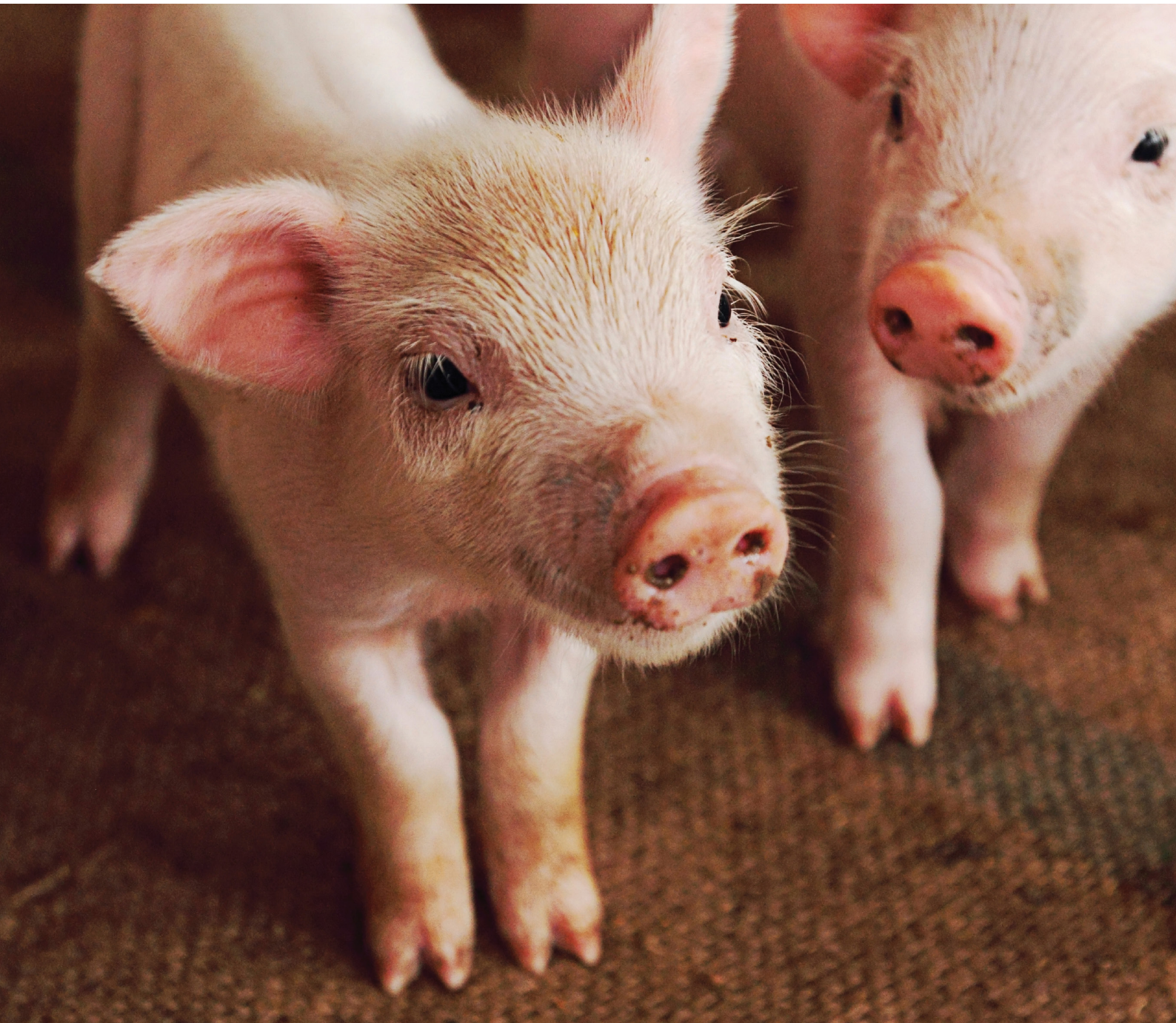
NZVA
New Zealand Veterinary Association

Guide to prudent use of antimicrobial agents in

Pigs



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Foreword

Good anti-microbial usage and authorising practices at farm level are essential tools to ensure that both the needs of the food industry and the expectations of consumers are met.

In many cases, antimicrobial agents are life-saving medicines both within human and veterinary medicine. One of the largest threats against public and animal health is, however, the increase in antimicrobial resistance. Antimicrobial-resistant bacteria can be transferred between animals and humans and thus, in the case of the veterinary use of antimicrobials, the benefits must be weighed-up against the possible effects on public health.

Resistance development can be counteracted by the responsible use of antimicrobials, good hygiene and active disease control. Active advice to animal owners on, for example, hygiene and vaccination also plays an important part.

In July 2015 the New Zealand Veterinary Association produced an aspirational statement, "By the year 2030 New Zealand Inc. will not need antibiotics for the maintenance of animal health and wellness." This is an aspirational statement that means the veterinary profession is taking leadership on the issue of antimicrobial stewardship.

Clearly antimicrobial therapy will still be relevant and animal welfare is the overriding factor. However, by taking this position the profession is removing itself from dependency on, and possible misuse of, antimicrobials in the effort to ensure that these drugs remain valuable weapons in the therapeutic armoury, not only of veterinarians themselves, but also the human medical profession.

The objective of this document is to provide a guide that can be used when deciding upon a course of treatment and it is written for current New Zealand conditions and practices.

Antimicrobial treatment is normally only indicated if both of these criteria are fulfilled:

- A bacterial infection is known to be present (or when there is sufficient cause to suspect that an actual bacterial infection is present)
- The infection, in all likelihood, will not resolve without the support of antimicrobial therapy.

If there are equivalent methods of treatment by which antimicrobial agents are not used, these should be the chosen courses of therapy. It is of fundamental importance that antimicrobial agents should only be used when absolutely necessary and that the occurrence of infections should be counteracted, whenever possible, by means of preventative measures.

Prophylactic antimicrobial treatment can in a few specific situations be required with specific surgical procedures, where the risk for bacterial infection is high or where an infection can drastically worsen the prognosis. The prophylactic use of antimicrobial agents should never be implemented to compensate for poor hygiene.

When possible, the actual infectious agent should be demonstrated by means of laboratory examination. This is especially important in cases of therapy failure, relapse and on other occasions when antimicrobial resistance can be suspected. Samples should always be taken pre-treatment from infections that arise postoperatively.

The risk of antimicrobial resistance should always be taken into consideration when choosing an antimicrobial agent. This means that the antimicrobial agent and the route of administration should be chosen so that the animal's normal flora is affected as little as possible (so-called narrow-spectrum antimicrobials). With this in mind, local treatment when correctly implemented can be preferable, provided that its effect is thought to be sufficient. Any effect on the normal flora can also be minimised if the course of treatment is kept as short as possible and is then discontinued if the indication is no longer thought to be applicable.

As antibiotic usage and resistance profiles may differ between regions these guidelines are naturally broad, encompassing principles, and individual veterinary practices are encouraged to develop their own authorising habits based upon these principles.

The term "antimicrobial agent" is used rather than "antibiotic" in this Guide. The term antimicrobial agent is as defined by the World Organisation for Animal Health (OIE) and means a naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (kills or inhibits growth of microorganisms) at concentrations attainable in vivo.

Anthelmintics and substances classed as disinfectants or antiseptics are excluded from this definition. Antimicrobial agents are inclusive of anti-bacterials, anti-virals, anti-fungals and anti-protozoals.

The guiding objective is that milk and meat should be produced from healthy animals under generally accepted agricultural conditions, with minimal and controlled use of antimicrobial agents.

Acknowledgments

These guidelines have been formulated by the Antimicrobial Working Group appointed by the NZVA.

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Core principles

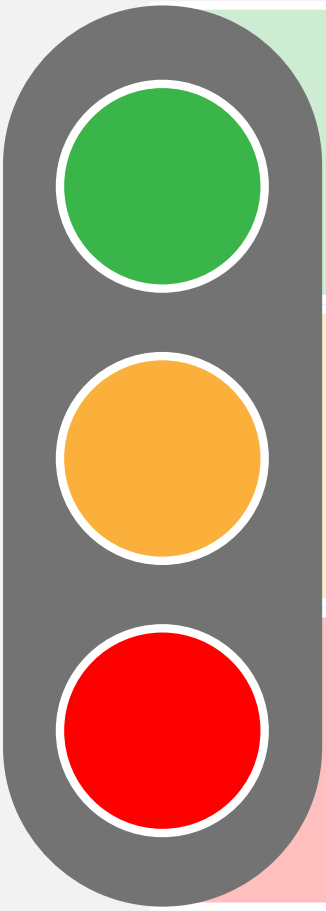
1. All farmers and their veterinarians must be totally committed to producing safe food.
2. Farms should be managed to reduce the risk of disease challenge and, therefore, the need to use antibiotics and other medicines.
3. Farmers and their veterinarians should draw up, implement and regularly review an appropriate herd health plan that outlines routine preventive treatments (e.g. biosecurity, hygiene approaches, vaccination programmes etc.) and disease control policy.
4. Antibiotics should only be authorised by a veterinarian when there is evidence of a susceptible bacterial infection, treatment is necessary to maintain animal health and welfare and no other treatment such as drainage or antisepsis is likely to be effective. Treatment should be restricted to individual animals where possible.
5. Choice of antibiotic should be based on knowledge of common pathogens and local laboratory data.
6. Antibiotics and dose regimes should be chosen to minimise the development of clinically significant resistance in people or animals.
7. An appropriate withholding time must be applied before the slaughter of treated animals.
8. Accurate information recording the identity of the treated animals, the nature of the condition being treated, drugs used and withholding period must be kept.

Antimicrobial classification

The traffic light antimicrobial principle in veterinary medicine is designed to:

1. promote judicious and effective veterinary antimicrobial use
2. limit potential selection for key mechanisms of resistance
3. acknowledge that efficacy of antimicrobials for human therapy is prioritised

The traffic light system ranks antimicrobials according to an amalgam of both OIE and WHO guidelines.



Green antimicrobials

1. Procaine penicillin
2. Penethamate hydriodide
3. Tetracyclines

Green does not mean an antimicrobial is 'safer' nor that it is not important in human medicine. Where possible, green antimicrobials are recommended against known susceptible organisms. Green light antimicrobials should not be used in situations where efficacy is in doubt – in this instance, an orange or red choice is appropriate.

Orange antimicrobials

1. Aminoglycosides
2. Semi-synthetic penicillins (ampicillin/clavulanic acid, cloxacillin)
3. 1st and 2nd generation cephalosporins
4. Lincosamides
5. Potentiated sulphonamides

Orange refers to antimicrobials that are either of a different class or have specialised features, such as beta lactamase inhibition, that make them of more critical relevance to human therapy. Orange light antimicrobials should not be used where efficacy is in doubt.

Red antimicrobials

Treatment of refractory conditions (human and veterinary). Veterinary diagnosis and evidence indicates need; efficacy of other classes is limited.

1. 3rd and 4th generation cephalosporins
2. Fluoroquinolones
3. Macrolides

Red light antimicrobials are antimicrobial classes used in veterinary medicine that are deemed of highest importance in human therapy.

If a "red light" antimicrobial is deemed the most appropriate (culture and sensitivity testing may be required) then it should be used in preference to a green or orange antimicrobial that has limited efficacy.

General guidelines classifying antimicrobials according to a three tier (traffic light) system have been adopted by the New Zealand Veterinary Association and have been well accepted by the New Zealand veterinary profession.

The NZVA classifications are based on (but differ slightly from) the World Health Association (WHO) classification and consider the World Organization for Animal Health (OIE) recommendations as well.

They are less restrictive and classified to suit practical guidelines for veterinary practice in New Zealand.

The two classification systems agree on the red category. All other antimicrobials used by veterinary clinicians are either critically to or highly important to human medicine.

It is important to realise that the NZVA green traffic light category does not represent "safe" antimicrobials classes and nor does a red antimicrobial mean "do not use."

The front line or first choice antimicrobials principle in veterinary medicine:

1. limits the classes of antimicrobials used
2. in theory, limits the mechanisms of resistance that are selected for
3. delivers a first-line tool kit of antimicrobials likely to be effective in most cases.

If a "red light" antimicrobial is deemed the most appropriate (culture and sensitivity testing may be required) then it should be used in preference to a green or orange antimicrobial that has limited efficacy.

Regardless of color, use of an antimicrobial that is not effective increases risk with no benefit. It is total amount of antimicrobial use that is the major driver for antimicrobial resistance.

Any decision to use antimicrobials must be a clinical judgement incorporating, when possible, the following principles:

1. Consideration should always be given to the antimicrobials pharmacokinetic and pharmacodynamic properties to ensure enough of the appropriate antibiotic is available at the biophase
2. Culture and susceptibility should be utilised, when clinically relevant, to aid in the selection of an antimicrobial.
3. A narrow-spectrum antimicrobial should be used in preference to a broad-spectrum antimicrobial whenever appropriate.

The 5 R's

The 5 Rs is an acronym originating in the UK in application to animal welfare but now equally applied to antimicrobial stewardship and refers to reduction, refinement and replacement (where possible) of antimicrobials and also responsibility (taking ownership of the issue) and review (constantly monitoring progress).

Reduction

Reduction is achieved by:

1. Preventative measures:
   a. Husbandry
   b. Vaccination
   c. Monitoring
   d. Training
2. Elimination of use of antimicrobials where they are of limited or no use, (for example, in uncomplicated viral infections or in a lame cow where hoof trimming only is needed) this requires.
   a. Accurate diagnosis
   b. Training
   c. Treatment guidelines detailing when not to use antimicrobials
3. Use of topical/local antimicrobials in preference to systemic delivery.

Refinement

Continuously evaluate authorising practises and therapeutic plans, based on:

a. Response to treatment with reference to the desired treatment outcomes
b. Repeat cases
c. Clinical studies
d. In-house and local resistance data
e. Industry use guidelines

Replacement

Selection pressure can be reduced with adoption of an alternative, non-antimicrobial, approach. For example, vaccination and rodent control for prevention of leptospirosis.

The decision to use an alternative must be evidence based on, and take into consideration, the health and welfare outcomes for the animal. Replacement should only be instigated when there is peer reviewed evidence that this will be equally or more effective than antimicrobial treatment.

Responsibility

Without engagement, understanding and personal responsibility of all people involved in the authorisation, treatment and management of stock, antimicrobial stewardship plans cannot hope to achieve the desired outcomes.

Engagement will be achieved through:

1. Positioning of a programme and clear description of the 'reasoning' to all involved
   a. What's in it for me?
   b. What's in it for the animals?
   c. What's in it for the business?
   d. What's in it for the industry and community?
2. Ensuring understanding of the core principles not just the operational procedures
3. Encouragement of 'upward leadership' – empowerment of team members to contribute to success of the plan, bring new ideas and innovation and refine the processes.

Review

A stewardship plan is a 'living document' and will be subject to periodic (at least annually) review to ensure objectives are met.

1. Animal health and welfare outcomes remain top priority and monitored to ensure they are achieved.
2. Protocols should be reviewed for compliance and relevance by the veterinarian on a yearly basis.
3. There should be awareness of any susceptibility data available to ensure appropriate selection of antimicrobials, maximise efficacy and monitor resistance in target pathogens.
4. Investigation of strategies that can be employed to improve stewardship of antimicrobials within a veterinary practice should occur on an on-going basis.

Common pathogens in the disease of pigs and the ages in which they are seen

(From AVA antimicrobial prescribing guidelines for pigs)

Age in weeks	Clinical signs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Enterotoxigenic (non-haemolytic) *Escherichia coli*	Diarrhoea																					
Clostridium perfringens	Diarrhoea																					
(Rotavirus)	Diarrhoea																					
(Coccidiosis)	Diarrhoea																					
Enterotoxigenic and enterotoxaemic (haemolytic) *Escherichia coli*	Diarrhoea, sudden death																					
(Mulberry heart disease)	Sudden death																					
Streptococcus suis	Meningitis, lameness, sudden death																					
Haemophilus parasuis	Polyserositis, lameness, sudden death																					
Mycoplasma hyorhinis	Polyserositis, sudden death																					
Salmonellae	Diarrhoea, sudden death																					
Mycoplasma hyosynoviae	Lameness																					
(Porcine circovirus associated disease)	Sudden death, Ill thrift																					
Lawsonia intracellularis	Diarrhoea, ill thrift, sudden death																					
Brachyspira hyodysenteriae	Diarrhoea																					
Mycoplasma hyopneumoniae +	Coughing, sudden death																					
Actinobacillus pleuropneumoniae+	Coughing, sudden death																					
Erysipelas	Diamond skin lesions, lameness, sudden death																					

+ Includes secondary invaders, such as *Pasteurella multocida*, *Bordetella bronchiseptica*, *Streptococcus suis* and *Klebsiella pneumoniae*, which may exacerbate primary infections. Diseases or pathogens in parentheses are included for completeness, although they are not treated with antimicrobial drugs. In the last 20 years the global impact of the *porcine circovirus type 2* (PCV2) vaccines has been significant. In Australia, as elsewhere, their deployment has facilitated reduced reliance on antimicrobial treatments and metaphylaxis. In apparently normal herds PCV2 vaccines have reduced post weaning mortality rates by 3-6% without the need for concurrent antimicrobial treatment.[12]

Authorising guidelines

Pathogen	Clinical signs	Prevention	First line	Second line	Notes
Actinobacillus pleuropneumoniae	Coughing, sudden death	Vaccine	Penicillin, Amoxicillin	Tilmicosin	Cephalosporins not recommended
Brachyspira hyodysenteriae (Swine dycentery)	Diarrhoea	Hygiene	Tiamulin	Lincomycin Tylosin	Monensin not recommended
Clostridium perfringens	Diarrhoea	Hygiene, thermal comfort, colostrum management	Penicillin, Amoxicillin	Tylosin Tulathromycin	Cephalosporins not recommended
Enterotoxigenic (non-haemolytic) Escherichia coli	Diarrhoea	Vaccine, hygiene, thermal comfort, colostrum management	Fluids + oral Neomycin Trimethoprim/sulpha	Marbofloxacin	
Enterotoxigenic or enterotoxaemic (haemolytic) Escherichia coli	Diarrhoea, sudden death	Live oral autogenous vaccine, thermal comfort, diet, organic acids in feed/water, bromelain extract	Neomycin, Trimethoprim/sulpha	Marbofloxacin	Cephalosporins not recommended
Erysipelothrix rhusiopathiae	Diamond skin lesions, lameness, sudden death	Vaccine	Penicillin, Amoxicillin	Lincomycin Tylosin	
Haemophilus parasuis	Sudden death, polyserositis lameness	Air quality, space allowance, vaccination	Penicillin, Amoxicillin	Tulathromycin	
Isopora suis	Diarrhoea	Hygiene, prophylactic toltrazuril	Toltrazuril		As a coccidiostat Toltrazuril is not colour rated
Lawsonia intracellularis (Proliferative enteritis)	Diarrhoea, ill thrift, sudden death	Vaccine, hygiene	Tylosin	Tiamulin Marbofloxacin	Intracellular parasite Penicillins and aminoglycosides ineffective
Leptospirosis	Abortions occurring 2–4 weeks before term	Vaccination, rodent control, and feed and water free of Leptospira organisms.	Penicillin	Amoxicillin	High rates of pig-to-pig transmission among swine reared in confinement.
Mycoplasma hypopneumoniae (Enzootic pneumonia)	Coughing, sudden death	Vaccine, air quality, space allowance	Tiamulin Tetracycline	Tylosin Marbofloxacin	
Mycoplasma hyorhinis	Lameness, arthritis	Air quality, space allowance	Tiamulin Tetracycline	Lincomycin Tylosin	
Pasteurella multocida	Coughing, sudden death	Air quality, space allowance	Oxytetracycline, Penicillin, Amoxicillin	Trimethoprim/sulpha Marbofloxacin	
Salmonellae	Diarrhoea, sudden death	Hygiene, thermal comfort, organic acids in feed/water	Neomycin	Trimethoprim/sulpha Marbofloxacin	Cephalosporins not recommended
Streptococcus suis	Meningitis, lameness, sudden death	Air quality, space allowance	Penicillin	Trimethoprim/sulpha Tylosin	Cephalosporins not recommended
Streptococcus hyicus	Exudative epidermatitis	Hygiene	Penicillin, Amoxicillin	Tiamulin Trimethoprim/sulpha	

Note that tiamulin was not rated on the NZVA traffic light system but, as it is a class of antibiotic not used in human medicine, it will be of lower importance to WHO and hence is designated green here.

Recommended dose rates for antimicrobials in pigs

Note: Many of these dose rates are taken from the *AVA Antimicrobial Prescribing Guidelines for Pigs* but there are important differences between countries. Several of the products registered in Australia are not available in New Zealand so have been excluded. Australia does not register fluoroquinolones for use in food producing animals but New Zealand does, albeit with strict conditions.

The practitioner must also be aware that these are best practice guidelines and some uses and/or dose rates may be off label. Therefore, they need to be aware of relevant food withholding periods and provide advice to owners per the VCNZ COPC expectations for use of off-label medicines.

Drug	Route	Dose rate	Duration
Amoxicillin	IM	7 mg/kg	SID 3–5 days
Amoxicillin LA	IM	15 mg/kg	Repeat after 48 hours
Amoxicillin	Oral in water	20 mg/kg	3–5 days
Amoxicillin	Oral in feed	20 mg/kg 500 ppm in feed	5 days
Lincomycin	Oral in water	10 mg/kg 33 mg/L	Treat for 5 days after the disappearance of bloody stools (Swine dysentery) for a maximum of 10 days
Lincomycin	Oral in feed	40–100 ppm *B hyodysenteriae* 220 ppm *M hypopneumoniae*	A maximum of 21 days or, in the case of swine dysentery, until clinical signs disappear
Enrofloxacin	IM	2.5 mg/kg	3–5 days
Marbofloxacin	IM	2 mg/kg	3 days
Marbofloxacin	IM	10 mg/kg	Once
Neomycin	IM	2–4 mg/kg	Every 6–12 hours for 3–14 days as indicated
Neomycin	Oral in water	8–22 mg/kg	3–5 days
Neomycin	Oral in feed	8–22 mg/kg 100–200 ppm	3–7 days
Oxytetracycline Short acting	IM	4–9 mg/kg	SID 3–5 days
Oxytetracycline Long acting	IM	20–30 mg/kg	Once
Oxytetracycline	Oral in feed	25 mg/kg 550–1100 ppm for leptospirosis 20 mg/kg 450 ppm for other diseases	7–14 days
Penicillin procaine	IM	12–15 mg/kg	SID 3–5 days
Penicillin benzathine	IM	13 mg/kg total penicillin	Single dose Repeat after 3 days
Tiamulin	Oral in water	8.8 mg/kg – 25.5/100ml water for *Brachyspira hyodysenteriae* 17.6 mg/kg – 25.5 g/200L water for *Mycoplasma hypopneumoniae*	3–5 days 6 days
Tilmicosin	Oral in water	15–20 mg/kg	5 days
Tilmicosin	Oral in feed	8–24 mg/kg	14 days
Tulathromycin	IM	2.5 mg/kg	Once
Trimethoprim/sulpha			
Tylosin	IM	5–10 mg/kg	7 days
Tylosin	Oral in water	25 mg/kg *Brachyspira hyodysenteriae* 6–12 mg/kg *Lawsonia intracellularis*	7 days
Tylosin	Oral in feed	40–100 ppm	Up to 21 days for treatment of ileitis at 100 ppm

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