VDL/pdf/Susceptibility-Summary-Porcine-2019.pdf</u>
- 7. O'Neill, Jim, et al. Tackling drug-resistant infections globally: final report and recommendations of the review on antimicrobial resistance. 2016 May 19. <u>https://amrreview.org/sites/default/files/160525_Final%20paper_with%20cover.pdf</u>