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AN INTRODUCTION TO TIAMUTIN®



As a world leading animal health company Novartis, manufacturer of Tiamutin®, is proud to be a major sponsor of the 2002 IPVS Congress, source of so much new and significant research information.

Over the past 22 years Tiamutin, the original member of the pleuromutilin family of antibiotics, has evolved as the leading therapeutic product for “pneumo-enteric” diseases.

Tiamutin is highly effective against traditional pig diseases like swine dysentery and enzootic pneumonia, yet is still a valuable weapon against emergent diseases such as ileitis and mycoplasmal arthritis. Tiamutin is not only the long-proven aid for the pig family industry but definitely an antibiotic “in step with time”.

It is our hope that these Proceedings – a collection of papers presented on Tiamutin at the 2002 IPVS – will be a reminder of Novartis Animal Health’s commitment to the global pig industry and assist you in your production related decisions.



In vitro susceptibility test of *Mycoplasma hyopneumoniae* to anti-microbial agents

Twenty-seven Thai field isolates of *Mycoplasma hyopneumoniae* were tested against nine antimicrobial agents.

Minimum Inhibitory Concentrations (MICs) - Ranges, 50% and 90% (mg/ml)

MICs for MH field isolates + reference strain (n = 27+1)			
	Range	50%	90%
Chlortetracycline	<0.024 - 3.125	0.39	1.56
Josamycin	<0.006 - 0.195	0.048	0.097
Lincomycin	<0.006 - 0.39	0.048	0.097
Nalidixicacid	<0.024 - 100	25	50
Oxytetracycline	<0.024 - 0.78	0.195	0.39
Spectinomycin	<0.024 - 100	0.39	1.56
Tiamulin	<0.006 - 0.097	0.006	0.048
Tilmicosin	<0.024-3.125	0.39	1.56
Valnemulin	<0.006	<0.006	<0.006

Key facts

- *M.hyopneumoniae* strains were exquisitely sensitive to tiamulin and valnemulin.
- Tiamulin: 2 times more active than lincomycin / josamycin, 8 times oxytetra-cycline.
- Valnemulin: 16 times more active than lincomycin / josamycin, 65 times oxytetra-cycline.
- Valnemulin is the most effective product against *M.hyopneumoniae*, even more effective than tiamulin.
- Moderate susceptibility was found to tilmicosin, oxy- and chlortetracycline.
- All tested isolates showed less sensitivity to spectinomycin and nalidixic acid.

P.Thongkamkoon & others

IN VITRO SUSCEPTIBILITY TEST OF *MYCOPLASMA HYOPNEUMONIAE* TO ANTIMICROBIAL AGENTS

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INTRODUCTION AND OBJECTIVES

Mycoplasmosis of swine or MPS, caused by *Mycoplasma hyopneumoniae* (MH) is a very important disease in the pig production industry. In Thailand it is also a serious economic problem. In 1997-98 the PRDC surveillance showed that all twelve investigated farms were infected and about 73.5 % of the sample pigs (147/200) were MH positive (9). Good hygiene management, vaccination and antibiotics are effective prevention and control measures of the disease. The susceptibility of microorganisms to antimicrobial agents may vary from place to place, due to different field isolates and how and what antibiotics are used. An MIC study of some MH field isolates will provide useful data to select effective antibiotics for treatment of the disease and reduce the residue risk from non-effective ones; also, it will be of benefit to pig production and consumers. The objectives of this study were 1) to determine the minimum inhibitory concentrations (MICs) for nine antimicrobial agents against 27 MH fields isolate and 2) to study the trend of drug resistance in Thailand.

MATERIALS AND METHODS

The 27 local isolates and 1 reference, J strain of MH, were kept at – 80°C and cultured in modified Friis's broth then subcultured for 3-4 times until the microorganism could grow rapidly within 2-3 days in 3-4 ml. broth. These were stored at – 80°C, with a small volume used to determine the culture concentration by ten-fold dilution and count on an agar plate. Eight anti-microbial drugs with concentration at 100 - 400 ug/ml. were prepared. The MH was taken from the stock to make a concentration at 5x10⁴ cfu/ml with modified Friis's broth and incubated at 35°C for 2 hours. 25 ul of broth was inserted into all wells of the 96 well microtiter plate except for the first column. 25 ul of antibiotic stock solution was inserted into all wells in the first and second column and diluted from the second column through to the last column. 175 ul of prepared isolates was added to this, one isolate per two rows. So for 28 isolates, 7 microtiter plates were used per antibiotic. The plates were covered and incubated at 37°C until the MH grew and was

inspected by change of colour in the control culture tube. Results for the MIC value of each drug which could inhibit MH growth is listed(8).

RESULTS AND DISCUSSION

All isolates were highly susceptible to valnemulin, tiamulin, josamycin and lincomycin, moderately susceptible to tilmicosin, chlortetracycline (CTC) and oxytetracycline (OTC) and less susceptible to spectinomycin and nalidixic acid. Valnemulin showed very highly activity against all MH isolates. MIC 90 was less than 0.006 ug/ml. Tiamulin was less active with MIC90 at 0.05 ug/ml, which was the same result as Surrey (4). The MIC range for CTC and OTC were not as high, compared to the data from Japan, whereas the MIC range for tiamulin, tilmicosin and lincomycin were similar to our study (5).

The use of antibiotics in each country was not the same so that results of the MICs range for certain drugs in each country were different. In Korea, the MICs range for tiamulin and OTC were higher than in this study (6). But data in Cambridge (2) gave the same result for OTC. In France, MIC90 for OTC was five fold higher than our study (1). Compare to data of Saitanu et al (7), the MICs range for many kinds of anti-microbial agents used in the pig industry in Thailand were in the same range and showed no evidence of resistance. It was concluded that most drugs tested in this study could be used effectively for the prevention and control of MPS in Thailand.

Table 1. MICs for *M. hyopneumoniae* determined by microtiter plate test

Drug	MIC (ug/ml) ^a from MH (n = 28)		
	range	50%	90%
Chlortetracycline	<0.024-3.125	0.39	1.56
Josamycin	<0.006-0.195	0.048	0.097
Lincomycin	<0.006-0.39	0.048	0.097
Nalidixicacid	<0.024-100	25	50
Oxytetracycline	<0.024-0.78	0.195	0.39
Spectinomycin	<0.024-100	0.39	1.56
Tiamulin	<0.006-0.097	0.006	0.048
Tilmicosin	<0.024-3.125	0.39	1.56
Valnemulin	<0.006	<0.006	<0.006

^a50% and 90%, MIC at which 50 and 90% of the strains tested, respectively are inhibited.

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A study on the minimum inhibitory concentration (MIC) of some antimicrobial agents against *Brachyspira hyodysenteriae* isolates detected from fattening farms in Thailand

Seven Thai field isolates of *Brachyspira hyodysenteriae* were tested against five antimicrobial agents. Minimum Inhibitory Concentrations (MICs) – Ranges and average values (mg/ml)

Isolates No.	Tiamulin	Valnemulin	Oxytetracycline	Lincomycin	Tylosin
1	2	0.25	256	64	512
2	2	0.25	256	64	512
3	4	0.25	128	64	512
4	2	0.5	128	64	512
5	0.125	0.25	256	8	512
6	0.125	0.25	128	8	256
7	0.125	0.25	128	8	512
Average value	1.482	0.286	182.9	40	475.4

Key facts

- Test results confirm the remarkable sensitivity of *B. hyodysenteriae* strains to the pleuromutilins (tiamulin, valnemulin).
- Valnemulin is the most effective product against *B. hyodysenteriae*, even more effective than tiamulin.
- Low susceptibility was found to lincomycin.
- All tested isolates showed resistance to oxytetracycline and tylosin.

S. Luengyosluechakul & others

A STUDY ON THE MINIMUM INHIBITION CONCENTRATION (MIC) OF SOME ANTIMICROBIAL AGENTS AGAINST *BRACHYSPIRA HYODYSENTERIAE* ISOLATES DETECTED FROM FATTENING FARM IN THAILAND

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INTRODUCTION AND OBJECTIVES

Swine Dysentery (SD) is emphasized as a severe mucohemorrhagic enterocolitis of pigs in most parts of pig-rearing areas of the world so as in Thailand. The large anaerobic spirochete causative agent, *Brachyspira hyodysenteriae* (Bh), characterize by its powerful B-hemolysin on blood agar when propagate and has 7 to 14 periplasmic flagellas inserted at each cell end (3). SD may cause a tremendous financial loss due to the high mortality, poor growth rate together with poor feed conversion and the cost of treatment. Recover pigs of subsided clinical sign and symptom may shed the organisms in their faeces up to 70 days (4). Attempts to control the disease based on an accurate field and laboratory diagnosis and the proper drug therapies against Bh. However, problems of antibacterial resistance at different levels do occur among field practices. The objective of this study is to indicate the minimum inhibition concentration (MIC) of the commonly used anti-microbial agents against Bh isolates detected from fattening pig farms in Thailand.

MATERIALS AND METHODS

Fresh blood tinged faecal samples of clinical cases with history of acute or chronic mucohemorrhagic diarrhoea in grower and finisher pigs were collected from 10 farms in central part of Thailand. Bacterial isolation was undertaken on selective media under anaerobic condition with the atmosphere of 80% N₂, 10% H₂, 10% CO₂ incubated at 42°C for a period of one week. At intervals of every other day the bacterial growth on blood agar was observed. Bacterial identification for Bh colony is characterized by a beta hemolysin together with the positive ring test and the production of indole. The MIC of TML (Tiamulin), VML (Valnemulin), OTC (Oxytetracycline), LIN (Lincomycin) and TLS (Tylosin) against each positive isolate are undertaken by the agar dilution method (1).

RESULT AND DISCUSSION

All together there were 7 field isolates of Bh obtained from pig farms during the second half of 2001. An in vitro evaluation of 5 different anti-microbial agents has been carried out, and the results are as follows. The

MIC for TML begins as low as 0.125 mg/ml to 4.0 mg/ml, with the average value of 1.482 mg/ml. VML begins as low as 0.25 mg/ml to 0.5 mg/ml, with the average value of 0.286 mg/ml. OTC begins as 128 mg/ml to 256mg/ml, with the average value of 182.9 mg/ml. LIN begins as 8 mg/ml to 64 mg/ml, with the average value of 48 mg/ml. And TLS begins as 256 mg/ml to 512 mg/ml, with the average value of 475.4 mg/ml. Table 1 shows the susceptibility of each isolates to different anti-microbials. When we compare the two lowest MICs of TML to VML, it is 5.2 times higher in TML.

Table 1. The MICs of antimicrobials to Bh field isolates

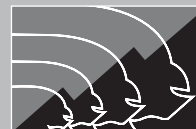
Isolates	TML (mg/ml)	V ML (mg/ml)	OTC (mg/ml)	LIN (mg/ml)	TLS (mg/ml)
1	2	0.25	256	64	512
2	2	0.25	256	64	512
3	4	0.25	128	64	512
4	2	0.5	128	64	512
5	0.125	0.25	256	8	512
6	0.125	0.25	128	8	256
7	0.125	0.25	128	8	512

No resistance occurs to VML among the tested isolates. None of them has the MIC which greater than 1 mg/ml, brings to support the related work of Dalziel (1996) with TML in the UK. TML has the MIC of 0.125 mg/ml for 3 isolates, the other 4 isolates are of greater than 1 mg/ml (2-4mg/ml). This reveals trends of the resistance but only in some areas. Other tested antimicrobials are of less sufficient value to treat SD.

It is concluded that VML and TML are the only recommended two antimicrobial agents with sufficient MIC value to cope the production problem caused by Bh during the time of survey. Other agents are either not approved for use or only partly active against Bh.

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The impact of tiamulin administered in the water on the performance of growing swine with clinical porcine proliferative enteritis

An artificial infection study was carried out to test the efficacy of tiamulin by administration in water at 60 ppm for 5 days.

SUMMARY OF THE PERFORMANCE RESULTS

Treatment Groups	Group 1 (n=9)	Group 2 (n=9)	Group 3 (n=9)	P value
LI Challenge	No	Yes	Yes	—
Tiamulin	0 ppm	60 ppm	0 ppm	—
Mean bodyweights (kg)				
Day 0 (challenge)	0.84	10.61	10.84	—
Day 7 (administer trt)	13.94 a	12.39 b	12.48 b	<.01
Day 12 (remove trt)	16.96 a	14.28 b	13.69 b	<.001
Day 22 (necropsy)	22.86 a	18.42 b	15.16 c	<.05
Performance parameters Days 7-22				
ADG, g (+SD)	594 a (+154)	402 b (+195)	179 c (+185)	<.05
ADFI, g (+SD)	1146 a (+149)	908 b (+179)	855 b (+172)	<.05
ADG:ADFI	0.518 a	0.424 a	0.201 b	<.05
ADWI, g (+SD)	3116 a (+805)	2457 b (+764)	2592 b (+1033)	—
Mortality	0/9	0/9	0/9	—

ADG = average daily weight gain; ADFI = average daily feed intake;
ADWI = average daily water intake

abc Means with the same letter are not different (P value stated)

Key facts

- Challenge with *Lawsonia intracellularis* (dose 1×10^9) organisms had a dramatic negative impact on the performance of the pigs.
- Administration of tiamulin in the water provided significant ($p < 0.05$) improvement in weight gain and feed conversion compared to the infected unmedicated control group.
- Tiamulin administered in the water is highly effective in minimizing the impact of PPE on growth performance.

THE IMPACT OF TIAMULIN ADMINISTERED IN THE WATER ON THE PERFORMANCE OF GROWING SWINE WITH CLINICAL PORCINE PROLIFERATIVE ENTERITIS

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INTRODUCTION

Tiamulin is a pleuromutilin antimicrobial approved for the control of porcine proliferative enteropathies when administered in the feed. The efficacy of tiamulin administered in feed or water has also been demonstrated in pure culture challenges of *Lawsonia intracellularis* (1). The objective of this evaluation was to assess the impact of tiamulin administered in the water at 60 ppm for 5 days on the growth performance of young growing swine using a mucosal homogenate challenge model.

MATERIALS AND METHODS

Crossbred pigs (large white breeds) between 5-6 weeks of age (9.0-12.2 kg) were obtained from a commercial herd with no history of PPE or recent antibiotic therapy and transported to a research barn. On Day 0, pigs were individually identified using ear tags, weighed, and blocked by weight. Nine pigs were randomly selected within blocks as non-challenged controls and received non-medicated water (Group 1) and the remaining pigs were restrained and orally dosed with sufficient mucosal homogenate (obtained from intestines of previously infected pigs) to challenge each pig with approximately 1×10^9 *Lawsonia intracellularis* organisms.

Seven days following challenge (day 0), the pigs were randomly assigned to receive either tiamulin hydrogen fumarate (Denagard) at 60 ppm in the water for 5 days (Group 2, n=9), or non-medicated water (Group 3, n=9). All pigs were housed in individual pens on slatted cement flooring with solid pen dividers between pens and open wire gating toward the aisles. Clinical observations were conducted daily (days 0-15), individual bodyweights were recorded on days -7, 0, 5 and 15, individual water consumption was recorded daily (days 0-15), and individual feed consumption was monitored from days 0-15). Bodyweight and water consumption were analyzed using repeated measures ANOVA (2). Average daily gain (ADG), average daily feed intake (ADFI), and feed efficiency (ADG/ADFI) were analyzed using ANOVA (2). Based upon actual water consumption, bodyweights, and water analysis, the average tiamulin dosage was 9.26 mg/kg/day (4.21 mg/lb/day) during the 5-day treatment period.

RESULTS AND DISCUSSION

The impact of PPE on growth performance was dramatic. Although there was no mortality in any of the three groups, weight gain in group 3 (challenge controls) was reduced to 30% of group 1 (non-challenged controls) from day 0-15 (179 v 594 g/hd/d). The administration of tiamulin in the water did provide significant ($p < 0.05$) improvement in weight gain compared to group 3, but was significantly lower than group 1. The PPE challenge also significantly ($p < 0.05$) reduced feed and water intake and negatively impacted feed conversion when comparing groups 1 and 3. The administration of tiamulin significantly ($p < 0.05$) improved feed conversion comparing group 2 and 3.

See Summary of Performance Results on previous page.

CONCLUSIONS

Based upon results of this mucosal homogenate challenge, PPE infection had a dramatic negative impact on performance in young growing pigs this was ameliorated with the administration of tiamulin in the water. Prevention of PPE should be the primary goal; however, in production systems where this is not possible, tiamulin administered in the water is very effective in minimizing the impact of PPE on growth performance.

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In vitro susceptibility of *Brachyspira hyodysenteriae* strains isolated in the Czech Republic from 1996 to 2001

The antimicrobial susceptibility of *B. hyodysenteriae* strains against different anti-microbials was tested between 1996 and 2001. The isolates originated from a selected number of farms representing 8% of the pig production in Czech Republic.

MIC₅₀ of various antimicrobial agents for field isolates of *B. hyodysenteriae*

Drugs/yr	1996/97 n = 20	1998 n = 20	1999 n = 20	2000 n = 20	2001 n = 20	1996- 2001
Tiamulin	0.06	0.125	0.125	0.50	1.0	0.250
Valnemulin	< 0.03	< 0.03	0.06	1.0	2.0	0.125
Lincomycin	32	16	32	32	32	32
CTC	2	2	4	2	4	4
AIT	25	12.5	25	25	25	25
Tylosin	> 128	> 128	NT	NT	NT	
Ipronidazole	1.0	1.0	NT	NT	NT	
Olaquinox	0.25	1.0	NT	NT	NT	
Salinomycin	0.25	0.25	NT	NT	NT	

MIC₉₀ of various antimicrobial agents for field isolates of *B. hyodysenteriae*

Drugs/yr	1996/97 n = 20	1998 n = 20	1999 n = 20	2000 n = 20	2001 n = 20	1996- 2001
Tiamulin	0.250	0.250	1.0	2.0	4.0	2.0
Valnemulin	< 0.03	0.125	2.0	4.0	8.0	4.0
Lincomycin	32	64	64	32	64	64
CTC	8	8	8	4	8	8
AIT	50	25	25	50	50	50
Tylosin	> 128	> 128	NT	NT	NT	
Ipronidazole	4.0	1.0	NT	NT	NT	
Olaquinox	1.0	1.0	NT	NT	NT	
Salinomycin	1.0	0.5	NT	NT	NT	

Not tested, AIT – Acetylisovaleryltylosin, CTC-Chlortetracycline

Key facts

- Tiamulin and valnemulin showed the lowest MIC values of all tested drugs.
- Distinct resistance of the tested *Brachyspira* strains to tylosin and lincomycin was found during the evaluation period.
- Trial results reveal a trend of gradually increasing MIC values for tiamulin and valnemulin.
- Tiamulin and valnemulin are the drugs of choice for the treatment of swine dysentery in the Czech Republic.

IN VITRO SUSCEPTIBILITY OF *BRACHYSPIRA HYODYSENTERIAE* STRAINS ISOLATED IN THE CZECH REPUBLIC FROM 1996 TO 2001

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INTRODUCTION AND OBJECTIVES

Since 1998 a dramatic increase of farms with clinical forms of swine dysentery has been registered. This was due to two predisposing factors:

- 1.) The State Veterinary Service registered swine dysentery as a contagious disease with compulsory reports before 1996. After adoption of EU legislation swine dysentery was removed from the list of contagious diseases of pigs and, therefore, it began to spread to many new farms.
- 2.) The growth promoter olaquinox and the nitroimidazoles with anti-dysenteric activity were widely used and prohibited at the end of 1998. Systematic bacteriological diagnosis of swine dysentery, including MIC (minimal inhibitory concentration) test, was started in 1996 and periodical surveillance was provided in large-scale farms. The aim of our study was to evaluate antimicrobial susceptibility of *B. hyodysenteriae* strains isolated during the last five years.

MATERIAL AND METHODS

One hundred field strains of *B. hyodysenteriae* isolated from 63 pig farms between 1996 and 2001 were investigated. The strains were confirmed by strong haemolysis testing of biochemical activity according to Fellström and Gunnarsson (1995) (3) and polymerase chain reaction (2). The strains of *B. hyodysenteriae* were stored at -80°C using cryopreservative medium. MIC values for tiamulin, valnemulin (Novartis), lincomycin (Pharmacia/Upjohn), chlortetracycline (Sigma), acetylisovaleryltylosin (Eco), tylosin (Elanco), ipronidazole (Farchemia), olaquinox (Bayer) and salinomycin (Hoechst) were determined by the agar dilution method in Wilkins-Chalgren anaerobe agar (Oxoid) supplemented with 5% defibrinated ovine blood. Three-day cultures were suspended in Tryptose soya broth (BBL) and adjusted to 1×10^6 CFU/ml. Thereafter, $20 \mu\text{l}$ suspension of each strain was inoculated on surface of agar medium with two-fold dilutions of anti-dysenteric drugs and control plate. The plates were incubated anaerobically at 37°C for 3 days. The lowest concentration of drug

that prevented haemolysis was assessed as MIC value. Each strain was tested repeatedly three times. Type strain of *B. hyodysenteriae* (B78-ATCC 27164^T) was used as control. Tylosin, ipronidazole, olaquinox and salinomycin were tested only at the end of 1998 after growth promoters and nitroimidazoles were prohibited and the majority of strains were resistant to tylosin *in vitro*.

RESULTS AND DISCUSSION

Values of MIC₅₀ and MIC₉₀ for *B. hyodysenteriae* strains isolated during five years are summarized in Table 1 and 2. MICs for majority of drugs were high in the monitored years, except for the pleuromutilins (tiamulin, valnemulin). According to the interpretive criteria proposed by Rønne and Szancer (1990) (5) about 80% of the strains were resistant to lincomycin and tylosin. No standards were available for chlortetracycline and acetylisovaleryltylosin, which have been authorized for use with pigs in the Czech Republic since 2000. Surprisingly MIC₉₀ values for acetylisovaleryltylosin were lower than MIC₉₀ tylosin. On the other hand, pleuromutilins had the lowest MIC values of all tested drugs. But the MIC₉₀ values have been gradually increasing in the last two years. These results have to be interpreted with some caution as most of the strains were obtained from farms with poor hygienic conditions (i.e. deep litter, continuous operation) with inappropriate use of antimicrobial drugs in spite of swine dysentery. However, similar trends as indicated in this study were also observed in the UK (1) and Belgium (4).

Based on our results, pleuromutilins should be the first choice of drugs for early treatment of swine dysentery in the Czech Republic with a limitation for its use for preventive purposes. The only drugs that remain for eradication programs are tiamulin and valnemulin, which showed solid results. In contrast with EU countries, valnemulin was widely used in the Czech Republic from the beginning of its approval in November 1998. Last year approx. 50% of the yearly production of pigs (2.5 million) were treated by the pleuromutilins. Monitored farms represented only 8% of the production.

Table 1: Comparison of 9 anti-dysenteric drugs for MIC₅₀ to *B. hyodysenteriae* strains

Drugs/yr	1996/97 n = 20	1998 n = 20	1999 n = 20	2000 n = 20	2001 n = 20	1996- 2001
Tiamulin	0.06	0.125	0.125	0.50	1.0	0.250
Valnemulin	< 0.03	< 0.03	0.06	1.0	2.0	0.125
Lincomycin	32	16	32	32	32	32
CTC	2	2	4	2	4	4
AIT	25	12.5	25	25	25	25
Tylosin	> 128	> 128	NT	NT	NT	
Ipronidazole	1.0	1.0	NT	NT	NT	
Olaquinox	0.25	1.0	NT	NT	NT	
Salinomycin	0.25	0.25	NT	NT	NT	

Table 2: Comparison of 9 anti-dysenteric drugs for MIC₉₀ to *B. hyodysenteriae* strains

Drugs/yr	1996/97 n = 20	1998 n = 20	1999 n = 20	2000 n = 20	2001 n = 20	1996- 2001
Tiamulin	0.250	0.250	1.0	2.0	4.0	2.0
Valnemulin	< 0.03	0.125	2.0	4.0	8.0	4.0
Lincomycin	32	64	64	32	64	64
CTC	8	8	8	4	8	8
AIT	50	25	25	50	50	50
Tylosin	> 128	> 128	NT	NT	NT	
Ipronidazole	4.0	1.0	NT	NT	NT	
Olaquinox	1.0	1.0	NT	NT	NT	
Salinomycin	1.0	0.5	NT	NT	NT	

Not tested, AIT – Acetylisovaleryltylosin, CTC-Chlortetracycline

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