

# The effect of a metaphylactic pulse dosing in-feed antimicrobial strategy on finishing pig health and performance

Don Walter, DVM; J. Tyler Holck DVM, MS, MBA; Steve Sornsen, DVM, MS; Chad Hagen, PhD; Isabel Turney Harris, DVM, PhD

## Summary

**Purpose:** To compare the effect of metaphylactic pulse dosing with either a continuous-feed antimicrobial medication strategy or no feed medication on finishing pig health and performance.

**Methods:** Barrows (n = 1092) from a herd naturally infected with endemic respiratory pathogens were assigned by pen to one of three treatment groups: a “Continuous” group that received alternating doses of tiamulin plus chlortetracycline on weeks 2,4,7,10, and 13 interspersed with a reduced concentration of chlortetracycline alone during weeks 3,5,6,8,9,11, and 12; a “Pulse” group, which received in-feed pulse dosing with tiamulin plus chlortetracycline only in weeks 2,4,7,10, and 13 with no medication during the other study weeks; or nonmedicated Controls that received nonmedicated feed throughout the trial. Growth performance, survivability, and seroconversion to various pathogens were measured.

**Results:** Both metaphylactic Pulse and Continuous medication strategies improved growth rate, feed intake, feed conversion efficiency, and survivability in the presence of naturally occurring mycoplasma and viral (swine influenza virus, porcine reproductive and respiratory syndrome virus) respiratory disease compared to Controls. Pulse but not Continuous medication permitted sufficient natural exposure to *Mycoplasma hyopneumoniae* to stimulate active humoral immunity.

**Implications:** Both feed medication strategies significantly improved performance versus nonmedicated controls. Metaphylactic pulse dosing with appropriate

antimicrobials may improve growth performance while permitting exposure to and stimulation of active immunity against endemic mycoplasma pneumonia.

**Keywords:** swine, pulse dosing, metaphylaxis, antibiotic, feed medication, tiamulin, chlortetracycline, serology, *Mycoplasma hyopneumoniae*.

**Received:** May 12, 1999

**Accepted:** December 15, 1999

The effectiveness of tiamulin or the tetracycline derivatives in controlling porcine bacterial and mycoplasma pneumonia is markedly enhanced when the two antibiotics are given concurrently.<sup>1–6</sup> Nontraditional medication strategies, such as pulse dosing with this combination of antibiotics, have been shown to be effective for controlling a variety of pig diseases.<sup>6–9</sup> Pulse dosing is the practice of providing a limited number of short-term medication “pulses” at therapeutic doses, separated by nonmedicated intervals. Pulse doses may vary in number and duration depending upon the circumstances.

Pulse dosing is predicated upon the hypothesis that intermittent therapeutic antimicrobial medication allows natural exposure to endemic pathogens, but will abbreviate the infection incubation process before a costly clinical disease outbreak can occur. Allowing natural exposure to stimulate acquired active immunity provides animals with long-term protection (e.g., to slaughter or entry into the breeding herd) once the short-term protection of medication is discontinued. While the rationale behind pulse dosing is intuitively logical,

we are unaware of any data supporting this specific hypothesized immune mechanism.

The present study was conducted to determine

- whether in-feed pulse dosing was as effective in controlling the clinical and growth-limiting effects of respiratory disease as continuous in-feed medication; and
- whether pulse dosing allowed pigs to mount an immune response to natural exposure to respiratory pathogens.

## Materials and methods

This 16-week study was conducted in a commercial, single-source, age-segregated sow farm/nursery/finisher (three-site system) in the Midwest. The rate and efficiency of weight gain in this herd was typically depressed approximately 8–12 weeks after pigs were placed into finishing. Feed consumption, however, remained close to normal during this period. Diagnostic evidence of infectious respiratory disease due to viral, mycoplasma, and bacterial pathogens was common but inconsistent.

## Treatments

One thousand one hundred and four (1104) 11-week-old barrows from a single source were placed in the building over a 2-day period in August 1997. On the first day after placement, all pigs were individually weighed and identified with an eartag. One thousand ninety-two (1092) pigs were selected for the study (one dead pig and 11 pigs with extreme high or low weights were excluded from allotment).

Selected pigs were blocked by weight and randomly allotted to pens within blocks on the day after the initial weighing. Pens within blocks were randomly assigned to one of the following treatments:

- “Continuous” group, which received tiamulin hydrogen fumarate (Denagard™ 10 Medicated Premix, Boehringer Ingelheim Vetmedica Inc.;

DW: Boehringer Ingelheim Vetmedica Inc., 1051 Barrington Road, Iowa City, Iowa 52245; JTH: Novartis Animal Health US, Inc. SS: Seaboard Farms; CH, Iowa Select Farms; ITH: Iowa State University

This article is available online at <http://www.aasp.org/shap.html>.

Walter D, Holck JT, Sornsen S et al. The effect of a metaphylactic pulse dosing in-feed antimicrobial strategy on finishing pig health and performance. *Swine Health Prod.* 2000;8(2):65–71.

St. Joseph, Missouri) at 35 g per ton during weeks 2, 4, 7, 10, and 13 of the study (Table 1). During these weeks, barrows also received continuous in-feed chlortetracycline hydrochloride (HCl)(AUREOMYCIN® 90 Granular Premix, Roche Vitamins Inc.; Parsippany, New Jersey) at a dose of 22 mg per kg (10 mg per lb) bodyweight (BW) daily. During weeks 3, 5, 6, 8, 9, 11, and 12, chlortetracycline HCl was added to the feed daily at a rate of 100 g per ton. Nonmedicated feed was offered during weeks 1 and 14–16.

- “Pulse” group, which received concurrent feed medication of tiamulin hydrogen fumarate at 35 g per ton plus chlortetracycline HCl at a dose of 22 mg per kg (10 mg per lb) BW daily during weeks 2, 4, 7, 10, and 13 as a ‘pulse’ medication (Table 1). Nonmedicated feed was provided during the remaining weeks (1, 3, 5, 6, 8, 9, 11, 12, and 14–16); or
- nonmedicated “Control” group, which received nonmedicated feed throughout the study.

## Housing

The research barn was a tunnel-ventilated finishing facility with natural ventilation capability. It contained 44 pens, each measuring 3 × 6 m (10 × 19 feet) and equipped with one five-hole dry feeder and two nipple waterers. The floor was totally slatted concrete with under-slat scrapers for manure removal. The barn was managed in an all-in–all-out (AIAO) manner and was one of 10 barns on a continuous-flow finishing site.

Two replicate pens of pigs for each of three treatment groups were represented within each of seven blocks. A total of 42 pens were included in the study, with 26 pigs per pen for an initial stocking density of

approximately 0.69 m<sup>2</sup> (7.3 sq. ft) per pig.

## Growth

Pigs were individually weighed at allotment and at the end of the study (16 weeks post-allotment). Pen weights were collected by moving the entire pen of pigs onto a pen scale located at the end of the barn on a biweekly basis.

## Feed

Feed was offered ad libitum to all pigs in all pens. Feed was delivered to each pen feeder using a Mosdal feed cart and the weight of feed delivered to each feeder was recorded. Identical diets were offered to all three treatment groups at all times during the study with the exception of the added medication (Table 1). Diet formulations were adjusted on a biweekly basis, and remaining feed was removed, weighed, and subtracted from the amount of feed delivered to determine net feed disappearance.

## Health

Two pigs from each pen were randomly selected and serially bled biweekly beginning on allotment day. The sera were stored until testing at -70°C. Samples were tested using

- porcine respiratory and reproductive syndrome enzyme-linked immunosorbent assay (Herd Check™ PRRSV Antibody Test Kit, IDEXX Corp.; Westbrook, Maine),
- *Mycoplasma hyopneumoniae* Tween 20 ELISA (performed by Boehringer Ingelheim Vetmedica),
- swine influenza hemagglutination-inhibition assay (SIV HI) (performed by Iowa State University Veterinary Diagnostic Laboratory),
- *Salmonella* mix-ELISA (Danish mix-ELISA procedure performed by Boehringer Ingelheim Vetmedica),
- *Lawsonia intracellularis* indirect-

fluorescent antibody (IFA) assay (performed by Boehringer Ingelheim Vetmedica); and

- transmissible gastroenteritis virus hemagglutination-inhibition assay (TGEV HI) (performed by Iowa State University Veterinary Diagnostic Laboratory).

Pigs were not vaccinated for any of the monitored diseases. In conformity with standard site procedure, affected pigs were injected with tylosin during weeks 1–6 of the study; all injections of tylosin were discontinued by week 6 of the study. During weeks 7–14, individual pigs affected with respiratory diseases were injected with penicillin derivatives.

## Statistical analysis

Performance data were analyzed using repeated-measures ANOVA techniques using the pen as the experimental unit for all production data.  $\chi^2$  analysis was used to assess mortality data. Serologic data were evaluated using statistical process control methods<sup>10,11</sup> to estimate the timing of serologic changes.

## Economic analysis

Potential economic benefits of antibiotic inclusion in the feed were analyzed with a partial budget.<sup>12–15</sup> Partial budget analysis provides a powerful tool to assess the cost effectiveness of therapeutic interventions.<sup>16</sup> It requires that only those factors affected by the treatment be included in the analysis, such that:

$$\text{Net benefit or loss of an intervention} = \text{associated changes in revenues} - \text{associated changes in cost}$$

Because in this study we determined that final bodyweight, feed intake, and mortality differed significantly between the Control and the two treatment groups, but not between the Pulse and Continuous groups,

**Table 1:** Study timeline

Treatment	Week															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Continuous	–	T	C	T	C	C	T	C	C	T	C	C	T	–	–	–
Pulse	–	T	–	T	–	–	T	–	–	T	–	–	T	–	–	–
Control	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
T	Tiamulin + CTC															
C	CTC 100															
–	No treatment															

we compared the average of the two treatment groups to the nonmedicated control, but did not compare between different antibiotic regimes. Accordingly, final bodyweight, feed intake, and mortality were included in an economic model consistent with the study design, which assumed constant growth over a 16-week period, such that:

$$\begin{aligned} \text{Net benefit or loss per group} = & \\ & (\text{increase in lb of hogs marketed} \times \\ & \quad \text{market price of hogs}) - \\ & (\text{increase in lb of feed consumed} \times \text{cost of feed}) - \\ & \text{treatment cost} \end{aligned}$$

Dividing this sum by the initial number of animals in the group yields the quantity net benefit or loss per head. Although the treatment costs in the Continuous group were higher than those in the Pulse group because the Continuous group received 7 additional weeks of chlortetracycline at 100 g per ton, we used an average treatment cost for both groups of \$2.30 per head for the economic analysis.

The outcome of partial budget analysis depends greatly on both the local cost structure of the operation under study and the prevailing market conditions.<sup>13</sup> However, sensitivity analysis<sup>15,17</sup> provides a means to systematically vary uncertain factors in the analysis. Therefore we created a matrix wherein both feed cost and market hog price were varied, and the net benefit or loss associated with antibiotic inclusion treatment was assessed over a wide range of financial scenarios.

## Results

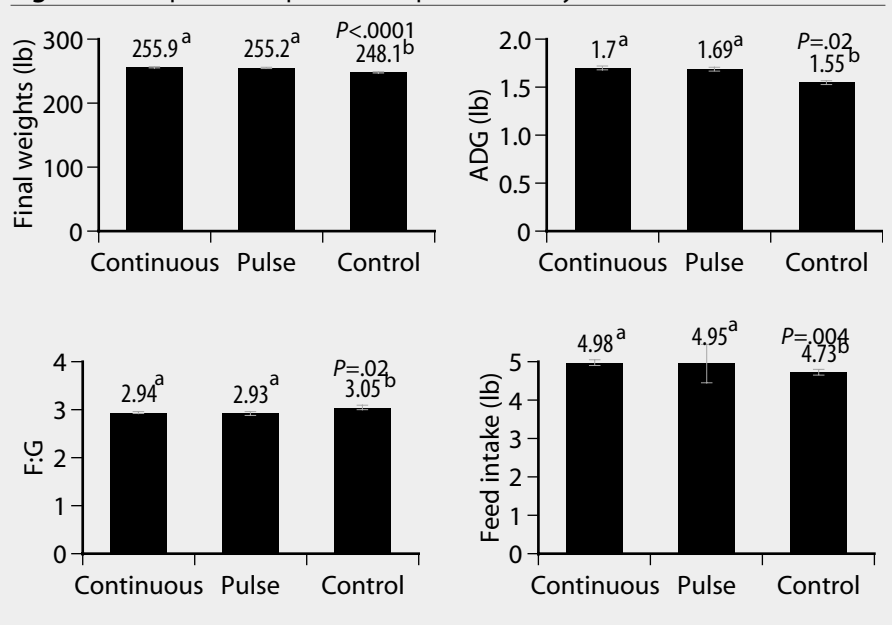
### Allotment and final body weights

Body weights did not differ among treatment groups at allotment (63 lb; 28.6 kg). Pigs in the Control group ( $P < .0001$ ) had significantly lower final weights (i.e., at week 16) than those in the Continuous and Pulse groups (Figure 1), but bodyweights did not differ significantly between the Continuous and Pulse groups. Final weight (Continuous = 116.3 kg [255.9 lb], Pulse = 116.0 kg [255.2 lb]) differences were significant ( $P < .0001$ ) between each of the seven blocks at the beginning and end of the study. No interaction was detected between treatment and block.

### Growth rate

Average daily gain (ADG) was significantly ( $P = .02$ ) greater in both medicated groups

**Figure 1:** Comparison of production parameters by treatment



a, b Control is significantly different from Continuous/Pulse

(Continuous = 754 g [1.66 lb] per day, Pulse = 732 kg [1.61 lb] per day) compared to the Control group (695 g [1.53 lb] per day) during the first 2 weeks on trial, even though treated pigs received medicated feed only during week 2. Average daily gain was greater for both medicated groups compared to controls for the overall study period ( $P < .0001$ ; Figure 1).

### Feed intake and feed efficiency

Both medicated groups had significantly improved overall feed intake ( $P = .004$ ) and feed conversion efficiency ( $P = .02$ ) compared to Controls. There were no significant differences in feed intake or feed conversion efficiency between the Pulse and Continuous groups (Figure 1).

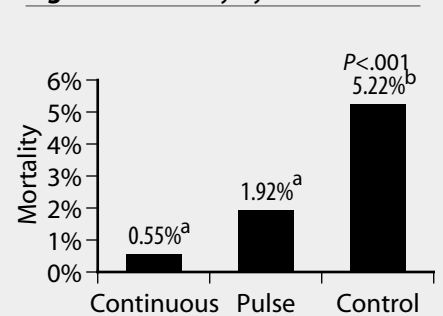
### Mortality

Both medicated groups had significantly lower mortality rates than the Control group ( $P < .001$ ; Figure 2). There was no significant difference in mortality rate between the Pulse and Continuous groups.

### Serologic response

Pigs were seronegative to PRRSV at the initiation of the study, with a sampling frequency (42) adequate to detect a 10% prevalence rate with a 99% degree of confidence. Seroconversion to PRRSV was evident after 2 weeks, with 43% of the animals testing positive (based upon an S:P ratio breakpoint of 0.4) on the ELISA test.

**Figure 2:** Mortality by treatment



a, b Control is significantly different from Continuous/Pulse

All tested animals had seroconverted to PRRSV by week 4. PRRSV ELISA titers peaked 6 weeks into the study (Figure 3). There were no differences in seroconversion to PRRSV detected among treatments.

Low and declining titers to SIV were present at the beginning of the study in all treatment groups. A significant rise in SIV titers occurred at 12 weeks in all three treatment groups (Figure 4). No differences in seroconversion to SIV were detected among the study groups.

Fourteen percent of the pigs tested were seropositive (S:P ratio breakpoint of 0.25) to *M. hyopneumoniae* at the initiation of the study, with positive animals present in each of the treatment groups. A significant rise in *M. hyopneumoniae* titers occurred beginning at 12 weeks in both the Pulse

and the Control groups, and at 16 weeks for the Continuous group (Figures 5 and 6).

Pigs were seropositive to TGEV at the initiation of the study with significant increases in titers at 4 weeks in all three treatment groups. TGEV seroconversion coincided with an observed increase in diarrhea throughout the barn. No differences in TGEV titers were detected among treatments.

There was minimal seroconversion to *Lawsonia intracellularis* and *Salmonella* at weeks 0 and 16, with no significant differences between groups.

### Cost:benefit analysis

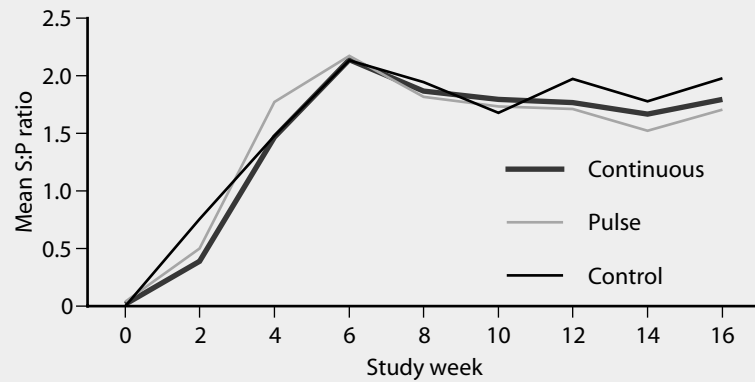
Assuming a fixed growth period, the economic advantage to using in-feed medications (due to additional pork produced [greater weight gain and reduced mortality]) more than offset the cost of medication under most of the feed cost and market hog price scenarios we modeled for this herd (Table 2). As an example, the use of feed medication was projected to be profitable when finishing feed costs were \$0.06 per lb and market hog prices were >\$22 per cwt. The sensitivity analysis constructed from this trial resulted in a net benefit of \$1-\$5 per head with live animal market prices of \$30-\$50 per cwt for this herd.

### Discussion

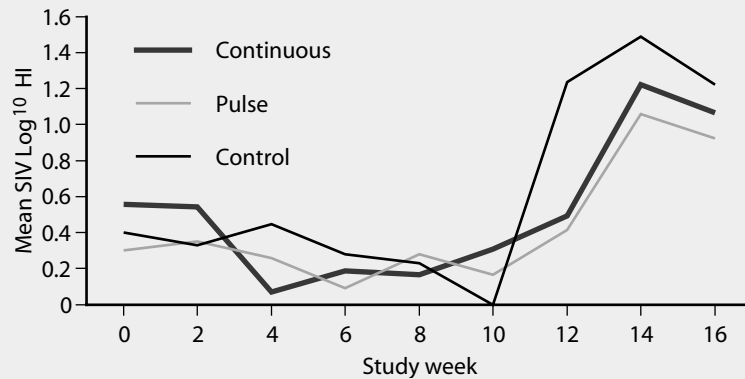
Because antibiotics do not affect viruses, the similar serologic response to the three viruses tested—PRRSV, SIV, and TGEV—in all three treatment groups was not unexpected. The serologic profile we observed for PRRSV was similar to those generated in controlled exposure studies with naïve animals,<sup>18</sup> although we observed a slower decline in titers at 12–16 weeks. The PRRSV serology suggests that pigs were exposed to PRRSV soon after being placed in the study facility, with additional exposure occurring 10–14 weeks post-placement. The serologic profile for SIV is consistent with waning maternal immunity at placement and exposure 8–12 weeks post placement. The progression of exposure to the viruses tested was: TGEV prior to arrival, PRRSV at 0–2 weeks, and SIV at 8–12 weeks post placement, with no differences in exposure detected among treatment groups.

Although we did not perform slaughter

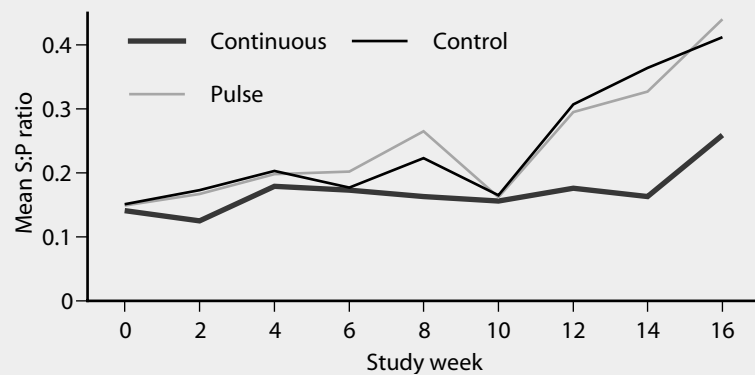
**Figure 3: PRRSV ELISA antibody response**



**Figure 4: SIV hemagglutination inhibition antibody response**



**Figure 5: *Mycoplasma hyopneumoniae* TWEEN 20 antibody response**

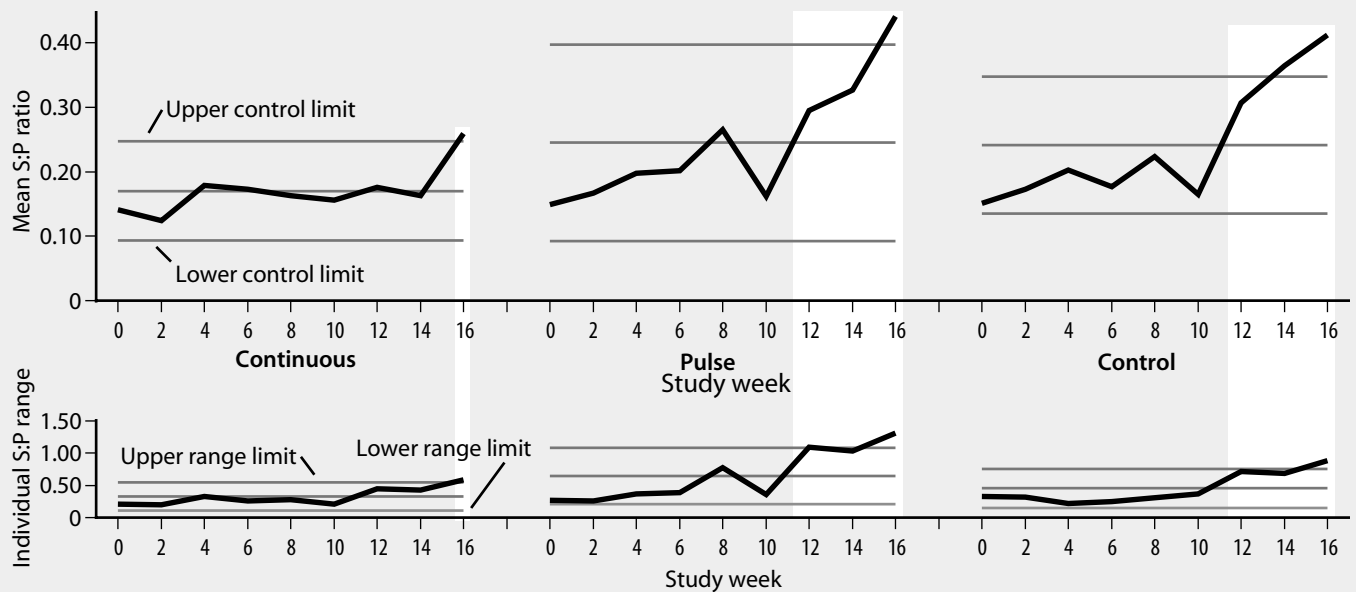


checks or necropsy symptomatic pigs to confirm the presence of mycoplasma-associated respiratory disease, seroconversion to *M. hyopneumoniae* has been shown to be associated with the development of gross lesions of mycoplasmal pneumonia and clinical signs typical of the disease.<sup>19–21</sup>

Results suggest that adequate exposure to *M. hyopneumoniae* for detectable changes in serologic response occurred between weeks 8–12 for the Pulse and Control groups, but was delayed in the Continuous group until weeks 14–16, when continuous medication had been withdrawn. This difference in serologic response suggests that

the pigs in the Control and Pulse groups received adequate natural exposure to *M. hyopneumoniae* during the nonmedicated period(s) to generate an active immune response. The Continuous group, although housed in the same airspace with the other groups and continuously exposed to *M. hyopneumoniae*, apparently received inadequate *M. hyopneumoniae* exposure to stimulate an immune response until the continuous medication was withdrawn late in the study (weeks 14–16). It is unlikely that the penicillin derivatives with which we injected affected pigs during the period of seroconversion to *M. hyopneumoniae* functioned as a confounder in this study,

**Figure 6:** *Mycoplasma hyopneumoniae* TWEEN 20 statistical process control serological analysis. Highlighted areas indicate timeframe of significant *M. hyopneumoniae* seroconversion.



**Table 2:** Economic analysis of treatment of respiratory disease

Pig price per cwt	Feed cost per pound					
	0.045	0.050	0.055	0.060	0.065	0.070
0.20	-0.04	-0.17	-0.30	-0.43	-0.56	-0.69
0.22	0.31	0.17	0.04	-0.09	-0.22	-0.35
0.24	0.65	0.52	0.39	0.26	0.13	-0.01
0.26	0.99	0.86	0.73	0.60	0.47	0.34
0.28	1.34	1.21	1.08	0.95	0.81	0.68
0.30	1.68	1.55	1.42	1.29	1.16	1.03
0.35	2.54	2.41	2.28	2.15	2.02	1.89
0.40	3.40	3.27	3.14	3.01	2.88	2.75
0.45	4.26	4.13	4.00	3.87	3.74	3.61
0.50	5.12	4.99	4.86	4.73	4.60	4.47
0.55	5.98	5.85	5.72	5.59	5.46	5.33
0.60	6.84	6.71	6.58	6.45	6.32	6.19

since penicillin is ineffective against *M. hyopneumoniae*.<sup>22</sup>

Seroconversion to *M. hyopneumoniae* using a monoclonal blocking ELISA assay has been shown to occur as early as 8 days post-infection in an experimental *M. hyopneumoniae* aerosol challenge study.<sup>20</sup> Seroconversion was detected as early as 9 days post-intratracheal challenge using a Tween-20 ELISA assay.<sup>23</sup> When exposed to these intratracheally challenged pigs, in-contact controls seroconverted using the Tween 20 ELISA assay as early as 7 days post-exposure.<sup>23</sup> ELISA seroconversion to *M. hyopneumoniae* is a reliable indicator of the presence of antibody, which may be due to passive maternal transfer, vaccination, or natural exposure. In the present study seroconversion to *M. hyopneumoniae* occurred in mid-to-late finishing in unvaccinated

pigs. This is well past the age when maternal immunity would have declined to an undetectable degree, indicating seroconversion was due to natural exposure. Protective immunity develops in swine recovering from mycoplasmal pneumonia.<sup>22</sup> Therefore, seroconversion due to natural exposure in the Control and Pulse-medicated pigs in the present study suggests that protective, active immunity developed in those groups.

Continuous medication improved growth performance but may have prevented stimulation of active immunity against mycoplasmal pneumonia, leaving animals immunologically naïve and potentially susceptible to subsequent re-exposure to *M. hyopneumoniae* when medication was withdrawn. Continuous feed antibiotic medication has also been shown to decrease the

prevalence of seroconversion to *Lawsonia intracellularis* in experimentally infected pigs.<sup>24</sup> The lack of a difference in growth performance we observed between the Pulse and Continuous groups suggests that pulse dosing is adequate to protect growth performance while permitting an active immune response, which may potentially provide long-term protection against endemic disease.

The nomenclature of human medicine with regard to “pulse,” “intermittent,” or “discontinuous” dosing differs somewhat from that of veterinary medicine. In human medicine, these terms refer primarily to once-daily dosing with antibiotics rather than the multiple daily doses that are typically prescribed.<sup>25,26</sup> In swine veterinary practice, the duration of medication pulses as well as the duration of the nonmedicated intervals are usually on the order of days or weeks.<sup>6–8</sup>

Mechanisms that contribute to the reported success of pulse dosing in human medical practice include the post-antibiotic effect (PAE),<sup>26,27</sup> post-antibiotic sub-minimum inhibitory concentration (MIC) effect (PA SME),<sup>27</sup> delayed tissue antibiotic depletion kinetics,<sup>28</sup> post-antibiotic leukocyte enhancement (PALE),<sup>29,30</sup> and adhesion inhibition.<sup>31</sup> Some of these effects are relatively short-lived<sup>32</sup> and it is not known whether they would contribute significantly to the outcome of veterinary pulse dosing as described herein. However the

interaction between sub-MICs of antibiotics and the immune system (especially phagocytosis) is probably of great importance<sup>27</sup> and the contribution of a functional immune system to the role of antibiotics in resolving infectious disease is recognized.<sup>33,34</sup> Our observation that seroconversion to *M. hyopneumoniae* was inhibited in pigs dosed with the low inclusion rate of 100 g per ton CTC (after pulse dosing with therapeutic levels of tiamulin and CTC) was somewhat surprising in light of the low dose administered, and may possibly be due to a PA SME or related mechanism. The PA SME differs fundamentally from the PAE and SME phenomena, even though its name implies similarity. Briefly, the PAE refers to the continued suppression of bacterial growth after administration of the drug is discontinued, an effect that generally persists for <2–4 hours.<sup>27</sup> The SME refers to decreased expression of virulence factors (e.g., adhesins, toxins, normal morphology, etc.), not necessarily decreased bacterial growth, when an organism is exposed to sub-MIC levels of drug.<sup>35</sup> SMEs of tiamulin against *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* virulence factor expression including reduced production of capsular polysaccharides, iron-regulated proteins, and hemolysins have been demonstrated.<sup>36</sup> The PA SME refers to a *prolonged period of growth suppression* (and concomitant virulence factor expression) when bacteria are exposed to sub-inhibitory concentrations of drug *after supra-inhibitory concentrations*.<sup>27</sup> Prolonged growth suppression of *M. hyopneumoniae* might explain the lack of seroconversion in the presence of natural exposure in the continuously medicated group of pigs in the present study, although a PA SME specifically for chlortetracycline against *M. hyopneumoniae* has not been reported.

The strategic use of pulse dosing is an example of 'metaphylactic' use of antimicrobials. Metaphylaxis can be defined as 'early treatment' after natural exposure to endemic disease organisms. With metaphylactic applications, some pathogen exposure generally occurs but intervention is initiated prior to an actual disease outbreak. The present study provides evidence that pulse dosing in this metaphylactic manner may facilitate the added benefit of stimulating active immunity (via natural exposure to endemic pathogens) for long-

term immunologic protection once the short-term 'cover' of medication is discontinued. Pulse dosing also decreased the total duration of antibiotic use from 12 weeks to 5 weeks in this herd, a potentially important additional consideration in light of current concerns regarding potential overuse of antimicrobials in food animal production. Metaphylaxis, implemented properly, may actually provide better health and performance with reduced antimicrobial use than traditional prophylactic or therapeutic approaches.

It is unlikely that there will be any 'cook book' metaphylactic program suitable for every herd. Diagnostics are needed to identify the organisms involved, their antimicrobial susceptibility profile, when they infect pigs, and when clinical disease typically occurs in that production system. Knowledge of the spectrum of activity and tissue distribution of the available antimicrobial options is needed to design a rational antimicrobial intervention plan whether it is prophylactic, metaphylactic, or therapeutic in intent. Swine practitioners are well equipped to provide that service, information, and advice to their pork producing clients.

Strategic pulse dosing may be appropriate for conditions where:

- management techniques (such as early weaning and age-segregated rearing) are unable to exclude infection of all piglets resulting in disease outbreaks in later stages of production;
- vaccines may not exist or may not be perceived to be cost-effective for the production-limiting diseases present;
- vaccination prior to disease exposure does not occur;
- multiple disease challenges exist, requiring the use of a broad-spectrum intervention tool; or
- continuous use of dietary antimicrobials is unacceptable.

## Implications

- Both Pulse and Continuous feed medication strategies significantly improved performance versus nonmedicated Controls as measured by growth rate, feed intake, feed conversion efficiency, and survivability.
- Metaphylactic pulse dosing with appropriate antimicrobials may

improve growth performance while permitting exposure to and stimulation of active immunity against mycoplasmal pneumonia.

- Continuous medication may improve growth performance without permitting sufficient natural exposure to and stimulation of active immunity against mycoplasmal pneumonia, leaving animals immunologically naïve and potentially susceptible to subsequent re-exposure when medication is withdrawn.

## Acknowledgements

The authors thank Jeff Beekhuizen, Kevin Karhoff, Court Garloff, Dale Polson, Dave Baum, and the Health Management Center team of Boehringer Ingelheim Vetmedica Inc. for their valuable assistance in the conduct and analysis of this study.

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