RESEARCH REPORT

PUBLIC HEALTH/WORKER SAFETY

Title: Comparison of antibiotic treatment regimens for naturally occurring, multi-etiology disease challenges in commercial wean-to-finish swine facilities. – **NPB #19-048**

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Date Submitted: 26 May 2021

Industry Summary:
Objectives of this study were to compare the efficacy of current water-soluble and injectable antibiotic treatment regimens during naturally occurring, multi-etiologic swine disease challenges ("coinfections") in growing pigs raised under commercial conditions and to produce a validated research protocol that can be applied by veterinarians and producers to test the value of antimicrobial treatment options under the specific conditions of their pig flows and health statuses.

In one or both studies, the whole population (pen) injection treatment resulted in the lowest and statistically significant percentages of total removals, post-treatment removals with 7 days of treatment, and the frequency of re-treatments. Overall, there were no statistical differences between treatments regarding the rest of the production parameters of average daily gain, total mortality or 7 days post-treatment mortality.
Clinical outcome variables were also collected, but ultimately not reported given the clinical impact of IAV-S in both studies. IAV-S causes elevated rectal temperatures, which led to the classification of a majority of pigs as treatment failures, despite meeting all other criteria.

There are three key findings for industry: 1) it is expensive (both in direct cost and labor) to collect accurate data in the field regarding antimicrobial treatment efficacy, 2) virus exposure and the resulting clinical impact can mask the clinical efficacy of antimicrobial treatment, and 3) mass injection of a pen at a specific time point was superior to the other treatment regimens available in this study.

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Key Findings:

- It is expensive (both in direct cost and labor) to collect accurate data in the field regarding antimicrobial treatment efficacy and may rival the cost of tightly controlled laboratory challenge studies.
- Virus exposure and the resulting clinical impact can mask the clinical efficacy of antimicrobial treatment. Controlling virus impacts has the potential to improve antimicrobial efficacy.
- Mass injection of a pen at a specific time point was superior to the other treatment regimens available in this study.

Keywords: antibiotic efficacy, mass treatment, respiratory disease, nursery, mortality, ADG, clinical score, re-treatment

Scientific Abstract:

Objectives of this study were two-fold. First, to compare the efficacy of current water-soluble and injectable antibiotic treatment regimens during naturally occurring, multi-etiologic swine disease challenges (“coinfections”) in growing pigs raised under commercial conditions. Second to produce a validated research protocol that can be applied by veterinarians and producers to test the value of antimicrobial treatment options under the specific conditions of their pig flows and health statuses.

To meet these objectives, three rooms of a hotel-style commercial nursery were modified to allow for treatment randomization. Four antibiotic treatment regimens were selected prior to study initiation for comparison: 1) Whole population water 2) Whole population injection 3) Targeted injection (i.e. spot treatment) 4) Baseline (combination of population water and targeted injection). Two studies were carried out within the three rooms. Production outcome variables included average daily gain, total mortality, 7 days post-treatment mortality, total removals, 7 days post-treatment removals, total first re-treatments, 7 days post-treatment first re-treatments, total second re-treatments, and 7 days post-treatment second re-treatments.

Overall, there were no statistical differences between treatments regarding the production parameters of average daily gain, total mortality or 7 days post-treatment mortality. In one or both studies, the whole population injection treatment resulted in the lowest and statistically significant percentages of total removals, 7 days post-treatment removals, total first re-treatments, 7 days post-treatment first re-treatments, total second re-treatments, and 7 days post-treatment second re-treatments.

Clinical outcome variables were also collected, but ultimately not reported given the addition of IAV-S in both studies. IAV-S causes elevated rectal temperatures, which led to the classification of a majority of pigs as treatment failures, despite meeting all other FDA GFI #178 treatment success criteria (Table 6). More work needs to be done to determine the best utilization and interpretation of this criteria when considering natural disease outbreaks under commercial conditions, where multi-etiology challenges will impact the treatment outcome.

Introduction:

The author would like to note that a facility modification was made prior to study initiation. The study was transitioned from a commercial wean-to-finish facility to a commercial nursery given the increased likelihood for disease, resulting in the need for more frequent antibiotic use in a shorter period of time. Given the shortened production phase, several study replications could also be pursued.

In September of 2018, the Food and Drug Administration (FDA) released a five-year blue print detailing plans to advance antibiotic stewardship in veterinary settings.[1] The perception of overuse of antibiotics in production animal species was addressed and described as a contribution to increased antibiotic resistance. The FDA also specified goals for the development of strategies to monitor and report antibiotic use within veterinary settings, making it clear that production-orientated benefits (i.e. ADG, ADFI and FC) should not be primary considerations. Rather, antibiotic efficacy in terms of treatment, control and prevention success must be the focus of future objective, research-based evaluations. To date, most efficacy studies are performed under laboratory conditions with intentional pathogen exposure to a small number of pigs. This approach typically results in a

defined exposure period for the population along with control measures for co-infections, thus increasing the likelihood of recovery without the use of an antibiotic.

There is currently a lack of scientifically validated data published within peer-reviewed literature regarding the treatment, control and/or prevention efficacy of antibiotic agents used for naturally occurring swine disease outbreaks and coinfections in commercial settings. Rather than relying only on the current course, which is to monitor real-time antibiotic consumption, an opportunity exists to balance that with real-time efficacy data, while also addressing the FDA's five-year blue print.

Objectives:
1. Compare the efficacy of current water-soluble and injectable antibiotic treatment regimens during naturally occurring, multi-etiologic swine disease challenges ("coinfections") in growing pigs raised under commercial conditions.

2. Produce a validated research protocol that can be applied by veterinarians and producers to test the value of antimicrobial treatment options under the specific conditions of their pig flows and health statuses.

Materials & Methods:
The protocol for all nursery studies were reviewed and approved by the ISU Institutional Care and Animal Use Committee (IACUC). One pilot study to refine procedures was performed on a healthy cohort and two data collection studies (studies "two" and "three") were conducted consecutively in three rooms of a commercial, hotel-style nursery. Each room was modified to provide fresh or medicated water delivery to each individual pen according to treatment. Each room was designed to hold approximately 1,000 pigs in forty pens. The number of pigs enrolled in each study was dependent on the number of pigs received and will be further discussed in the results section.

Prior to the study, candidate antibiotic treatment regimens were identified for use by the partnering production company's veterinary team with collaboration from the research team. The four treatment regimens were defined as 1) Whole population water 2) Whole population injection 3) Targeted injection (i.e. spot treatment) 4) Baseline (combination of population water and targeted injection). The baseline treatment represented the existing company's standard operating procedure for the pig flow. Specific antibiotics were selected for individual and mass medication based on affected organ system, current health status, pig flow history, and contemporaneous diagnostics. Pen was the experimental unit and pig was the observational unit. Eight pens were dedicated as hospital pens for the study period and were excluded from the treatment groups. The remaining thirty-two pens within each room were pre-assigned randomly within horizontal blocks designed to eliminate geographic biases (Figure 1). Pre-placement meetings were

held between the research, on-farm and partnering veterinary team to determine roles and responsibilities prior to each turn.

Lessons learned in the pilot study were ultimately used to refine the procedures for studies two and three. Individual pig data collected from the pilot study were not analyzed and will not be further discussed. All research pigs in studies two and three were ear tagged and individually weighed within 24 hours of farm arrival and again at six weeks of placement, prior to farm exit. After all the pigs were weighed, ear tagged and placed in the starting pen, body weights were balanced across treatments to be within one tenth of a pound. Standard management remained in place until a clinical "disease outbreak" or need for mass antibiotic treatment occurred. At that point, the farm manager, veterinary team and research team collectively initiated the trial treatments. Diagnostics were collected prior to administration of the assigned antibiotic treatment regimens to the treatment pens. The research team then managed the rooms for a one-week period to complete antibiotic administration and data collection. At the conclusion of the week, the treatment pens returned to standard management. All additional targeted treatments, pig removals from the treatment pens and pig mortalities were recorded by the farm manager until the second weigh date.

Pigs for the studies were sourced from sow farm flows that historically struggled with multifactorial respiratory disease outbreaks during the nursery phase. Both studies had a respiratory "disease outbreak," study two occurred within one week of placement and study three at three weeks of placement. The outbreaks were characterized by coughing, nasal discharge, anorexia and lethargy. Treatment pens were scanned for potential sick pigs based on observational clinical signs and facility standard operating procedures. When a minimum threshold (study two = 2 pigs, study three = 3 pigs) of sick pigs per treatment pen was met, clinical parameters were collected on the sick pigs and the assigned treatment regimen was initiated. Clinical disease parameters (clinical) including depression, respiratory, enteric, lameness, and central nervous system (CNS) scores were defined (Table 5). Pigs that appeared sick were subjected to the clinical scoring prior to treatment initiation and after the treatment period to assess efficacy. The scoring definitions were adapted from the FDA's Guidance for Industry #178 - Recommended Study Design and Evaluation of Effectiveness Studies for Swine Respiratory Disease Claims (Table 6).[2] Forty-eight hours after the end of treatment, clinical parameters were repeated on the same subset of pigs from each pen.

In whole population injection pens, each pig was injected according to antibiotic label on the initial scoring day. In whole population water pens, the pen was only provided medicated water for five consecutive days. No injections were given during the treatment period. In targeted injection pens, each pig could only be injected once throughout the outbreak response, provided that individual pigs demonstrated clinical signs consistent with respiratory disease that necessitated antibiotic treatment. In baseline pens, the pen was provided medicated water for

five consecutive days and individual pigs could be target injected once throughout the outbreak response. During the treatment period, if any pigs became welfare concerns and needed further treatment, they were removed from the study pens and provided additional care. Removed pigs were managed according to the protocol approved by the ISU IACUC committee.

Diagnostics throughout both studies with clinical "disease outbreaks" confirmed viral infection with influenza A (IAV-S) and/or Porcine Reproductive and Respiratory Syndrome Virus (PRRSV), and bacterial co-infections with *Streptococcus suis, Mycoplasma hyorhinis*, and *Glaesserella parasuis*. In study two, IAV-S subtype H1N1 was detected. Whereas in study three, two IAV-S subtypes were detected including H1N1 and H1N2. In study three, a wild-type PRRSV was also detected at placement. PRRSV sequencing confirmed 100% homology to the originating sow farm's PRRSV strain from an outbreak in July of 2020.

After the second clinical evaluation, rooms were turned back to the farm manager to manage and record targeted treatments until the exit weight was collected by the research team. Production outcomes calculated included average starting weight, average exit weight, average daily gain, percent mortality, percent removal from the general population and percent targeted retreatments. Interim seven-day post-treatment rates were also calculated for mortality, removal and re-treatments.

Results:

The first objective of this project was to compare treatment regimens during naturally occurring, respiratory disease under commercial conditions. The results of this objective are summarized by study in the tables below. For study two, which occurred in March of 2020, the enrollment and final pig numbers are broken down by room in Table 1. Whereas, in Table 2, all rooms for study two were combined and analyzed by treatment to report production parameter estimates, along with statistically significant differences. Significance was set *a priori* at the level of $P<0.05$, with statistical differences denoted by different lettered superscripts. Results with the same superscript are not statistically different from each other. All statistical analysis was done using SAS version 9.4. General (or generalized where appropriate) linear models were used to explain the effect of treatment on a number of outcome variables, after accounting for room as a block effect. All least squares means and all pairwise differences of least squares means were presented and adjusted for multiple comparisons using Tukey's method. In Table 2, the term "total" refers to the time period of the entire turn, whereas "7 days post-treatment" refers to the 7 days after the clinical "disease outbreak" intervention and assessment was complete. Therefore, the research team had administered the antibiotic treatments and completed the follow-up clinical evaluations and the rooms were under the farm manager's control for 7 days. Removal is defined as moving the pig from their enrolled treatment pen to the hospital or no assigned treatment pen for further care. Re-

treatment is defined as antibiotic treatment delivered after the "disease outbreak" via targeted injection by the farm manager. This same information and terminology is presented for study three in Tables 3 and 4. For a complete glossary of terms, see Table 7.

Given the findings from study two and three (displayed in Tables 2 and 4), there were no statistical differences between antibiotic treatments for the production parameters of average body weight, average daily gain, total mortality or 7 days post-treatment mortality. However, there were significant differences for at least one of the studies regarding the percentage of total removals, 7 days post-treatment removals, total 1st re-treatments, 7 days post-treatment 1st re-treatments, total 2nd re-treatments and 7 days post-treatment 2nd re-treatments.

Table 1: Study Two Enrollment and Final Pig Numbers

	Study Two – March 2020			
	Room 14	**Room 15**	**Room 16**	**Total**
Number of Pigs Placed per Pen	23	23	23	
Number of Treatment Pens	32	32	32	
Number of Pigs Enrolled	736	736	736	2208
Number of Treatments	4	4	4	
Number of Pigs Enrolled per Treatment	184	184	184	
Final Number of Production Parameter Pigs	736	734*	736	2206
Final Number of Clinical Paramete Pigs	128^	62*	64	254*

*Two pigs were removed from the data set due to accidental re-treatment via target injection in Room 15.
^At project initiation, four pigs were used for clinical parameter collection in Room 14, this number was then reduced to two pigs in Rooms 15 and 16.

Table 2: Study Two Production Parameters

	Study Two – March 2020 (all rooms)				
Treatment	**Whole Population Water**	**Whole Population Injection**	**Targeted Injection**	**Baseline (Whole Population Water + Targeted Injection)**	
Drug Regimen	Chlortetracycline (10 mg/lb.) + tiamulin hydrogen fumarate (3.5 mg/lb.)	Enrofloxacin (3.4 mg/lb.)	Enrofloxacin (3.4 mg/lb.)	Chlortetracycline (10 mg/lb.) + tiamulin hydrogen fumarate (3.5 mg/lb.) +/- Enrofloxacin (3.4 mg/lb.)	
Number of Pens per Treatment	24	24	24	24	

Number of Pigs per Treatment	552	552	550	552	2206
Average Starting Weight (lbs.)	11.5	11.5	11.5	11.5	
Average Exit Weight (lbs.)	47.2	47.6	47.1	47.8	
Average Daily Gain (lbs.)	0.84	0.85	0.84	0.86	
Total Mortality (%)	1.3%	0.7%	1.3%	0.9%	
7 Days Post-Treatment Mortality (%)	0.7%	0.0%	0.2%	0.2%	
Total Removals (%)	5.7%[a]	4.8%[a]	8.1%[b]	5.0%[a]	p<0.05
7 Days Post-Treatment Removals (%)	4.4%[b]	1.1%[a]	1.2%[a]	3%[b]	p<0.05
Total 1st Re-Treatment (%)	19.4%[b]	14.5%[a]	18.6%[b]	18.8%[b]	p <0.05
7 Days Post-Treatment 1st Re-Treatment (%)	12.3%[b]	5.3%[a]	8%[a]	11.5%[b]	p<0.0575
Total 2nd Re-Treatment (%)	3.6%[b]	1.4%[a]	3.8%[b]	3.6%[b]	p<0.02
7 Days Post-Treatment 2nd Re-Treatment (%)	0.2%	0.0%	0.0%	0.7%	

Table 3: Study Three Enrollment and Final Pig Numbers

	Study Three – September 2020			
	Room 14	**Room 15**	**Room 16**	**Total**
Number of Pigs Placed per Pen	28	28	27	
Number of Treatment Pens	32	32	32	
Number of Pigs Enrolled	896	896	864	2656
Number of Treatments	4	4	4	
Number of Pigs Enrolled per Treatment	224	224	216	
Final Number of Production Parameter Pigs	892*	879*	846*	2617
Final Number of Clinical Paramete Pigs	94	94	92	280^

*Pigs were removed from the data set due to mortality, missing removal date or missing exit weight, four pigs in Room 14, seventeen in Room 15 and eighteen in Room 16.

^For this turn, three pigs were used for clinical parameter collection in all rooms, five of the 283 pigs were removed from the data set for the above reasons.

Table 4: Study Three Production Parameters

	Study Three - September 2020 (all rooms)				
Treatment	**Whole Population Water**	**Whole Population Injection**	**Targeted Injection**	**Baseline (Whole Population Water + Targeted Injection)**	
Drug Regimen	Chlortetracycline (10 mg/lb.) + tiamulin hydrogen fumarate (3.5 mg/lb.)	Enrofloxacin (3.4 mg/lb.)	Enrofloxacin (3.4 mg/lb.)	Chlortetracycline (10 mg/lb.) + tiamulin hydrogen fumarate (3.5 mg/lb.) +/- Enrofloxacin (3.4 mg/lb.)	
Number of Pens per Treatment	24	24	24	24	

Number of Pigs per Treatment	657	654	654	652	2617
Average Starting Weight (lbs.)	15.1	15.1	15.2	15.2	
Average Exit Weight (lbs.)	45.7	45.9	45.5	46.0	
Average Daily Gain (lbs.)	0.75	0.75	0.74	0.75	
Total Mortality (%)	2.4%	3.6%	3.5%	2.8%	
7 Days Post-Treatment Mortality (%)	1.2%	0.3%	0.3%	1.2%	
Total Removals (%)	9%[a]	14%[b]	13.4%[b]	13%[b]	P<0.03
7 Days Post-Treatment Removals (%)	1.2%	0.9%	1.5%	1.5%	
Total 1st Re-Treatment (%)	26.3%	22.9%	25.2%	23.3%	
7 Days Post-Treatment 1st Re-Treatment (%)	18.4%[c]	3.6%[a]	9.1%[b]	15.3%[c]	p<0.0008
Total 2nd Re-Treatment (%)	9.1%	8.3%	11.0%	7.8%	
7 Days Post-Treatment 2nd Re-Treatment (%)	3.3%[b]	0.0%[a]	1.2%[a]	1.2%[a]	p<0.014

The second objective of this project was to produce a validated research protocol that could be applied by veterinarians and producers to test the value of antimicrobial treatment options considering their pig flows and health statuses. To satisfy this objective, a preliminary research protocol has been created for veterinarians and producers to utilize within their farms applying recommendations from FDA Guidance for Industry #85 – Good Clinical Practice3 and FDA Guidance for Industry #178. This protocol includes defined treatments, randomization procedures with an example, an Excel® pivot table protocol to balance treatments by weight, research pen and room signage, all recording sheets, clinical score and FDA definitions, a treatment decision flowchart, treatment marking scheme, general supply list and an example communication tree. To access this protocol search the following keywords: "nursery antibiotic efficacy" on the piglivability.org website.

Discussion:

Overall, the utilization of whole population injection in study two resulted in the lowest percentage of pigs removed throughout the entire turn and the 7 days after study completion. In addition, whole population injection resulted in the lowest percentage of total 1st re-treatments, 1st re-treatments within 7 days of study completion and total percentage of 2nd re-treatments. This study also had a significant difference between treatments regarding the percentage of pigs removed from treatment pens throughout the turn. The target injection pigs, were statistically more likely to be removed throughout the turn (8.1%) than the whole population water, whole population injection and baseline (combination of population water and targeted injection) treatment pigs (5.7%, 4.8% and 5%) ($p<0.05$). Within 7 days of treatment completion, the whole population water and baseline treatment pigs were statistically more likely to be removed from the general population (4.4 and 3%) than the whole population injection and targeted injection treatment (1.1 and 1.2%) ($p<0.05$).

For the percentage of total 1st time re-treatments, the whole population water, targeted injection and baseline treatment pigs were statistically more likely to be re-treated (19.4, 18.6 and 18.8%) than the whole population injection treatment (14.5%) ($p<0.05$). Whereas, in the 7 days after the trial, only the whole population water and baseline treatment pigs were statistically more likely to receive their 1st re-treatment (12.3 and 11.5%) than the whole population injection and targeted injection treatments (5.3 and 8%) ($P<0.0575$). For total 2nd re-treatment, whole population injection treatment pigs were statistically less likely to be re-treated a second time after the trial end (1.4%) compared to the whole population water, targeted injection and baseline treatments (3.6%, 3.8% and 3.6%) ($p<0.02$).

For study three, the use of whole population injection also resulted in lower percentages of removals 7 days post-treatment and re-treatments, but not all were statistically significant. Regarding total removals, the whole population water pigs were less likely to be removed throughout the entire turn, a statistical difference that was not seen with removals from the 7-day post-treatment window, when an impact from the antibiotic regimen would be expected. The pigs in study three were PRRSV positive in addition to the IAV-S, *Streptococcus suis, Mycoplasma hyorhinis*, and *Glaesserella parasuis* that were detected for both studies. Specifically for study three, there was a significant difference in total removals, with the whole population water pigs being less likely to be removed (9%) than the whole population injection, targeted injection and baseline treatments (14, 13.4, 13%) ($p<0.03$) for the entire turn. There were also significant differences in the 7 days post-treatment 1st re-treatment between the four treatments. The whole population water and baseline pigs were most likely to be retreated (18.4 and 15.3%), followed by the targeted injection pigs (9.1%) and lastly, the whole population injection pigs (3.6%) ($p<0.0008$). For the 7 days post-treatment 2nd re-treatment, the whole population injection, targeted injection and baseline pigs were less likely to receive a second retreatment (0%, 1.2% and 1.2%), compared to the whole population water treatment (3.3%) ($p<0.014$).

The clinical parameters collected to assess antibiotic efficacy in terms of treatment, control and prevention success in the field were complicated by the presence of IAV-S in both studies. Since IAV-S moves through pig populations rather quickly, the number of pigs with clinical signs and elevated rectal temperatures rapidly climbs. The superinfection of IAV-S, meant that the clinical scoring was not reflective of bacterial pathogens nor the efficacy of antimicrobial treatment, since elevated rectal temperature was the most common abnormality at initial assessment and the most likely cause of treatment failure classification in the absence of other bacterial clinical signs. Using the scoring definitions adapted from the FDA's GFI #178, pigs are automatically a treatment failure when their rectal temperature is ≥104°F. Such temperatures are common with IAV-S, along with extreme variation in timing of clinical signs and fever during a natural disease outbreak with co-infections.

Therefore, for studies two and three, a subset of clinical parameter pigs had fevers just prior to treatment initiation (collection point one), while others had fevers after the treatment period (collection point two). A fever would automatically categorize enrolled pigs as a treatment failure per FDA treatment success and failure criteria, although not indicating any impact of antibiotics on the bacterial pathogens that may be present. The objective assessment of the clinical picture was masked by IAV-S; therefore, we did not statistically measure clinical success rate for any of the antimicrobial regimens.

The other clinical disease parameters of depression, respiratory, enteric, lameness and CNS scores were also collected at both time points for both studies. This objective criterion is also not well aligned when IAV-S is a co-infector. IAV-S does not traditionally cause severe long-term clinical signs. However, it does cause fever, anorexia, lethargy, coughing and nasal discharge. Inflammation of the bronchioles quickly leads to secondary bacterial infections, necessitating antibiotic treatment.

Considerations for this project include that the scoring definitions adapted from the FDA's GFI #178 document may not be appropriate when evaluating the treatment, control and prevention success of antibiotic use during natural disease outbreaks, under commercial conditions, with viral co-infections. This project also did not utilize a control or placebo treatment group, given the commercial and welfare implications. There was no blinding in order to allow the research team to correctly administer the randomized antibiotic treatments. Subjectively, clinical differences between treatment groups were observed, but this was not found statistically. Pigs were subjectively enrolled based on clinical signs and facility standard operating procedures versus setting inclusion criteria based on collection point one scores. Feed antibiotics were not modified, but held consistent across all treatments.

Some final lessons learned from this project include that this research protocol can be implemented to compare production parameter data given the appropriate amount of people, time, farm management and project management. In order to implement this protocol under commercial settings, outbreak timing can have a major impact on whether production parameter differences are found. Veterinarian and producer goals should drive when data collection occurs during a commercial outbreak. Exit weights collected closer to the outbreak and treatment are more likely to reflect the outcome of the antibiotic regimens, whereas weights collected later may be influenced by other factors.

Given natural disease outbreaks, there will be a wide variation in disease stage at treatment that will ultimately affect cure rate. Therefore, during commercial outbreaks with viral co-infections, these recommended criteria may not be appropriate to distinguish cure rate. Traditionally, this criterion has been successful during antibiotic efficacy studies, which occur under controlled

environmental conditions and involve timed bacterial inoculation. Therefore, efficacy studies have a more predictable reduction of clinical scores and rectal temperatures than under commercial conditions with naturally occurring co-infections.

Future work is needed to more appropriately define antibiotic treatment success and failure criteria under mixed etiology conditions. Keys for success include additional research funding, increased collaboration with production partners, protocol refinements, along with long-term implementation. This work will allow the swine industry to advance their antibiotic stewardship efforts in line with the FDA's five-year blue print goal of monitoring and reporting antibiotic use based on antibiotic efficacy data, versus the current course of monitoring real-time antibiotic consumption. Ultimately, veterinarians and producers will have more data to judiciously and cost-effectively make antibiotic treatment decisions given their health conditions and pig flow challenges.

While well conducted field-based trials have the potential to provide data and conclusions that are more readily applied and more clearly reflective of the conditions producers are confronted with, they suffer from more confounding variables. In this particular study, the infection of the test pigs with influenza made it nearly impossible to collect the important clinical outcomes data that might be useful to justify current treatment regimens in the regulatory and public health arenas.

References:

1. Food and Drug Administration Center for Veterinary Medicine. Supporting Antimicrobial Stewardship in Veterinary Settings – Goals for Fiscal Years 2019-2023. 2018. Available at: www.fda.gov/media/115776/download. Accessed 10 November 2020.
2. U.S. Department of Health and Human Services, Food and Drug Administration. FDA Guidance for Industry #178 - Recommended Study Design and Evaluation of Effectiveness Studies for Swine Respiratory Disease Claims. 2007. Available at: https://www.fda.gov/media/69903/download. Accessed 10 November 2020.
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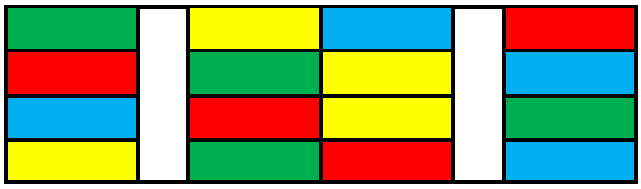
Figure 1: Pen treatment randomization by room (3) for studies two and three.



Whole Population Water (8)
Whole Population Injection (8)
Targeted Injection (8)
Baseline = Whole Population Water + Targeted Injection (8)
Hospital Pens = No Assigned Treatment (8)

Table 5: Clinical disease parameters (clinical) collected and adapted from FDA GFI #178 by Nickel, Rademacher and Karriker.

Depression/ABC Score	
Score	**Definition**
0 = Normal	Alert, active, normal appetite, well-hydrated, coat normal
1 or A = Mild	Moves slower than normal, slightly rough coat, may appear lethargic but upon simulation appears normal ("A" Pig - "Individual Pig Care from Zoetis" chart)
2 or B = Moderate	Inactive, may be recumbent is able to stand, gaunt, may be dehydrated ("B" Pig -"Individual Pig Care from Zoetis" chart)
3 or C = Severe	Down or reluctant to get up, gauntness evident, dehydrated ("C" Pig - "Individual Pig Care from Zoetis" chart)
Respiratory Score	
Score	**Definition**
0 = Normal	No clinical signs present: nasal discharge, cough, increased respiratory rate, increased respiratory effort
1 = Mild	1-2 clinical signs present: nasal discharge, cough, increased respiratory rate, increased respiratory effort
2 = Moderate/Severe	3-4 clinical signs present: nasal discharge, cough, increased respiratory rate, increased respiratory effort
Enteric Score	
Score	**Definition**
0 = Normal	Normal fecal consistency, no diarrhea
1 = Mild	Diarrhea present, still holds a shape
2 = Moderate/Severe	Diarrhea present, does not hold a shape = liquid
Lameness Score	
Score	**Definition**
0 = Normal	Pig moves easily with no discomfort or abnormalities
1 = Mild	Pig is weight bearing, but lame on at least one limb
2 = Moderate/Severe	Pig is non-weight bearing on at least one limb
CNS Score	
Score	**Definition**
0 = Normal	Pig is alert and active
1 = Mild	Pig is ataxic, laterally recumbent with attempts to move/right itself, centrally aware
2 = Moderate/Severe	Pig is laterally recumbent, not centrally aware, paddles, displays nystagmus
Rectal Temperature	

Table 6: FDA GFI #178 treatment success and failure criteria for Swine Respiratory Disease (SRD) studies.

Success	Failure

Alive, and	All pigs that do not meet the definition of "success" on the evaluation day(s).
Depression Score = 1 or 0 (out of 3), and	
Clinical score = 1 or 0 (out of 3), and	
Temperature <104°F	

Table 7: Glossary of terms.

Term	**Definition**
Production Parameter Pigs	All pigs housed in rooms 14-16 for each trial, data collection included individual start and exit weights, calculated average daily gain, mortality, removal and any re-treatment rates.
Clinical Parameter Pigs	A total of 2-4 pigs per pen housed in rooms 14-16 for each trial, data collection included individual rectal temperature, along with depression, respiratory, enteric, lameness and CNS scores (depending on clinical sign observed).
Average Starting Weight (lbs.)	The average start or entry weight of pigs by treatment in pounds.
Average Exit Weight (lbs.)	The average exit or final weight of pigs by treatment in pounds.
Average Daily Gain (lbs.)	The average of all individual pig weights divided by the number of individual days on feed, reported in pounds ((pig exit or final weight – pig start or entry weight)/number of days on feed).
Total Days on Feed	The time period accounting for the entire turn, from start weight collection to exit weight collection.
7 Days Post-Treatment	The time period accounting for the 7 days after the antibiotic regimens were administered by the research team and follow-up clinical evaluations were complete. The first 7-day period that the rooms were turned back to the farm manager for management.
Total Mortality (%)	The death percentage by treatment for the entire turn (number pigs that died divided by number of pigs started).
7 Days Post-Treatment Mortality (%)	The death percentage by treatment in the 7 days post-treatment.
Total Removals (%)	The percentage of pigs by treatment that were removed from enrolled treatment pens to a hospital or no assigned treatment pens for further care throughout the entire turn (number of pigs that were removed divided by the number of pigs started).
7 Days Post-Treatment Removals (%)	The percentage of pigs by treatment that were removed from enrolled treatment pens to a hospital or no assigned treatment pens for further care in the 7 days post-treatment.

Total 1st Re-Treatments (%)	The percentage of pigs by treatment that received their 1st re-treatment post-"disease outbreak" via targeted injection by the farm manager for the entire turn.
7 Days Post-Treatment 1st Re-Treatments (%)	The percentage of pigs by treatment that received their 1st re-treatment by targeted injection from the farm manager in the 7 days after the antibiotic regimens were administered and follow-up clinical evaluations were complete.
Total 2nd Re-Treatments (%)	The percentage of pigs by treatment that received a 2nd re-treatment post-"disease outbreak" via targeted injection by the farm manager for the entire turn.
7 Days Post-Treatment 2nd Re-Treatments (%)	The percentage of pigs by treatment that received a 2nd re-treatment by targeted injection from the farm manager in the 7 days after the antibiotic regimens were administered and follow-up clinical evaluations were complete.